Clinical Sciences

Fruits and Vegetables Consumption and Risk of Stroke
A Meta-Analysis of Prospective Cohort Studies

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Background and Purpose—We conducted a meta-analysis to summarize evidence from prospective cohort studies about the association of fruits and vegetables consumption with the risk of stroke.

Methods—Pertinent studies were identified by a search of Embase and PubMed databases to January 2014. Study-specific relative risks with 95% confidence intervals were pooled using a random-effects model. Dose–response relationship was assessed by restricted cubic spline.

Results—Twenty prospective cohort studies were included, involving 16981 stroke events among 760629 participants. The multivariable relative risk (95% confidence intervals) of stroke for the highest versus lowest category of total fruits and vegetables consumption was 0.79 (0.75–0.84), and the effect was 0.77 (0.71–0.84) for fruits consumption and 0.86 (0.79–0.93) for vegetables consumption. Subgroup and meta-regression showed that the inverse association of total fruits and vegetables consumption with the risk of stroke was consistent in subgroup analysis. Citrus fruits, apples/pears, and leafy vegetables might contribute to the protection. The linear dose–response relationship showed that the risk of stroke decreased by 32% (0.68 [0.56–0.82]) and 11% (0.89 [0.81–0.98]) for every 200 g per day increment in fruits consumption (P for nonlinearity=0.77) and vegetables consumption (P for nonlinearity=0.62), respectively.

Conclusions—Fruits and vegetables consumption are inversely associated with the risk of stroke. (Stroke. 2014;45:1613-1619.)

Key Words: fruit ■ meta-analysis ■ stroke ■ vegetables

During the past 4 decades, age-adjusted stroke incidence rate in high-income countries decreased by 42% (from 163 to 94 per 100 000 person-years), whereas the stroke incidence rate more than doubled (from 52–117 per 100000 person-years) in low- to middle-income countries. The rates of age-adjusted stroke mortality and disability-adjusted life years lost were also higher in low-income countries than in middle-income or high-income countries. Stroke was also the leading causes of death in China in 2010 (1.7 million deaths). Improving diet and lifestyle is critical for cardiovascular disease risk reduction in the general population. In particular, a diet rich in vegetables and fruits is highly recommended, because it meets the micronutrient, macronutrient, and fiber requirements without adding substantially to overall energy consumption. However, the prevalence of low fruits and vegetables consumption is high worldwide, and especially in low- and middle-income countries. According to the bulletin of the World Health Organization, increasing individual fruits and vegetables consumption to ≥600 g per day could reduce the burden of ischemic stroke by 19% worldwide and 10% to 15% among members of the European Union. In recent years, many prospective cohort studies have been conducted to assess the effect of fruits and vegetables consumption on the risk of stroke, and both positive and negative associations were found, and the magnitude of association (relative risk [RR] with 95% confidence interval [CI]) varied from 0.35 (0.13–0.96) to 1.35 (0.92–1.97). Results from the recent prospective cohort studies have not been summarized with a meta-analysis, and the dose–response relationship as well as the potential threshold effect of fruits and vegetables consumption on the risk of stroke is also unknown. In addition, studies with relatively small number of participants might be underpowered to detect the effect, and even small health effects of fruits and vegetables consumption on the risk of stroke could have considerable public health consequences considering the popularity of fruits and vegetables consumption; thus, we conducted a meta-analysis to quantitatively assess the effect of fruits and vegetables consumption on the risk of stroke.

Methods

Literature Search and Selection
All relevant studies were identified by searching PubMed (1947 to January 2014) and Embase (1974 to January 2014) databases, using the search terms (((stroke) OR cerebrovascular disease) OR cerebral hemorrhage) OR cerebral
infarction) AND ((fruit*) OR vegetable*), restricting to studies conducted in humans. We also used information of bibliographies from retrieved articles. For inclusion, studies had to fulfill the following criteria: a prospective cohort design; exposure of interest was fruits or vegetables; outcome of interest was stroke; and RR (95% CI) was provided. If multiple published reports from the same study cohort were available, we included the one with the largest number of cases.

