Eur J Epidemiol
DOI 10.1007/s10654-014-9960-x

META-ANALYSIS

Tea consumption and risk of cardiovascular outcomes and total mortality: a systematic review and meta-analysis of prospective observational studies

Chi Zhang · Ying-Yi Qin · Xin Wei · Fei-Fei Yu · Yu-Hao Zhou · Jia He

Received: 5 May 2014 / Accepted: 15 October 2014

Abstract Studies that investigated the association between tea consumption and the risk of major cardiovascular events have reported inconsistent results. We conducted a meta-analysis of prospective observational studies in order to summarize the evidence regarding the association between tea consumption and major cardiovascular outcomes or total mortality. In July 2014, we performed electronic searches in PubMed, EmBase, and the Cochrane Library, followed by manual searches of reference lists from the resulting articles to identify other relevant studies. Prospective observational studies that reported effect estimates, with 95 % confidence intervals (CIs), for coronary heart disease (CHD), stroke, cardiac death, stroke death, or total mortality for more than two dosages of tea consumption were included. A random-effects meta-analysis was performed to determine the risk of major cardiovascular outcomes associated with an increase in tea consumption by 3 cups per day. Of the 736 citations identified from database searches, we included 22 prospective studies from 24 articles reporting data on 856,206 individuals, and including 8,459 cases of CHD, 10,572 of stroke, 5,798 cardiac deaths, 2,350 stroke deaths, and 13,722 total deaths. Overall, an increase in tea consumption by 3 cups per day was associated with a reduced risk of CHD (relative risk [RR], 0.73; 95 % CI: 0.53–0.99; $P = 0.045$), cardiac death (RR, 0.74; 95 % CI: 0.63–0.86; $P < 0.001$), stroke (RR, 0.82; 95 % CI: 0.73–0.92; $P = 0.001$), total mortality (RR, 0.76; 95 % CI: 0.63–0.91; $P = 0.003$), cerebral infarction (RR, 0.84; 95 % CI: 0.72–0.98; $P = 0.023$), and intracerebral hemorrhage (RR, 0.79; 95 % CI: 0.72–0.87; $P < 0.001$), but had little or no effect on stroke mortality (RR, 0.93; 95 % CI: 0.83–1.05; $P = 0.260$). The findings from this meta-analysis indicate that increased tea consumption is associated with a reduced risk of CHD, cardiac death, stroke, cerebral infarction, and intracerebral hemorrhage, as well as total mortality.

Keywords Tea · Cardiovascular disease · Total mortality · Dose–response · Meta-analysis

Chi Zhang, Ying-Yi Qin, Xin Wei and Fei-Fei Yu have contributed equally to this article.

Electronic supplementary material The online version of this article (doi:10.1007/s10654-014-9960-x) contains supplementary material, which is available to authorized users.

C. Zhang
Department of Neurosurgery, Shanghai Seventh People's Hospital, Shanghai 200137, China

Y.-Y. Qin · F.-F. Yu · J. He (✉)
Department of Health Statistics, Second Military Medical University, Shanghai 200433, China
e-mail: hejia63@yeah.net

X. Wei
Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Y.-H. Zhou (✉)
Department of Rehabilitation Institute, Shanghai Seventh People's Hospital, Shanghai 200137, China
e-mail: zhou_ly@126.com

Introduction

Tea, particularly black tea and green tea, is a commonly consumed beverage in many populations and has been reported to contribute both favourably and adversely to major cardiovascular outcomes [1, 2]. Black tea is the main tea beverage in the United States, Europe, and Western Asia, whereas green tea is more popular in China, Japan, and Korea

Published online: 30 October 2014

[3]. The role of tea in cardiovascular disease prevention is supported by various studies [4, 5]. A large number of cohort studies have shown that increased tea consumption is associated with a decreased risk of major cardiovascular outcomes [6–10]. However, another study suggest that consumption of black tea may increase the risk of cardiac death and total mortality [11]. Because of the widespread consumption of tea, even small effects could have a large impact on public health. However, data regarding the subsequent effects of tea consumption on major cardiovascular outcomes are limited and inconclusive.

The relation between tea consumption and a decreased risk of stroke was first revealed by Sato [12]. Moreover, later, in the Zutphen Study [13, 14], the risk of cardiac death and stroke was found to be lower in subjects who reported regular tea consumption. The reason for these findings could be that tea contains polyphenols, such as catechins and flavonols, that act as powerful antioxidants. Previous meta-analyses [15] have assessed whether tea consumption is associated with the risk of stroke, and suggested that daily consumption of either green or black tea equalling 3 cups per day could prevent the onset of ischemic stroke. Controversially, the results of Peters' meta-analysis [16] indicated that the risk of coronary heart disease (CHD) in the United Kingdom and of stroke in Australia increased with tea consumption, whereas the risk decreased in other regions, particularly in continental Europe. Additional unanswered questions remain, including whether these associations are applicable to cardiac death or total mortality, and whether associations differ according to sex, ethnicity, and the type of tea. Traditional meta-analyses mainly focused on the relationship between high versus low tea consumption and the risk of vascular outcomes; the range of tea consumption and the cut-off values for the categories differed between studies.

In the present study, we conducted a systematic review and meta-analysis of prospective observational studies to determine the association between tea consumption and cardiovascular morbidity and mortality across sexes, ethnic populations, and types of tea. Furthermore, we performed a dose–response meta-analysis to quantitatively elucidate the optimal tea consumption for the general population.

Methods

Data sources, search strategy, and selection criteria

This review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement, 2009 (Checklist S1) [17].

We systematically searched the PubMed, Embase, and Cochrane Library electronic databases (from database inception to July 2014) for studies in humans, with no language restrictions. We only included prospective observational studies, in order to avoid the potential flaws of recall bias and exposure misclassification in retrospective studies. Any prospective observational study that examined the relationship between tea consumption and major cardiovascular outcomes (CHD, cardiac death, stroke, stroke mortality, cerebral infarction, intracerebral hemorrhage, subarachnoid hemorrhage, and total mortality) was eligible for inclusion in our study, and no restrictions were placed on publication status (published, or in press). Our core search included the following terms: "tea" AND ("cardiovascular disease" OR "coronary disease" OR "coronary thrombosis" OR "ischemic heart disease" OR "myocardial infarction" OR "stroke" OR "coronary stenosis" OR "coronary restenosis" OR "cardiac death") AND ("cohort" OR "cohort studies" OR "nest case control" OR "nest case–control studies"). If a site-specific dataset had been published more than once, we used the most recent publication. We reviewed the reference lists of the identified reports, reviews, meta-analyses, and other relevant publications to find additional pertinent studies. In addition, we contacted authors to obtain any unpublished supplementary data. The medical subject heading, methods, population, study design, exposure, and outcome variables of these articles were used to identify relevant studies.

