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Review

Flavonol intake and stroke risk: A meta-analysis of cohort studies

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ABSTRACT

Objective: Epidemiologic findings are inconsistent regarding the association between flavonol intake and the risk for stroke. The aim of this study was to determine whether an association exists between them in observational studies.
Methods: We searched the PubMed and EMBASE databases for studies conducted from 1966 to August 2013. Prospective cohort studies that provided relative risk (RR) estimates with 95% confidence intervals (CIs) for the association between flavonol intake and risk for stroke were included. A random effects model was used to combine study-specific risk estimates.
Results: The meta-analysis included eight studies, with 5228 stroke cases among 280 174 participants. The summary RR indicated a significant association between highest flavonol intake and reduced risk for stroke (summary RR, 0.86; 95% CI, 0.75–0.99). Furthermore, an increase in flavonol intake of 20 mg/d was associated with a 14% decrease in the risk for developing stroke (summary RR, 0.86; 95% CI, 0.77–0.96). Subgroup analyses suggested a significant inverse association between highest flavonol intake and stroke risk among men (summary RR, 0.74; 95% CI, 0.56–0.97) but not women (summary RR, 0.99; 95% CI, 0.85–1.16).
Conclusions: Higher dietary flavonol intake is associated with a reduced risk for stroke, especially among men. Our results support recommendations for higher consumption of flavonol-rich foods to prevent stroke.

Introduction

According to the World Health Organization, an estimated 6.2 million people died from stroke in 2008 [1]. Although the mortality rate has decreased due to advances in emergency medicine, stroke continues to represent a major cause of long-term disability worldwide [2]. Therefore, effective primary prevention strategies are needed to limit the growing burden of stroke.

Flavonoids are a family of bioactive polyphenolic compounds; they are present in many commonly consumed vegetables, fruits, and other plant-based foods [3]. Flavonol, the major representative of the flavonoid subclass, are the most widely distributed flavonoids in nature and are considered as the most active compounds within the flavonoids group. They are present in considerable amounts in our habitual diet and exhibit a wide range of biological activities [3–5].

During the past decade, many epidemiologic studies have evaluated the association between flavonol intake and the risk for stroke. Previous meta-analysis suggested that the highest dietary flavonol intake might be associated with lower rates of stroke [6]. However, it was limited because true differences in the level and range of intake between studies were not taken into account. Subsequently, several cohort studies with large sample sizes have been performed, but the results remain indeterminate. Hence, we chose to conduct a meta-analysis to update the evidence published up to August 2013 and to further evaluate whether there is a dose-response relationship between flavonol intake and the risk for stroke.

Z-MW, L-SW, and Z-JY conceived the idea and designed the study. Z-MW and Z-LN conducted the literature search and extracted the data. Z-MW, HZ, and BZ conducted the data analyses. All of the authors helped interpret the results and write and revise the manuscript. The authors declare that they have no competing interests.

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Materials and methods

Search strategy

A systematic literature search up to August 2013 was performed in the PubMed and EMBASE databases to identify relevant studies. We used search terms *flavonoids, flavonols, quercetin, kaempferol, myricetin,* combined with *stroke, cerebrovascular accident, brain ischemia, intracranial hemorrhages, cerebral hemorrhage, ischemic stroke, hemorrhagic stroke*, and *subarachnoid hemorrhage* in the full-text option, without language restrictions. The titles and abstracts were scanned to exclude any studies that were clearly irrelevant. We read the full texts of the remaining articles to determine whether they contained information on the topic of interest. Furthermore, we searched all references cited in original studies and in all reviews identified. Two authors (Z-MW and Z-LN) conducted all searches independently.

Eligibility criteria

To be eligible, studies had to meet the following inclusion criteria:

1. prospective cohort design;
2. exposure of interest was flavonol intake, and the outcome of interest was total stroke incidence or mortality (including ischemic stroke, cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage);
3. relative risk (RR) estimates with corresponding 95% confidence interval (CI) (or sufficient information to calculate them) were reported;
4. some adjustments for potential stroke risk.

If data were duplicated in more than one study, the most recent and complete study was eligible for inclusion.

Data extraction

Information from studies was extracted by two investigators independently using a predefined data extraction form. The following data were collected: First author's name; publication year; country of origin; participant age; sex; recruitment time; years of follow-up; intake assessment method; outcome assessment method; outcome; number of participants (cases and cohort size); RR estimates, and corresponding 95% CI for the highest versus lowest categories; and adjustment factors in the statistical analysis. For each study, the most completely adjusted estimate was extracted, the results were compared, and any discrepancies were resolved by consensus.