Data Extraction
Data we collected included the name of first author, year of publication, geographic location, duration of follow-up, participants’ age, sample size, number of cases, methods for the measurement of fruits and vegetables consumption, RR (95% CI) for the highest versus lowest fruits and vegetables consumption, and adjusted covariates. For dose–response analysis, the number of cases and participants (person-years) and RR (95% CI) for each category of fruits and vegetables consumption were also extracted. For each study, the median level of fruits and vegetables consumption for each category was assigned to each corresponding RR estimate. If upper boundary of the highest category was not provided, we assumed that the boundary had the same amplitude as the adjacent category.

Statistical Analysis
Study-specific logarithms of RR estimates were combined using a random-effects model, which considers both within-study and between-study variation. If the RRs for fruits and vegetables consumption were reported separately in a study, we first fist-pooled these 2 RRs and used the combined estimate for that study in the meta-analysis of total fruits and vegetables consumption and the risk of stroke. Statistical heterogeneity among studies was assessed using $I^2$ statistic, and $I^2=0.77$, and the re-estimated effect was 0.76 (0.70–0.83; $F=11.9\%$) after excluding the 2 studies$^{15,27}$ that did not correct for age. Borderline publication bias was found (P=0.05), and small-study effects$^{9,11,21}$ were found in the funnel plot (Figure II in the online-only Data Supplement). After excluding 3 studies with small-study effects, no publication bias was found (P=0.77), and the re-estimated effect was 0.81 (0.77–0.84; $F=0.00\%$). Sensitivity analysis showed that the overall pooled estimate did not vary substantially with the exclusion of any 1 study (Figure III in the online-only Data Supplement).

Fruits Consumption and Risk of Stroke
Highest versus lowest levels of total fruits and vegetables consumption were inversely associated with the risk of stroke (0.79 [0.75–0.84]; $F=16.6\%$; Figure 1), and the effect was 0.79 (0.74–0.83; $F=11.9\%$) after excluding the 2 studies$^{15,27}$ that did not correct for age. Borderline publication bias was found (P=0.05), and small-study effects$^{9,11,21}$ were found in the funnel plot (Figure II in the online-only Data Supplement). After excluding 3 studies with small-study effects, no publication bias was found (P=0.77), and the re-estimated effect was 0.81 (0.77–0.84; $F=0.00\%$). Sensitivity analysis showed that the overall pooled estimate did not vary substantially with the exclusion of any 1 study (Figure III in the online-only Data Supplement).

Results

Literature Search and Study Characteristics
The flow chart for study inclusion is shown in Figure I in the online-only Data Supplement. After excluding 5 case–control studies and 4 duplicate publications, 24 results from 20 prospective cohort studies$^{9,21,25–31}$ were included, because 2 results (male and female) were reported in 4 studies$^{11,16,26,29}$ Six studies were from the United States, 8 from Europe, and 6 from Asia (Japan and China). The mean duration of follow-up ranged from 3.09 to 37 years. Fruits and vegetables consumption were assessed with interviewer or self-administered food frequency questionnaire in all studies, except for 3 studies (24-hour recall)$^{31}$ dietary history method$^{30}$ 7-day household inventory).$^{21}$ Most of the studies adjusted for known risk factors of cardiovascular diseases such as smoking (but 1 study)$^{21}$ alcohol (but 3 studies)$^{13,19,21}$ blood pressure or hypertension (but 5 studies)$^{15,17,20,21,26}$ physical activity (but 4 studies)$^{7,21,26,30}$ and body mass index (but 3 studies)$^{21,28,30}$ Two studies did not correct for age.$^{5,27}$ The included studies met the quality score of 6 to 8 stars. Detailed information of included studies is shown in Table I in the online-only Data Supplement.

Quantitative Synthesis
The main results are summarized in the Table.