A study was eligible for inclusion if the following criteria were met: (1) the study had a prospective observational design (prospective cohort or nested prospective case–control study); (2) the study investigated the association between tea consumption and the risk of major cardiovascular outcomes; and (3) the authors reported effect estimates (risk ratio [RR], hazard ratio [HR], or odds ratio [OR]) and 95 % confidence intervals (CIs) for comparisons between high and low tea consumption (with more than 2 dosages). We excluded all case–control studies, because various confounding factors could bias the results.

The literature search was undertaken independently by two authors (CZ and XW) using a standardized approach. Any inconsistencies were resolved by discussion with the primary author (YHZ) and a consensus was reached. We excluded studies that were not published as full reports, which included conference abstracts and letters to editors.

Data collection and quality assessment

The following data elements were collected: first author or study group name, publication year, country, study design, assessment of tea consumption, sample size, number of incident outcomes, age at baseline, number of men and women, follow-up duration, effect estimate, comparison

categories, and covariates in the fully adjusted model. We also extracted data on the numbers of cases per person or per person-year, the effect of the different exposure categories, and 95 % CIs. For studies that reported several multivariable adjusted RRs, we selected the effect estimate that was adjusted for the greatest number of potential confounders.

The Newcastle-Ottawa Scale (NOS) was used to evaluate methodological quality [18, 19]. The NOS is a comprehensive tool that has been partially validated for evaluating the quality of observational studies in meta-analyses. The NOS [18] is based on the following three subscales: selection (4 items), comparability (1 item), and outcome (3 items). A "star system" (range 0–9) has been developed for assessment (Table S1). Data extraction and quality assessment were performed independently by two authors (CZ and XW). Information was examined and verified independently by an additional author (YHZ).

Statistical analysis

We examined the relationship between tea consumption and the risk of major cardiovascular outcomes on the basis of the effect estimate (RR or HR) and its 95 % CI published in each study. We first used the random-effects model to calculate summary RRs and 95 % CIs for high tea consumption compared to low tea consumption [20, 21]. The cut-off values for high and low intake were in compliance with the categories reported in the original studies. We then transformed category-specific risk estimates into estimates of the RR associated with every increase in tea consumption by 3 cups per day, using the generalized least-squares method for trend estimation [22, 23]. These estimates were calculated assuming the presence of a linear relationship between the natural logarithm of the RR and increasing tea consumption [22]. We converted all measures into cups per day, defining one cup as 125 mL of tea consumption. The value assigned to each tea consumption category was the mid-point for closed categories, and the median for open categories (assuming a normal distribution for tea consumption). We combined the RRs for each 3 cup-per day increase in tea consumption using random-effect meta-analysis [21]. Finally, we conducted a restricted cubic spline model based on the correlated natural log of RRs or HRs across the tea consumption categories to estimate a potential curvilinear association between tea consumption and major cardiovascular outcomes [22, 23]. To derive the dose–response curve, we modelled tea consumption using restricted cubic splines with three knots at fixed percentiles of 10, 50, and 90 % of the distribution. This method requires the effect measure with its variance estimate for at least three known categories of exposure [22].

We assessed heterogeneity between studies using the I^2 statistic as a measure of the proportion of total variation in estimates that was attributable to heterogeneity, where I^2 values of 25, 50, and 75 % correspond to the cut-off points for low, moderate, and high degrees of heterogeneity, respectively [24–26]. Subsequently, subgroup analyses were conducted for major cardiovascular outcomes, according to sex, ethnic background, and type of tea. Additional potential residual confounding factors, such as assessment of exposure, effect estimate, follow-up duration, study quality (NOS score [18]), and adjustment of covariates (including body mass index [BMI], daily energy intake, and blood pressure) were also conducted. We also performed a sensitivity analysis by removing each individual study from the meta-analysis [27]. Several methods were used to check for potential publication bias. Funnel plots for major cardiovascular outcomes were visually inspected. The Egger [28] and Begg [29] tests were also used to statistically assess publication bias. All reported P values were 2-sided, and $P < 0.05$ were considered statistically significant for all included studies. Statistical analyses were performed using STATA software (version 12.0; Stata Corporation, College Station, TX, USA).

Results

Of the 736 citations identified from database searches, 22 datasets from 24 articles [1, 6–14, 30–43] met the inclusion criteria. The study selection process is shown in Fig. 1. A manual search of the reference lists of these studies did not yield any new eligible studies. Among the included studies,

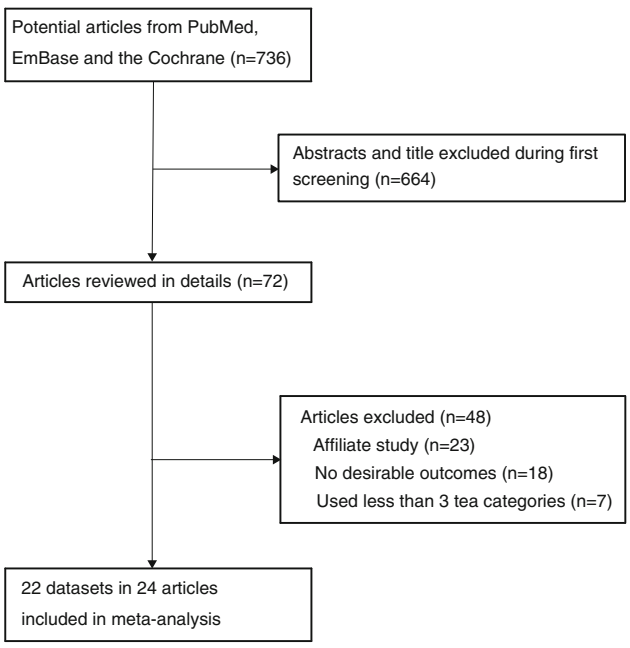

Fig. 1 Flow diagram of the literature search and studies selection process

nine were from Europe [6, 9–11, 13, 31, 32, 36, 43], seven were from the US [8, 34, 38–42], and six were from Asia [7, 12, 30, 33, 35, 37]. Table S2 summarizes the characteristics of the included studies. The analysis included 8,459 incident cases of CHD, 10,572 of stroke, 5,798 cardiac deaths, 2,350 stroke deaths, 13,722 total deaths, 5,861 cases of cerebral infarction, 818 of intracerebral hemorrhage, 344 of subarachnoid hemorrhage, and more than 856,206 individuals. The follow-up times varied from 3.8 years to 24.0 years in each individual study. The outcomes were CHD in seven studies [6, 9, 10, 30, 38, 40, 41], cardiac death in 12 studies [6–11, 14, 32, 33, 37, 42, 43], stroke in eight studies [6, 12, 13, 30, 31, 34, 35, 38], stroke mortality in five studies [6, 32, 33, 37, 43], total mortality in seven studies [6, 7, 10, 11, 37, 39, 43], cerebral infarction in four studies [30, 31, 35, 36], intracerebral hemorrhage in four studies [30, 31, 35, 36], and subarachnoid hemorrhage in two studies [31, 36]. Study quality was assessed using NOS [18], as shown in Appendix 1-Table S1.