Statistical analysis

The measure of effect of interest was RR with the corresponding 95% CI. Study-specific risk estimates were extracted from each article, and log risk estimates were weighted by the inverse of their variances to obtain a pooled risk estimate. Studies were combined by using the DerSimonian and Laird random effects model, which considers both within- and between-study variations [7]. We calculated the study-specific estimates for highest versus lowest level of exposure category.

To normalize the variation between studies for the difference in exposure categories, we calculated a risk estimate for an increment of flavonol intake of 20 mg/d for each study. For this analysis, we used the method proposed previously [8,9] to estimate study-specific slopes from the natural logarithm of the RR across categories of exposure. For each study, the median or mean level of flavonol intake for each category was assigned to each corresponding RR estimate. When the median or mean of per category was not provided in the article, we assigned to each class the dose corresponding to the midpoint of upper and lower boundaries. In studies that did not provide the number of cases and person-years in each exposure category, the variance-weighted least-square regression model was used to estimate the slopes. Because the lower boundary of the lowest category or the upper boundary of the highest category was usually open, we considered them of the same amplitude as the closest category. Then, we obtained the summary RR estimates by pooling the study-specific slopes, using the inverse of the corresponding variances as weights.

Q and I^2 statistics were used to examine whether the results of studies were homogeneous [10]. A two-tailed $P < 0.05$ was considered statistically significant. When statistical heterogeneity was detected, the sources of heterogeneity were explored by sensitivity analysis. Additionally, subgroup analysis was performed to analyze potential interactions. Publication bias was evaluated with Egger's regression asymmetry test in which a $P < 0.10$ was considered representative of statistically significant publication bias [11]. The present study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [12]. Statistical analyses were carried out with Stata 9.2 software (STATA Corp, College Station, TX, USA).

Results

Literature search

The details of literature search are shown in Figure 1; we identified 11 potentially relevant studies concerning flavonol intake and the risk for stroke [13–23]. One study [13] was excluded because it was not a prospective cohort study and did not satisfy the design criterion. Another study [14] was excluded because the same author updated it in 2002 [18]. A third study [15] was excluded because it used the same cohort as another study [20], and the latter provided information with a longer period of follow-up. Thus, our meta-analysis included eight papers [16–23].

Study characteristics

The characteristics of included studies are shown in Tables 1 and 2. Of these studies, one was carried out in the Netherlands [16], three in Finland [17,18,21], four in the United States [19,20, 22,23]. The length of follow-up ranged from 6.1 to 28 y. All studies provided risk estimates that were adjusted for age, smoking, and hypertension; seven studies adjusted for body mass index and serum cholesterol; six studies adjusted for diabetes mellitus and alcohol intake; four studies adjusted for physical activity, energy intake, and hormone use.

Highest versus lowest categories

RR estimates of stroke for highest compared with lowest flavonol intake for individual studies and all studies combined are shown in Figure 2. The overall results showed a statistically significant 14% reduction in risk for stroke with the highest flavonol intake (summary RR, 0.86; 95% CI, 0.75–0.99). There was a statistically significant heterogeneity among the study results ($P = 0.039$; $I^2 = 49.2\%$). The results for the stratified analysis of the highest flavonol intake by sex, geographic region, outcome, and years of follow-up are shown in Table 3. When it was

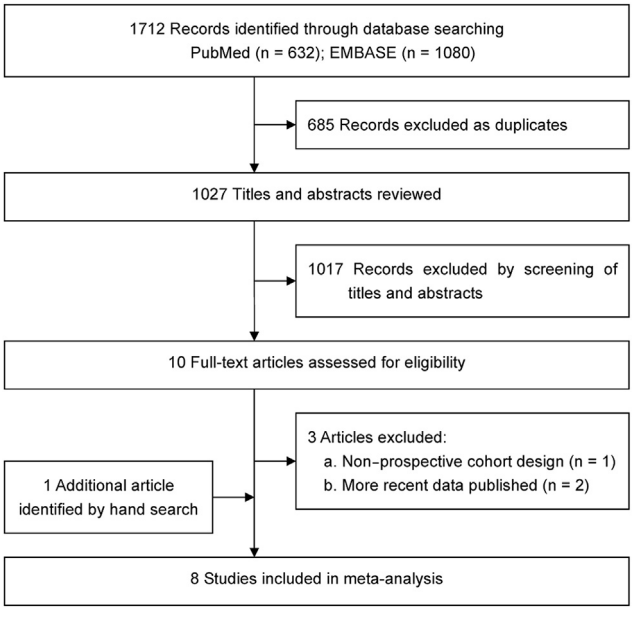

Fig. 1. Flowchart for identifying eligible studies.