Total Fruits and Vegetables Consumption and Risk of Stroke
Highest versus lowest levels of total fruits and vegetables consumption were inversely associated with the risk of stroke (0.79 [0.75–0.84]; $F=16.6\%$; Figure 1), and the effect was 0.79 (0.74–0.83; $F=11.9\%$) after excluding the 2 studies$^{15,27}$ that did not correct for age. Borderline publication bias was found (P=0.05), and small-study effects$^{9,11,21}$ were found in the funnel plot (Figure II in the online-only Data Supplement). After excluding 3 studies with small-study effects, no publication bias was found (P=0.77), and the re-estimated effect was 0.81 (0.77–0.84; $F=0.00\%$). Sensitivity analysis showed that the overall pooled estimate did not vary substantially with the exclusion of any 1 study (Figure III in the online-only Data Supplement).

Fruits Consumption and Risk of Stroke
Highest versus lowest levels of fruits consumption were inversely associated with the risk of stroke (0.77 [0.71–0.84]; $F=52.3\%$; Figure IV in the online-only Data Supplement), and the effect was 0.76 (0.70–0.83; $F=46.2\%$) after excluding the 2 studies$^{15,27}$ that did not correct for age. However, publication bias was found (P=0.02), and small-study effects$^{11,20,21}$ were found in the funnel plot. After excluding these 3 studies, no publication bias was found (P=0.27), and the re-estimated effect was 0.80 (0.74–0.87; $F=45.4\%$). Sensitivity analysis showed that the overall pooled estimate did not vary substantially with the exclusion of any 1 study.

For dose–response analysis, data from 8 prospective cohort studies$^{10,12,18,19,26,27,30}$ were used, including 9706 stroke cases. We found no evidence of statistically significant departure from linearity (P for nonlinearity=0.78), and the risk of stroke decreased by 32% (0.68 [0.56–0.82]) for every 200 g per day increment in fruits consumption. RR (95% CI) of stroke was 0.90 (0.84–0.96), 0.81 (0.72–0.90), 0.73 (0.62–0.86), 0.66 (0.55–0.82), 0.60 (0.46–0.79), 0.54 (0.34–0.69), and 0.45 (0.28–0.74) for 50, 100, 150, 200, 250, 300, and 400 g per day of fruits consumption, respectively (Figure 2).

Vegetables Consumption and Risk of Stroke
Highest versus lowest levels of vegetables consumption were inversely associated with the risk of stroke (0.86 [0.79–0.93]; $F=40.3\%$; Figure IV in the online-only Data Supplement), and no publication bias was found (P=0.78). The effect was 0.85
(0.78–0.93; $I^2=47.0\%$) after excluding the 2 studies that did not correct for age. The small-study effects were also detected in the funnel plot, and a similar result was found after excluding this single result (0.86 [0.80–0.93]; $I^2=33.7\%$). No individual study was found to have excessive influence on the pooled effect in sensitivity analysis.