Figures S1–S8 show the results of meta-analyses of RRs according to high versus low tea consumption. The summary RR showed that high tea consumption was associated with a reduced risk of CHD (RR, 0.53; 95 % CI: 0.28–0.98; $P = 0.043$), cardiac death (RR, 0.58; 95 % CI: 0.43–0.78; $P < 0.001$), stroke (RR, 0.67; 95 % CI: 0.53–0.85; $P = 0.001$), total mortality (RR, 0.59; 95 % CI: 0.40–0.87; $P = 0.007$), and cerebral infarction (RR, 0.78; 95 % CI: 0.67–0.92; $P = 0.002$), but not with any reduction in stroke mortality, intracerebral hemorrhage, or subarachnoid hemorrhage. Between-study heterogeneity was high for CHD, cardiac death, stroke, total mortality, cerebral infarction, and intracerebral hemorrhage, and moderate for stroke mortality and subarachnoid hemorrhage. Sensitivity analyses indicated that exclusion of any individual study did not change the results (data not shown).

All included studies were eligible for the dose–response meta-analysis. The results showed that a increment in tea consumption by 3 cups per day was associated with a reduced risk of CHD (RR, 0.73; 95 % CI: 0.53–0.99; $P = 0.045$; Fig. 2a), cardiac death (RR, 0.74; 95 % CI: 0.63–0.86; $P < 0.001$; Fig. 2b), stroke (RR, 0.82; 95 % CI: 0.73–0.92; $P = 0.001$; Fig. 3a), total mortality (RR, 0.76; 95 % CI: 0.63–0.91; $P = 0.003$; Fig. 3c), cerebral infarction (RR, 0.84; 95 % CI: 0.72–0.98; $P = 0.023$; Fig. 4a), and intracerebral hemorrhage (RR, 0.79; 95 % CI: 0.72–0.87; $P < 0.001$; Fig. 4b). However, increased tea consumption was not associated with stroke mortality (RR, 0.93; 95 % CI: 0.83–1.05; $P = 0.260$; Fig. 3b) or the risk of subarachnoid hemorrhage (RR, 0.91; 95 % CI: 0.41–2.03; $P = 0.818$; Fig. 4c). Heterogeneity between studies was high for CHD, cardiac death, stroke, total mortality, cerebral infarction, and subarachnoid hemorrhage, and moderate or low for stroke mortality and intracerebral hemorrhage.

Figure 5 shows that tea consumption of 1–3 and 1–5 cups per day seems to be associated with a reduced risk of cardiac death and in total mortality, respectively (P values of nonlinearity for these analyses were both 0.0008). However, we found no evidence of nonlinear relationships between tea consumption and the risk of CHD and stroke, or stroke mortality (Figures S9–S11). Because only a few studies were included in the meta-analysis, we have not presented the nonlinear trend for cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage.

In the subgroup analysis, we stratified studies into groups to examine the sources of study heterogeneity. The results of the subgroup analysis of RRs for an increase in tea consumption by 3 cups per day for CHD, cardiac death, stroke, stroke mortality, and total mortality are listed in Tables 1 and S3. We found that an increment in tea consumption by 3 cups per day was associated with a reduced risk of CHD if the participants were European or consumption of black tea. Similarly, we found that a 3 cups per day increase in the consumption of tea was associated with a reduced risk of cardiac death if the participants were women, Asian, European, or consumption of green tea; an increase of 3 cups of tea per day was associated with a reduced risk of stroke if the participants were men, Asian, or consumption of green tea; an increment in tea consumption by 3 cups per day was associated with a reduced risk of total mortality if the participants were women, Asian, or consumption of green tea. Furthermore, subgroup analyses of RRs for high versus low tea consumption for CHD, cardiac death, stroke, stroke mortality, and total mortality were also performed, and the results are listed in Table S4. The results were generally consistent with a stratified analysis for an increase in tea consumption by 3 cups per day.

A review of funnel plots could not rule out the potential for publication bias regarding major cardiovascular outcomes (Figures S12–S18). The Egger [28] and Begg [29] test results showed no evidence of publication bias for CHD, stroke, stroke mortality, total mortality, cerebral infarction, or intracerebral hemorrhage. However, we noted evidence of publication bias for cardiac death (P value for Egger: 0.033; P value for Begg: 0.019). The conclusions were not changed after adjustment for publication bias by the trim and fill method [44].

Discussion

Our large standardized meta-analysis shows that increased tea consumption is associated with a reduction in total mortality, and in the risk of CHD, cardiac death, stroke, cerebral infarction, and intracerebral hemorrhage, but has

