MOOSE Checklist

Dietary flavonoid intake and the risk of stroke: A dose-response meta-analysis of prospective cohort studies

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Criteria		Brief description of how the criteria were handled in the meta-analysis
Reporting of background should include		
√	Problem definition	Stroke is the second most common cause of death, as well as the fourth leading cause of lost productivity and the second highest cause of disability worldwide. The prevention of stroke is thus clearly an important public health priority. In recent decades, concern has mounted regarding the premature incidence and mortality associated with stroke, with growing interest in altering risk factors and reversing this global epidemic. Among the known risk factors for stroke, dietary factors, especially dietary flavonoid intake, have aroused particular attention. Clinical studies have shown that intakes of flavonoids reduce cardiovascular disease (CVD) risk. Additionally, experimental studies indicated that flavonoids have been shown to have both antioxidant and antithrombotic properties.
√	Hypothesis statement	Flavonoid intake decreases risk of stroke.
√	Description of study outcomes	Stroke.
√	Type of exposure or intervention used	Flavonoids
√	Type of study designs used	We included (1) original studies (eg, not review articles, meeting abstracts, editorials, or commentaries); (2) prospective cohort design (eg, not cross sectional design, case-control design).
√	Study population	We placed no restriction.
Reporting of search strategy should include		
√	Qualifications of searchers	The credentials of the two investigators WH and ML are indicated in the author list.
√	Search strategy, including time period included in the synthesis and keywords	PubMed from 1965 –January 2016 Embase from 1974 –January 2016 Cochrane library from 1990- January 2016 Keywords: (“flavonoids,” “polyphenols,” “phenolics,” “flavonols,” “flavones,” “quercetin,” “kaempferol,” “myricetin,” “isorhamnetin,” “apigenin,” “luteolin,” “proanthocyanidins,” “anthocyanins,” “anthocyanidins,” “flavan-3-ols,” “isoflavones,” and “stroke,” “cerebrovascular disease,” “cerebrovascular disorders,” “cerebral infarct,” “ischemic stroke,” “intracranial hemorrhage,” “intracranial artery disease,” “cardiovascular disease,” “myocardial ischemia,” “myocardial infarct,” “ischemic heart disease,” “coronary heart disease,” and “longitudinal studies,”

		"cohort studies," "prospective studies," "follow-up studies.").
√	Databases and registries searched	PubMed, Embase, and the Cochrane library
√	Search software used, name and version, including special features	We did not employ a search software. EndNote was used to merge retrieved citations and eliminate duplications
√	Use of hand searching	We hand-searched bibliographies of retrieved papers for additional references,
√	List of citations located and those excluded, including justifications	Details of the literature search process are outlined in the process of literature search and study selection. The citation list is available upon request
√	Method of addressing articles published in languages other than English	We placed no restrictions on language; local scientists fluent in the original language of the article were contacted for translation
√	Method of handling abstracts and unpublished studies	We had contacted a few authors for unpublished studies on the association.
√	Description of any contact with authors	We contacted authors who had conducted multivariate analysis with coronary heart disease as a covariate, but the exposure of interest was not intake of dietary flavonoids.
Reporting of methods should include		
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria were described in the methods section.
√	Rationale for the selection and coding of data	Data extracted from each of the studies were relevant to the population characteristics, study design, exposure, outcome, and possible effect modifiers of the association.
√	Assessment of confounding	Restricted the analysis to age- or sex-adjusted estimates only. Conducted sensitivity analyses by eliminating studies that had not adjusted for possible confounders.
√	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	The Newcastle-Ottawa Scale (NOS) was used to assess the quality of studies. The quality of cohort studies were evaluated in the following three major components: selection of the study group (0-4 stars), quality of the adjustment for confounding (0-2 stars) and assessment of outcome in the cohorts (0-3 stars). A higher score represents better methodological quality. The full score was 9 stars. Studies were graded as the high-quality if they met $>$8 awarded stars.
√	Assessment of heterogeneity	Heterogeneity of the studies were explored within two types of study designs using Cochrane's Q test of heterogeneity and I^2 statistic that provides the relative amount of variance of the summary effect due to the

		between-study heterogeneity.
√	Description of statistical methods in sufficient detail to be replicated	Description of methods of meta-analyses, sensitivity analyses, subgroup analyses, meta regression and assessment of publication bias are detailed in the methods.
√	Provision of appropriate tables and graphics	We included 1 flow chart, several summary tables and figures.
Reporting of results should include		
√	Graph summarizing individual study estimates and overall estimate	Figure 2, 3 and 4
√	Table giving descriptive information for each study included	Table 1 and Supplemental tables 1 and 2
√	Results of sensitivity testing	Table 2
√	Indication of statistical uncertainty of findings	95% confidence intervals were presented with all summary estimates, I^2 values and results of sensitivity analyses
Reporting of discussion should include		
√	Quantitative assessment of bias	Subgroup analyses indicate heterogeneity in strengths of the association due to most common biases in cohort studies.
√	Justification for exclusion	We excluded studies that had not adjusted for or were standardized by age or sex, a potential confounder, and used different exposure or outcome assessment for the comparison groups.
√	Assessment of quality of included studies	We discussed the results of the subgroup analyses, and potential reasons for the observed heterogeneity.
Reporting of conclusions should include		
√	Consideration of alternative explanations for observed results	We discussed that potential unmeasured confounders such as other chronic diseases may have caused residual confounding, but the measured factors that are correlated with such confounders would have mitigated the bias. We noted that the variations in the strengths of association may be due to true population differences, or to differences in quality of studies.
√	Generalization of the conclusions	Our meta-analysis suggests that dietary flavonoid intake may be inversely associated with risk of stroke. In addition, dose-response analysis found a statistically nonsignificant inverse association, with a relative risk of 0.91 (95% confidence intervals, 0.77-1.08) for each 100-mg/day increment of flavonoid intake.
√	Guidelines for future research	We recommend future preferably randomized

		controlled studies should explore what kind of flavonoids can reduce the risk of stroke.
√	Disclosure of funding source	No separate funding was necessary for the undertaking of this systematic review.