| Table. Summary Risk Estimates Between Vegetables and Fruits Consumption and Risk of Stroke |
|---------------------------------|-------------|-----------------|--------|--------|
| Exposure                        | N* | No. of Cases | Risk Estimate (95% CI) | $I^2$, % | $P$ Value† |
| Fruits and vegetables | 24 | 16981 | 0.79 (0.75–0.84) | 16.6 |
| Fruits                         | 19 | 15655 | 0.77 (0.71–0.84) | 52.3 | 0.09 |
| Vegetables                      | 16 | 14803 | 0.86 (0.79–0.93) | 40.3 |
| Outcome‡                        | N  | No. of Cases | Risk Estimate (95% CI) | $I^2$, % | $P$ Value‡ |
| Incidence                       | 17 | 12366 | 0.80 (0.75–0.85) | 5.40 | 0.98 |
| Mortality                       | 8  | 4833  | 0.78 (0.69–0.88) | 40.6 |
| Location where the study was conducted | N  | No. of Cases | Risk Estimate (95% CI) | $I^2$, % | $P$ Value‡ |
| United States                   | 7  | 3074  | 0.83 (0.75–0.91) | 0.00 | 1.00 |
| Europe                          | 8  | 10097 | 0.82 (0.75–0.89) | 25.6 | 0.99 |
| Asia                            | 9  | 3810  | 0.73 (0.65–0.81) | 10.4 | 0.22 |
| Sex                             | N  | No. of Cases | Risk Estimate (95% CI) | $I^2$, % | $P$ Value‡ |
| Male                            | 11 | 5357  | 0.75 (0.65–0.86) | 62.4 | 0.43 |
| Female                          | 10 | 3252  | 0.82 (0.75–0.91) | 12.4 |
| Age, y                          | N  | No. of Cases | Risk Estimate (95% CI) | $I^2$, % | $P$ Value‡ |
| >55                             | 13 | 10539 | 0.81 (0.77–0.85) | 4.50 | 0.34 |
| ≤55                             | 11 | 6442  | 0.76 (0.67–0.85) | 28.0 |
| Quality score (stars)           | N  | No. of Cases | Risk Estimate (95% CI) | $I^2$, % | $P$ Value‡ |
| 6                               | 6  | 1391  | 0.70 (0.51–0.97) | 52.7 | 1.00 |
| 7                               | 11 | 8117  | 0.78 (0.73–0.84) | 6.00 | 0.64 |
| 8                               | 7  | 7473  | 0.81 (0.76–0.86) | 0.00 | 0.91 |
| Adjusting for ≥6 of 7 covariates (smoking, alcohol, BP/hypertension, serum cholesterol, physical activity, BMI, ≥3 dietary variables) | | | |
| Yes                             | 11 | 11261 | 0.78 (0.71–0.86) | 34.8 | 0.93 |
| No                              | 13 | 5720  | 0.79 (0.74–0.85) | 1.60 |
| Follow-up duration, y           | N  | No. of Cases | Risk Estimate (95% CI) | $I^2$, % | $P$ Value‡ |
| >10                             | 16 | 14970 | 0.79 (0.74–0.84) | 23.5 | 0.47 |
| ≤10                             | 8  | 2011  | 0.85 (0.74–0.97) | 0.10 |
| Dietary assessment              | N  | No. of Cases | Risk Estimate (95% CI) | $I^2$, % | $P$ Value‡ |
| Self-administered               | 15 | 14678 | 0.80 (0.75–0.86) | 33.6 | 0.43 |
| Interviewer-administered        | 9  | 2305  | 0.76 (0.67–0.86) | 0.00 |
| Stroke subtypes                 | N  | No. of Cases | Risk Estimate (95% CI) | $I^2$, % | $P$ Value‡ |
| Ischemic                        | 13 | 9857  | 0.79 (0.74–0.85) | 26.5 | 0.72 |
| Hemorrhagic                     | 9  | 1811  | 0.78 (0.69–0.88) | 0.00 |
| Specific types of exposure       | N  | No. of Cases | Risk Estimate (95% CI) | $I^2$, % | $P$ Value‡ |
| Citrus fruits                   | 8  | 5795  | 0.72 (0.59–0.88) | 65.9 | 1.00 |
| Leafy vegetables                | 4  | 4925  | 0.88 (0.79–0.98) | 0.00 | 0.52 |
| Cruciferous vegetables          | 4  | 4925  | 0.85 (0.64–1.13) | 77.4 | 0.35 |
| Apples/pears                    | 2  | 4558  | 0.88 (0.81–0.97) | 0.00 | 0.30 |
| Onion/leek/garlic               | 2  | 4355  | 0.89 (0.79–1.01) | 0.00 | 0.27 |
| Root vegetables                 | 2  | 4355  | 1.04 (0.91–1.18) | 0.00 | 0.08 |
| Berries                         | 2  | 4714  | 1.05 (0.86–1.27) | 60.0 | 0.06 |

BMI indicates body mass index; BP, blood pressure; and CI, confidence interval.
*N indicates the number of results.
†$P$ values for meta-regression, location where the study was conducted (United States as reference), quality score (6 stars as reference), and specific types of exposure (citrus fruits as reference) were included as dummy variables in meta-regression.
‡Both the results for incidence and mortality of stroke were reported in 1 study.

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For dose–response analysis, data from 6 prospective cohort studies were used, including 8854 stroke cases. We found no evidence of statistically significant departure from linearity ($P$ for nonlinearity=0.62), and the risk of stroke decreased by 11% (0.89 [0.81–0.98]) for every 200 g per day increment in vegetables consumption. RR (95% CI) of stroke was 0.97 (0.95–1.00), 0.94 (0.87–1.01), 0.91 (0.81–1.01), 0.88 (0.77–1.00), 0.86 (0.74–1.00), 0.84 (0.71–1.01), and 0.80 (0.62–1.02) for 50, 100, 150, 200, 250, 300, and 400 g per day of vegetables consumption (Figure 3).