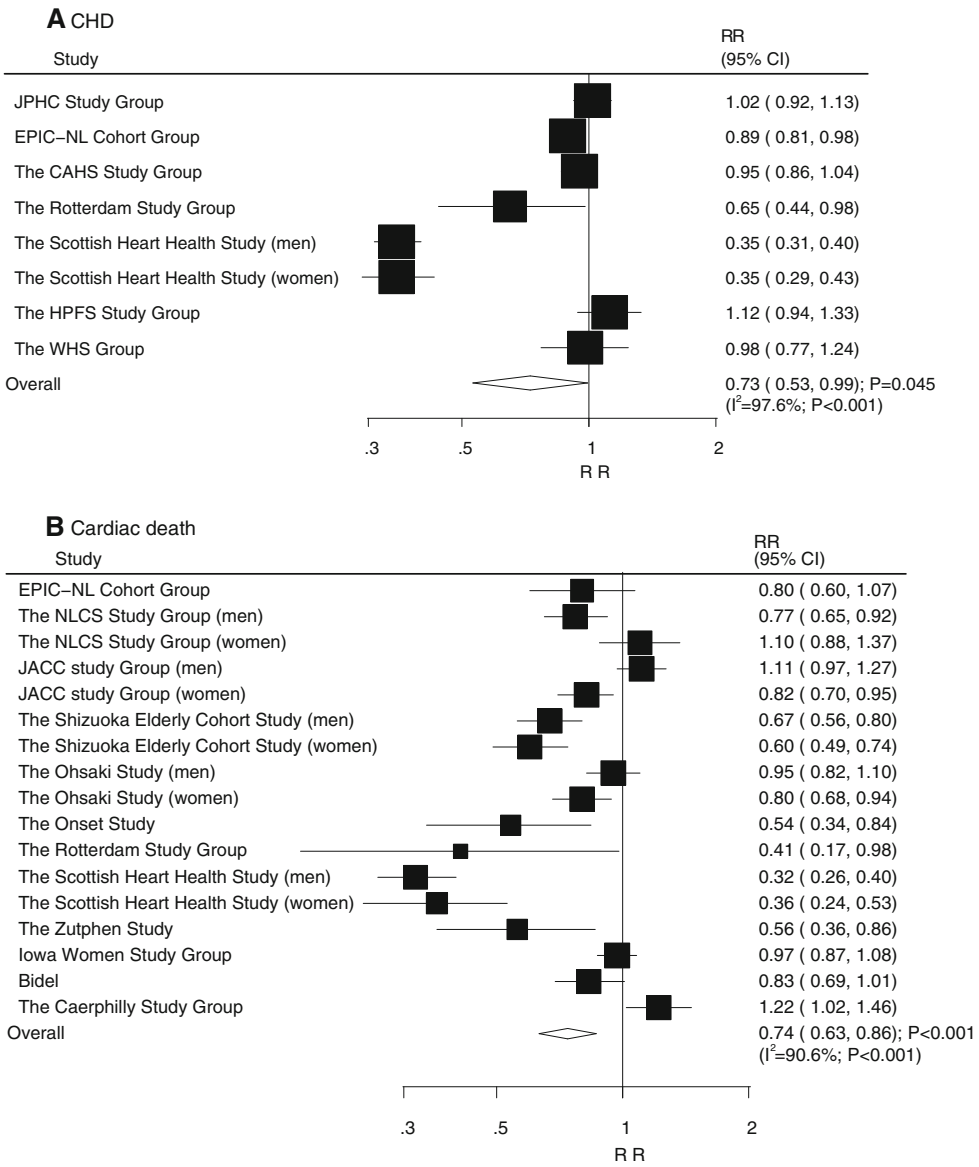

Fig. 2 Dose–response meta-analysis for per 3 cups per increment in tea consumption for CHD and cardiac death

no significant effect on stroke mortality or the risk of subarachnoid hemorrhage. Our findings extend the results of previous reviews [15], showing associations between increased tea consumption and the risk for CHD and cardiac death, as well as total mortality, and provide evidence that associations might differ within different sex, country, and tea-type subgroups for these three outcomes. For other outcomes, the magnitudes of associations between increased tea consumption and the risk of major cardiovascular outcomes were similar across sexes, populations of different ethnic backgrounds, and the types of tea.

Meta-analyses of observational studies are prone to biases and confounding factors that are inherent in the original studies. We restricted our analysis to prospective studies (cohort studies or nested case–control studies) and excluded traditional case–control studies, which are prone to recall and interviewer bias [45]. Furthermore, we assessed the methodological quality of the included studies, using the NOS system [18], and also evaluated the effect of tea consumption on major cardiovascular outcomes in specific populations in subgroup analyses. Our study showed that different subpopulations and consumption of different types of tea might be a source of significant heterogeneity in the association with the risk of some major cardiovascular outcomes. This is a possible reason for our findings being inconsistent with earlier reports [15] that increased tea consumption has no significant effect on the risk of intracerebral hemorrhage. Furthermore, the effect of ethnicity is underestimated, because mixed tea consumption (green and black tea) was more popular in western countries [3].

Increased tea consumption might play an important role in cardiovascular morbidity and mortality. The specificity of