Subgroup Analysis and Meta-Regression
As shown in the Table, the inverse association of fruits and vegetables consumption with the risk of stroke was consistent in subgroup analysis by stroke outcomes (incidence: 0.75–0.85; mortality: 0.78 [0.69–0.88]), geographic location (United States: 0.83 [0.75–0.91]; Europe: 0.82 [0.75–0.89]; Asia: 0.73 [0.65–0.81]), sex (male: 0.75 [0.65–0.86]; female: 0.82 [0.75–0.94]), age (≥55 years: 0.81 [0.77–0.85]; ≤55 years: 0.76 [0.67–0.85]), quality score (6 stars: 0.70 [0.51–0.97]; 7 stars: 0.78 [0.73–0.84]; 8 stars: 0.81 [0.76–0.86]), adjusting for ≥6 of 7 covariates (smoking, alcohol, blood pressure/hypertension, serum cholesterol, physical activity, body mass index, ≥3 dietary variables; yes: 0.78 [0.70–0.86]; no: 0.70 [0.51–0.97]), duration of follow-up (≥10 years: 0.79 [0.74–0.84]; ≤10 years: 0.85 [0.74–0.97]), dietary assessment (self-administered: 0.80 [0.78–0.85]; interviewer-administered: 0.76 [0.67–0.86]), and stroke subtypes (ischemic: 0.79 [0.74–0.85], hemorrhagic: 0.78 [0.69–0.88]). In subgroup analysis by specific types of fruits and vegetables, inverse association was found between the risk of stroke and citrus fruits (0.72 [0.59–0.88]), leafy vegetables (0.88 [0.79–0.98]), and apples/pears (0.88 [0.81–0.97]), but not with cruciferous vegetables (0.85 [0.64–1.13], onion/leek/garlic (0.89 [0.79–1.01]), root vegetables (1.04 [0.91–1.18]), and berries (1.05 [0.86–1.27]; Figure V in the online-only Data Supplement). All $P$ values from meta-regression were >0.05.

Discussion
In this meta-analysis, fruits and vegetables consumption was found to be inversely associated with the risk of stroke, and this inverse association was consistent in subgroup analysis. In addition, a linear dose–response relationship showed that the risk of stroke decreased by 32% and 11% for every 200 g per day increment in fruits and vegetables consumption, respectively.

Several biological mechanisms might explain the inverse association. Both short-term controlled intervention trials and prospective cohort studies have shown that an increase in fruits and vegetables consumption can lower blood pressure and also improve microvascular function, and favorable

![Figure 2](http://ahajournals.org)
effects on other cardiovascular risk factors, such as body mass index, waist circumference, total cholesterol and low-density lipoprotein-cholesterol,\textsuperscript{14} inflammation, and oxidative stress, were also found.\textsuperscript{35,36} Higher fruits and vegetables consumption increases micronutrient, carbohydrate, and fiber intakes, and possibly reduces fat intake.\textsuperscript{6} Nutrients such as potassium,\textsuperscript{37,38} folate,\textsuperscript{39,40} antioxidants (vitamin C, \(\beta\)-carotene, and flavonoids),\textsuperscript{41,42} and fiber\textsuperscript{43} have been shown to be significantly associated with a reduced risk for stroke.

A previous meta-analysis, based on 8 prospective cohort studies including 4917 stroke cases, found that the RR of stroke was 0.89 (0.83–0.97) for those with 3 to 5 servings per day and 0.74 (0.69–0.79) for those with >5 servings per day.\textsuperscript{24} Since then, 13 prospective cohort studies\textsuperscript{3–21} were also included in this meta-analysis, and results from 1 cohort were also updated.\textsuperscript{14} In addition, some issues arising from the inconsistent results of later studies still need to be confirmed, such as whether it is total fruits and vegetables intake that protects against cardiovascular disease, or fruit or vegetables alone, and whether the association is equally strong in both sexes, or is stronger in a particular subset of the population,\textsuperscript{32} and levels of fruits and vegetables intake that give the greatest protection remain unknown.\textsuperscript{7} This meta-analysis, based on 20 prospective cohort studies including 16981 stroke cases, should provide a better understanding about fruits and vegetables consumption and the risk of stroke with subgroup analysis and dose–response analysis.

As shown in Figure 1, inverse (significantly or not) association was found in all included studies, whereas stronger effects were found in 3 studies (0.35\textsuperscript{6}; male: 0.40, female: 0.47\textsuperscript{11}; 0.43).\textsuperscript{21} A stronger effect was found in a cohort with type 2 diabetes mellitus (0.35),\textsuperscript{2} between citrus fruit consumption and the risk of stroke (male: 0.40, female: 0.47),\textsuperscript{11} and between childhood intake of fruits and vegetables consumption and the risk of stroke (0.43).\textsuperscript{31} In this meta-analysis, a stronger risk estimate was also found for citrus fruit consumption than other categories, and for subjects aged \(\geq 55\) years than >55 years, although the differences were not significant. In addition, the possibility that younger people consume more fruit and vegetables and that their stroke risk is, therefore, lower and not because of the

![Figure 3. The dose–response analysis between vegetables consumption and the risk of stroke. The solid line and long dash line represent the estimated relative risk and its 95% confidence interval. Short dash line represents the linear relationship.](http://ahajournals.org)
may have a greater effect. The main characteristics and results of prospective cohort studies on healthy behaviors in clusters and the risk of stroke are shown in Tables II and III in the online-only Data Supplement. The effects of highest versus lowest score of dietary patterns, such as Mediterranean diet or alternate Mediterranean diet, recommended food, prudent pattern, healthy dietary pattern, vegetable diet pattern, Dietary Approaches to Stop hypertension diet, Healthy Eating Index or modified Alternative Healthy Eating Index, and Reduced-Salt Japanese Diet, on the risk of stroke in the included studies are not apparently greater than that of fruits and vegetables in our meta-analysis. However, highest versus lowest number of healthy behaviors (including physical activity, smoking, alcohol, diet, etc) showed a great reduction in the risk of stroke in Asians (0.24 [0.11–0.54]), 52 0.36 [0.22–0.58] and 0.24 [0.16–0.36], 53 0.25 [0.14–0.46]), 54 Europeans (0.33 [0.14–0.46]), 18 0.36 [0.14–0.46]), 54 0.25 [0.14–0.46]), 54 and Americans (0.34 [0.08–1.52], 55 0.43 [0.21–0.91], 56 0.31 [0.19–0.53] and 0.21 [0.12–0.36]), 57 indicating an interaction between healthy behaviors.

Other limitations should also be considered. First, bias such as misclassification of exposure (fruits and vegetables), outcome (stroke), and confounding factors is one of the main threats to the validity of the results. Misclassification of fruits and vegetables consumption could be of concern, and some participants might change their dietary habits during follow-up. However, similar results were found in self-administered dietary assessment group and interview-administered group, and in validation study showed that the food frequency questionnaire is a reasonable tool to assess intakes of fruits and vegetables. 58 In addition, nondifferential misclassification at baseline should have weakened the association. As shown in Table I in the online-only Data Supplement, all of the cases were ascertained by hospital records, death certificates, or interviewing their physicians, but the underlying cases of stroke might not be detected and might influence the results, which could be also influenced by the imprecise measurements of confounding factors. Second, although we extracted the RR that reflected the greatest degree of control for potential confounders, the extent to which they were adjusted and residual confounding by other unmeasured factors, such as coffee 59 and dairy foods, 60 should be considered. Third, results of subgroup analysis by specific categories of vegetables and fruits were based on limited number of studies. Fourth, in a meta-analysis of published studies, publication bias could be of concern because small studies with null results tend not to be published. After excluding the studies leading to small-study effect in the funnel plot, no evidence of significant publication bias was found in this meta-analysis.

In summary, results from this meta-analysis support the hypothesis that consumption of vegetables and fruits could reduce the risk of stroke.

Disclosures

None.

References

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