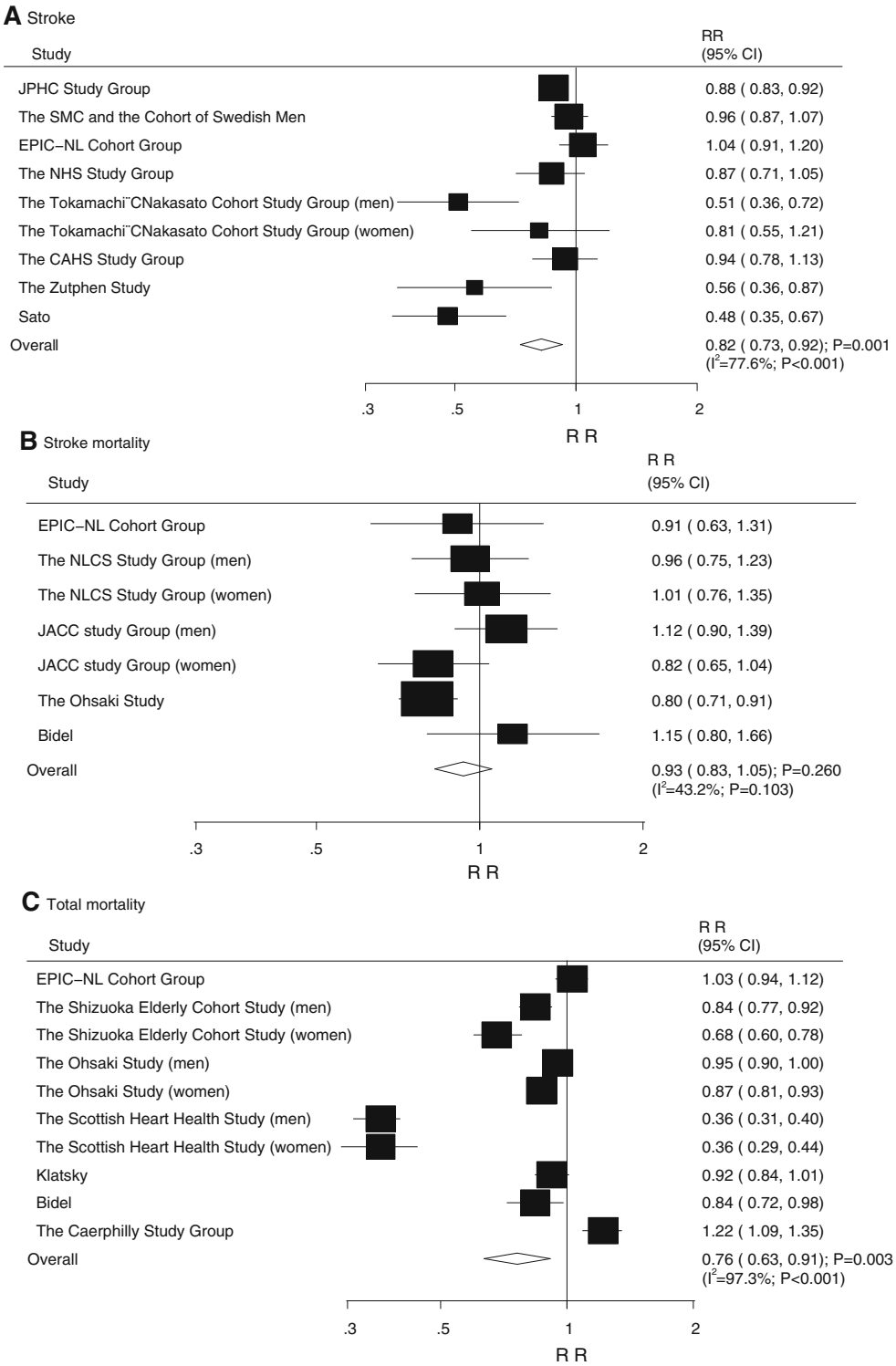

Fig. 3 Dose–response meta-analysis for per 3 cups per increment in tea consumption for stroke, stroke mortality and total mortality

these associations argues against confounding and bias, and for a possible causal link between increased tea consumption and a reduction in the risk of major cardiovascular outcomes. Some important confounding factors might not have been quantified, or quantified with sufficient precision, in these studies. In our current study, BMI seemed to be a major confounder in the association of increased tea consumption with the risk of CHD or cardiac death, and total mortality; daily energy intake seemed to be a confounding factor in the association between tea consumption and cardiac death, stroke and total mortality; and blood pressure was a potential confounding factor in the association of increased tea

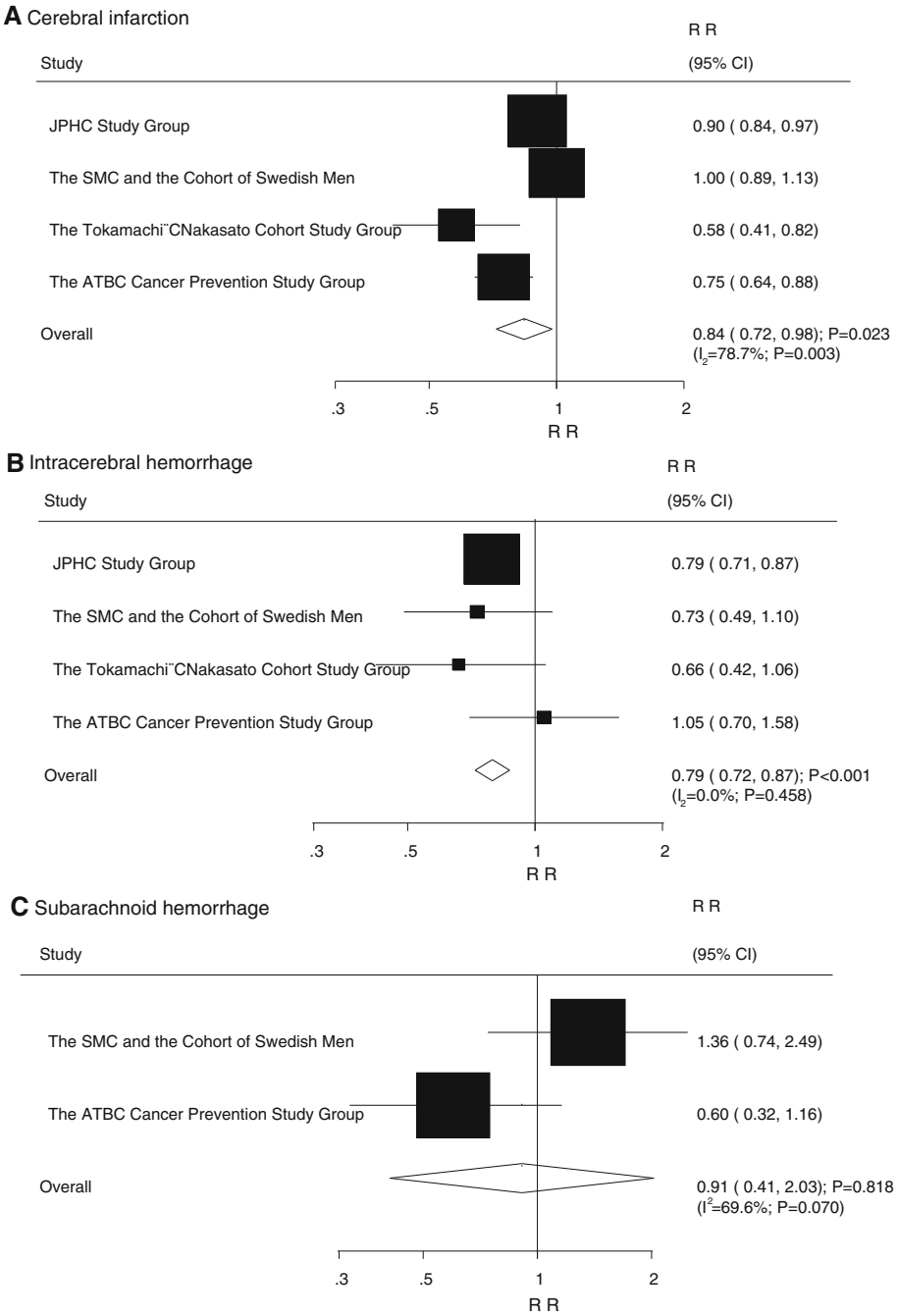

Fig. 4 Dose–response meta-analysis for per 3 cups per increment in tea consumption for stroke subtypes

consumption with stroke and total mortality. However, we could not determine the effect of these potential confounding factor on the risk of major cardiovascular outcomes, since too few studies were stratified by these factors.

In this meta-analysis, benefits were mainly detected in reducing the incidence of CHD, cardiac death, stroke, total mortality, cerebral infarction, and intracerebral hemorrhage. The possible reason for this could be that: (1) The polyphenolic flavonoids in tea have antioxidative properties that prevent the oxidation of low-density lipoproteins in vitro or vivo [46, 47]. Moreover, increased tea consumption also contributes high concentrations of autoantibodies against oxidized low-density lipoproteins in patients with atherosclerosis [48, 49]. (2) Although we found no significant associations between increased tea consumption and stroke mortality or subarachnoid hemorrhage, these conclusions may be unreliable because smaller numbers of trials were included in these subsets. (3) Our inclusion criteria restricted our meta-analysis to prospective observational studies and provide the evidence that

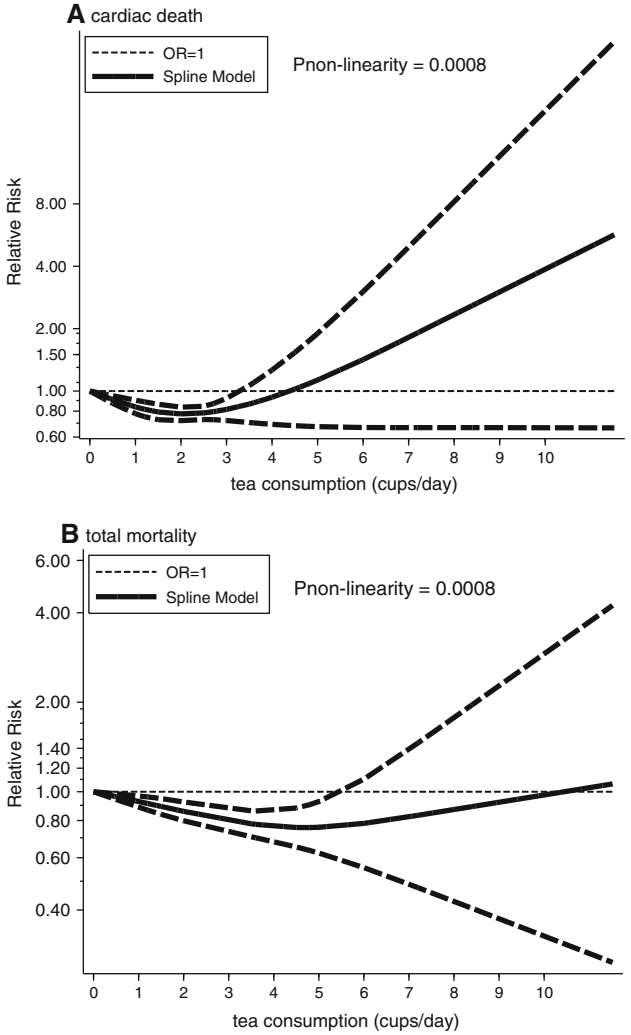

Fig. 5 Dose–response analysis for curvilinear association between tea consumption and relative risks of cardiac death or total mortality

increased tea consumption was associated with a lower risk of CHD, cardiac death, stroke, total mortality, cerebral infarction, and intracerebral hemorrhage; and (4) Subgroup group analyses indicated that the benefit of tea drinking was mainly the prevention of major cardiovascular outcomes in multi-subpopulations. The possible reasons for this could be that drinking both types of tea have been shown to reduce blood pressure, which is the primary strategy to limit risk of cardiovascular disease in humans.

From a review of a previous meta-analysis [15], it is notable that the evidence for the protective effect of tea consumption comes from a combination of retrospective case–control studies and cohort studies. In traditional case–control studies, because information that reflects past exposure is collected after cardiovascular morbidity and mortality are known, recall bias is inevitable and cannot be ignored [45]. Furthermore, the cut-off values for tea consumption categories differed between studies. Given the above limitations, one cannot conclude convincingly from those data that high tea consumption has a protective effect against major cardiovascular outcomes. In contrast with that review, we have reported our results stratified according to sex, ethnic background, and type of tea, and we considered several additional potential confounding factors. Moreover, our combined risk estimates using a random effect model were generally more conservative than the estimates from the previous review and provided relatively stronger evidence for the association of increased tea consumption with a reduction in the risk of major cardiovascular outcomes.

Compared with previous meta-analyses, ours has some obvious strengths. First, only prospective observational studies were included, which would eliminate selection and recall bias. Second, the large sample size allowed us to quantitatively assess the association of tea consumption with the risk of major cardiovascular outcomes, and thus our findings are potentially more robust than are those of any individual study. Third, the dose–response analysis included a wide range in the quantity of tea consumption, which allowed for accurate assessment of the dose relationship between tea consumption and the risk of major cardiovascular outcomes.

Our study had some limitations. First, data on stroke subtypes were available from only a few studies, which restricted the precise assessment of the dose–response relationship between tea consumption and these three types of stroke in some specific subsets of individuals. Second, the methods of assessing tea consumption differed across included studies, which could have biased the association between tea consumption and the risk of major cardiovascular outcomes. Third, the tea consumption level is generally assessed as the number of cups of tea consumed per day or per week, but cup size may vary considerably between different studies. We therefore converted all measures into cups per day and defined 125 mL of tea consumption as one cup to avoid potential confounding bias from cup size. Fourth, it is notable that consumption of green tea in Asian is more popular than in Western Countries. However, the factor of ethnicity is not available in our study, which might play an important role in the relationship between tea consumption and the risk of major cardiovascular events. Therefore, we just gave a relative results for the association between tea consumption and the risk of major cardiovascular events in several specific subpopulations. Finally, the adjusted models were different across the included studies, and these factors might play an important role in the development of major cardiovascular outcomes that could affect the result of our pooled analysis.

Despite the limitations, our findings have important public health implications. The reduction of cardiovascular

Table 1 Subgroup analysis of risk ratios per 3 cups per day increase in tea consumption for CHD, cardiac death, stroke, stroke mortality, and total mortality incidence according to sex, ethnic backgrounds, and types of tea

Outcomes	Group	Number of studies	RR and 95 % CI	*P* value	Heterogeneity (%)	*P* value for heterogeneity
CHD	*Sex*					
	Men	2	0.63 (0.20–1.95)	0.419	99.1	<0.001
	Women	2	0.58 (0.21–1.60)	0.297	97.7	<0.001
	Both	4	0.93 (0.85–1.02)	0.148	57.1	0.072
	Country					
	Asia	1	1.02 (0.92–1.13)	0.706	–	–
	US	3	1.00 (0.90–1.10)	0.954	24.9	0.264
	Europe	4	0.51 (0.29–0.92)	0.026	98.2	<0.001
	Type of tea					
	Green	1	1.02 (0.92–1.13)	0.706	–	–
	Black	3	0.90 (0.81–1.00)	0.048	46.1	0.157
	Mixed	4	0.60 (0.32–1.14)	0.121	98.1	<0.001
Cardiac death	*Sex*					
	Men	7	0.75 (0.55–1.02)	0.067	95.1	<0.001
	Women	6	0.76 (0.62–0.94)	0.011	87.7	<0.001
	Both	4	0.73 (0.58–0.91)	0.006	40.2	0.171
	Country					
	Asia	6	0.81 (0.68–0.97)	0.022	86.0	<0.001
	US	2	0.76 (0.43–1.33)	0.333	83.6	0.014
	Europe	9	0.66 (0.48–0.92)	0.013	93.2	<0.001
	Type of tea					
	Green	6	0.81 (0.68–0.97)	0.022	86.0	<0.001
	Black	3	0.86 (0.54–1.35)	0.508	81.0	0.005
	Mixed	8	0.64 (0.47–0.87)	0.004	93.7	<0.001
Stroke	*Sex*					
	Men	2	0.53 (0.40–0.69)	<0.001	0.0	0.744
	Women	3	0.70 (0.48–1.03)	0.067	79.2	0.008
	Both	4	0.94 (0.87–1.01)	0.111	52.8	0.096
	Country					
	Asia	4	0.66 (0.46–0.93)	0.019	86.3	<0.001
	US	2	0.91 (0.79–1.04)	0.151	0.0	0.574
	Europe	3	0.92 (0.76–1.11)	0.400	71.3	0.031
	Type of tea					
	Green	4	0.66 (0.46–0.93)	0.019	86.3	<0.001
	Black	3	0.98 (0.91–1.06)	0.597	0.0	0.590
	Mixed	2	0.73 (0.48–1.11)	0.146	68.8	0.074
Stroke mortality	*Sex*					
	Men	2	1.05 (0.89–1.23)	0.579	0.0	0.359
	Women	2	0.89 (0.73–1.09)	0.279	17.4	0.271
	Both	3	0.89 (0.72–1.10)	0.285	44.8	0.164
	Country					
	Asia	3	0.89 (0.73–1.10)	0.287	72.0	0.028
	Europe	4	1.00 (0.86–1.16)	0.952	0.0	0.820
	Type of tea					
	Green	3	0.89 (0.73–1.10)	0.287	72.0	0.028
	Black	1	0.91 (0.63–1.31)	0.614	–	–
	Mixed	3	1.01 (0.86–1.20)	0.870	0.0	0.724

Table 1 continued

Outcomes	Group	Number of studies	RR and 95 % CI	*P* value	Heterogeneity (%)	*P* value for heterogeneity
Total mortality	*Sex*					
	Men	4	0.77 (0.52–1.14)	0.190	98.7	<0.001
	Women	3	0.60 (0.40–0.92)	0.019	97.0	<0.001
	Both	3	0.94 (0.84–1.05)	0.254	67.5	0.046
	Country					
	Asia	4	0.84 (0.75–0.94)	0.002	87.5	<0.001
	US	1	0.92 (0.84–1.01)	0.076	–	–
	Europe	5	0.67 (0.42–1.10)	0.111	98.7	<0.001
	Type of tea					
	Green	4	0.84 (0.75–0.94)	0.002	87.5	<0.001
	Black	2	1.12 (0.95–1.32)	0.188	82.6	0.016
	Mixed	4	0.56 (0.33–0.95)	0.033	98.3	<0.001

morbidity and mortality continues to be an important public health issue for researchers, especially with regard to the relationship between lifestyle and major cardiovascular outcomes. Systematic reviews and meta-analyses are the most powerful tools for assessing these kinds of inconsistent associations. Therefore, our present study provides evidence that increased tea consumption might have a protective effect against CHD, cardiac death, stroke, cerebral infarction, and intracerebral hemorrhage, as well as reducing total mortality. Furthermore, the results of the dose–response analyses indicated that tea consumption of 1–3 and 1–5 cups per day seems to be associated with a reduction in the risk of cardiac death and in total mortality. These protective effects of increased tea consumption, stratified by additional potential confounding factors, need further investigation in additional trials.

Acknowledgments This study was funded by The Ministry of Science and Technology of China (2008ZX10002-007, 2008ZX10002-018, 2008ZX10002-025), The Leading Talents of Science in Shanghai 2010 (022), The Key Discipline Construction of Evidence-Based Public Health in Shanghai (12GWZX0602), The National Science Foundation of China (81373105). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of interest None of the author has a conflict of interest.

References

1. Rimm ER, Katan MB, Ascherio A, Stampfer MJ, Willett WC. Relation between intake of flavonoids and risk for coronary heart disease in male health professionals. Ann Intern Med. 1996;125:384–9.
2. Sone T, Kuriyama S, Nakaya N, Hozawa A, Shimazu T, Nomura K, Rikimaru S, Tsuji I. Randomized controlled trial for an effect of catechin-enriched green tea consumption on adiponectin and cardiovascular disease risk factors. Food Nutr Res 2011;55. doi: 10.3402.
3. Food and Agriculture Organization of the United Nations. Food balance sheets. 1996;1994–6.
4. Mink PJ, Scrafford CG, Barraj LM, Harnack L, Hong CP, Nettleton JA, Jacobs DR Jr. Flavonoid intake and cardiovascular disease mortality: a prospective study in postmenopausal women. Am J Clin Nutr. 2007;85:895–909.
5. Wang X, Ouyang YY, Liu J, Zhao G. Flavonoid intake and risk of CVD: a systematic review and meta-analysis of prospective cohort studies. Br J Nutr. 2014;111:1–11.
6. de Koning Gans JM, Uiterwaal CS, van der Schouw YT, Boer JM, Grobbee DE, Beulens JW, Verschuren WM. Tea and coffee consumption and cardiovascular morbidity and mortality. Arterioscler Thromb Vasc Biol. 2010;30:1665–71.
7. Suzuki E, Yorifuji T, Takao S, Komatsu H, Sugiyama M, Ohta T, Ishikawa-Takata K, Doi H. Green tea consumption and mortality among Japanese elderly people: the prospective Shizuoka elderly Cohort. Ann Epidemiol. 2009;19:732–9.
8. Mukamal KJ, Maclure M, Muller JE, Sherwood JB, Mittleman MA. Tea consumption and mortality after acute myocardial infarction. Circulation. 2002;105:2476–81.
9. Geleijnse JM, Launer LJ, Van der Kuip DA, Hofman A, Witteman JC. Inverse association of tea and flavonoid intakes with incident myocardial infarction: the Rotterdam Study. Am J Clin Nutr. 2002;75:880–6.
10. Woodward M, Tunstall-Pedoe H. Coffee and tea consumption in the Scottish Heart Health Study follow up: conflicting relations with coronary risk factors, coronary disease, and all cause mortality. J Epidemiol Community Health. 1999;53:481–7.
11. Hertog MG, Sweetnam PM, Fehily AM, Elwood PC, Kromhout D. Antioxidant flavonols and ischemic heart disease in a Welsh population of men: the Caerphilly Study. Am J Clin Nutr. 1997;65:1489–94.
12. Sato Y, Nakatsuka H, Watanabe T, Jousilahti P, Antikainen R, Tuomilehto J. Possible contribution of green tea drinking habits to the prevention of stroke. Tohoku J Exp Med. 1989;157:337–43.
13. Keli SO, Hertog MG, Feskens EJ, Kromhout D. Dietary flavonoids, antioxidant vitamins, and incidence of stroke: the Zutphen study. Arch Intern Med. 1996;154:637–42.
14. Hertog MG, Feskens EJ, Hollman PC, Katan MB, Kromhout D. Dietary antioxidant flavonoids and risk of coronary heart disease: the Zutphen Elderly Study. Lancet. 1993;342:1007–11.

15. Arab L, Liu W, Elashoff D. Green and Black Tea Consumption and Risk of Stroke: a meta-analysis. Stroke. 2009;40:1786–92.
16. Peters U, Poole C, Arab L. Does tea affect cardiovascular disease? A meta-analysis. Am J Epidemiol. 2001;154:495–503.
17. Moher D, Liberati A, Tetzlaff J, Altman DG. PRISMA group. Preferred Reporting Items for systematic reviews and meta-analyses: the PRISMA statement. Plos Med. 2009;6:e1000097.
18. Wells G, Shea B, O'Connell D. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa (ON): Ottawa Hospital Research Institute. 2009. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm.
19. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions, version 5.1.0.2011. www.cochrane-handbook.org.
20. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177–88.
21. Ades AE, Lu G, Higgins JP. The interpretation of random-effects metaanalysis in decision models. Med Decis Mak. 2005;25:646–54.
22. Orsini N, Bellocco R, Greenland S. Generalized least squares for trend estimation of summarized dose–response data. Stata J. 2006;6:40–57.
23. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose–response data, with applications to meta-analysis. Am J Epidemiol. 1992;135:1301–9.
24. Deeks JJ, Higgins JPT, Altman DG. Analyzing data and undertaking meta-analyses. In: Higgins J, Green S, editors. Cochrane handbook for systematic reviews of interventions 5.0.1. Oxford: The Cochrane Collaboration; 2008. chap 9:9.5.4.
25. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557–60.
26. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21:1539–58.
27. Tobias A. Assessing the influence of a single study in meta-analysis. Stata Tech Bull. 1999;47:15–7.
28. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629–34.
29. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50:1088–101.
30. Kokubo Y, Iso H, Saito I, Yamagishi K, Yatsuya H, Ishihara J, Inoue M, Tsugane S. The impact of green tea and coffee consumption on the reduced risk of stroke incidence in Japanese population: the Japan public health center-based study cohort. Stroke. 2013;44:1369–74.
31. Larsson SC, Virtamo J, Wolk A. Black tea consumption and risk of stroke in women and men. Ann Epidemiol. 2013;23:157–60.
32. Leurs LJ, Schouten LJ, Goldbohm RA, van den Brandt PA. Total fluid and specific beverage intake and mortality due to IHD and stroke in the Netherlands Cohort Study. Br J Nutr. 2010;104:1212–21.
33. Mineharu Y, Koizumi A, Wada Y, Iso H, Watanabe Y, Date C, Yamamoto A, Kikuchi S, Inaba Y, Toyoshima H, Kondo T, Tamakoshi A. JACC study group: coffee, green tea, black tea and oolong tea consumption and risk of mortality from cardiovascular disease in Japanese men and women. J Epidemiol Community Health. 2011;65:230–40.
34. Lopez-Garcia E, Rodriguez-Artalejo F, Rexrode KM, Logroscino G, Hu FB, van Dam RM. Coffee consumption and risk of stroke in women. Circulation. 2009;119:1116–23.
35. Tanabe N, Suzuki H, Aizawa Y, Seki N. Consumption of green and roasted teas and the risk of stroke incidence: results from the Tokamachi-Nakasato cohort study in Japan. Int J Epidemiol. 2008;37:1030–40.
36. Larsson SC, Männistö S, Virtanen MJ, Kontto J, Albanes D, Virtamo J. Coffee and tea consumption and risk of stroke subtypes in male smokers. Stroke. 2008;39:1681–7.
37. Kuriyama S, Shimazu T, Ohmori K, Kikuchi N, Nakaya N, Nishino Y, Tsubono Y, Tsuji I. Green tea consumption and mortality due to cardiovascular disease, cancer, and all causes in Japan: the Ohsaki Study. JAMA. 2006;296:1255–65.
38. Sesso HD, Paffenbarger RS Jr, Oguma Y, Lee IM. Lack of association between tea and cardiovascular disease in college alumni. Int J Epidemiol. 2003;32:527–33.
39. Klatsky A, Armsterong MA, Frienman G. Coffee, tea, and mortality. Ann Epidemiol. 1993;3:375–81.
40. Lopez-Garcia E, van Dam RM, Willett WC, Rimm EB, Manson JE, Stampfer MJ, Rexrode KM, Hu FB. Coffee consumption and coronary heart disease in men and women: a prospective cohort study. Circulation. 2006;113:2045–53.
41. Sesso HD, Gaziano JM, Liu S, Buring JE. Flavonoid intake and the risk of cardiovascular disease in women. Am J Clin Nutr. 2003;77:1400–8.
42. Yochum L, Kushi LH, Meyer K, Folsom AR. Dietary flavonoid intake and risk of cardiovascular disease in postmenopausal women. Am J Epidemiol. 1999;149:943–9.
43. Bidel S, Hu G, Qiao Q, Jousilahti P, Antikainen R, Tuomilehto J. Coffee consumption and risk of total and cardiovascular mortality among patients with type 2 diabetes. Diabetologia. 2006;49:2618–26.
44. Duvall S, Tweedie R. A nonparametric ''trim and fill'' method for assessing publication bias in meta-analysis. J Am Stat Assoc. 2000;95:89–98.
45. Schlesselman JJ. Case-control studies. Design, conduct, analysis. New York: Oxford University Press; 1982.
46. de Whalley CV, Rankin SM, Hoult JR, Jessup W, Leake DS. Flavonoids inhibit the oxidative modification of low density lipoproteins by macrophages. Biochem Pharmacol. 1990;39:1743–50.
47. Basu A, Sanchez K, Leyva MJ, Wu M, Betts NM, Aston CE, Lyons TJ. Green tea supplementation affects body weight, lipids, and lipid peroxidation in obese subjects with metabolic syndrome. J Am Coll Nutr. 2010;29:31–40.
48. Salonen JT, Yla-Herttuala S, Yamamoto R, Butler S, Korpela H, Salonen R, Nyyssönen K, Palinski W, Witztum JL. Autoantibody against oxidised LDL and progression of carotid atherosclerosis. Lancet. 1992;339:883–7.
49. Bergmark C, Wu R, de Faire U, Lefvert AK, Swedenborg J. Patients with early-onset peripheral vascular disease have increased levels of autoantibodies against oxidized LDL. Arterioscler Thromb Vasc Biol. 1995;15:441–5.