Dietary Fiber Intake and Risk of First Stroke A Systematic Review and Meta-Analysis

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Background and Purpose—Fiber intake is associated with reduced stroke risk in prospective studies, but no meta-analysis has been published to date.

Methods—Multiple electronic databases were searched for healthy participant studies reporting fiber intake and incidence of first hemorrhagic or ischemic stroke, published between January 1990 and May 2012.

Results—Eight cohort studies from the United States, northern Europe, Australia, and Japan met inclusion criteria. Total dietary fiber intake was inversely associated with risk of hemorrhagic plus ischemic stroke, with some evidence of heterogeneity between studies (I²; relative risk per 7 g/day, 0.93; 95% confidence interval, 0.88–0.98; I²=59%). Soluble fiber intake, per 4 g/day, was not associated with stroke risk reduction with evidence of low heterogeneity between studies, relative risk 0.94 (95% confidence interval, 0.88–1.01; I²=21%). There were few studies reporting stroke risk in relation to insoluble fiber or fiber from cereals, fruit, or vegetables.

Conclusions—Greater dietary fiber intake is significantly associated with lower risk of first stroke. Overall, findings support dietary recommendations to increase intake of total dietary fiber. However, a paucity of data on fiber from different foods precludes conclusions regarding the association between fiber type and stroke. There is a need for future studies to focus on fiber type and to examine risk for ischemic and hemorrhagic strokes separately. (Stroke. 2013;44:1360-1368.)

Key Words: diet ■ epidemiology ■ fiber ■ meta-analysis ■ stroke

Stroke and other cerebrovascular diseases are the second most common cause of death worldwide, and in 2008, accounted for 6.2 million deaths (11% of fatalities). In many developed countries the incidence of stroke has declined, largely because of improvements in hypertension management. However, the absolute number of strokes continues to increase with the expansion of the aging population in these counties. Data from the United States suggests that 78% of strokes are first attacks, with ischemic stroke being 10 times more common than hemorrhagic stroke in most western countries. Moreover, stroke is the leading cause of disability in many developed countries, and its primary prevention should, therefore, be a key public health priority.

Dietary fiber intake is associated with improvements in key modifiable risk factors for stroke, such as hypertension^{6,7} and hypercholesterolaemia.⁸ Greater fiber intake is also associated with improvements in insulin resistance, which has been suggested as a mechanism for the development of hypertension, through the compensatory hyperinsulinaemia, which can develop with insulin resistance.⁹ In addition, water-soluble fiber aids regulation of blood cholesterol levels by slowing the

absorption of cholesterol from the small intestine through the formation of viscous gels. ^{10,11}

Many epidemiological studies have examined stroke risk in relation to dietary fiber intake, ^{12–19} with some suggesting a protective association, ^{12,15,16,19} but others not. ^{13,14,17,18} Yet, to date, there are no published metadata. Consequently, the aim of this work was to collate and meta-analyze data relating total dietary fiber intake or fiber from key food sources and primary stroke events.

Methods

Search Strategy

Literature searches for articles published between January 1, 1990, to November 2009 and reporting an association between carbohydrate intake in any form with cardiometabolic health outcomes were conducted using 6 electronic databases: The Cochrane Library, MEDLINE, MEDLINE in-process, Embase, CAB Abstracts, ISI Web of Science, and BIOSIS. To extend this search from 2009 to May 30, 2012, MEDLINE, MEDLINE in-process, and Embase were researched, as these databases were the main source of included articles in the initial search. The top-up search was carried out just for articles reporting dietary fiber and incident stroke, but the same key terms were included. Key terms used, among others, included

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"fiber," "fibre," "cellulose," "lignin," "non starch polysaccharide" and other fiber subfractions, "stroke," and "transient ischemic accident/incident." Bibliographies of relevant articles were also screened and hand-searching of selected journals was carried out.

Study Selection

Initial screening of titles and abstracts was undertaken by members of the review team to remove those it was immediately apparent were not relevant, such as editorials, single case-study reports, and therapeutic approach articles. Prespecified guidelines were in place to ensure consistency between separate reviewers. Full-text copies of potentially relevant articles were read independently by 2 review team members and disagreements were settled by a third reviewer. A structured flow chart and detailed guidelines were used to determine eligibility for inclusion.

Eligible articles reported original research from prospective observational studies (with \geq 3-year follow-up), published in English language since 1990 and reporting incident first stroke events in relation to dietary fiber intake.

Prevention of primary stroke was the main focus for this work (not secondary prevention), and therefore, only studies with generally healthy participants were included, that is, cohort participants were not recruited specifically because of their ill health or personal history of disease.

Data Extraction

Data were extracted into a Microsoft Access database, with predefined fields which captured aspects of study design and quality as well as individual results (relative risks and confidence intervals), including cohort design, exposure type and quantity, case numbers, definition of outcome, and adjustments used within analyses. This method of data extraction was based on the approach used for the World Cancer Research Fund Second Expert Report. Methodological quality of studies was not evaluated using a formal scoring approach but aspects of study quality, such as follow-up duration, case ascertainment, and adjustment for various important confounders was investigated through metaregression.

Statistical Methods

Because different studies use different definitions for their exposure categories, we derived an estimated dose–response trend for each study, using the method recommended by Greenland and Longnecker.²¹ These dose–response trends were then combined using random effects meta-analysis. The method therefore computes study-specific slopes (with 95% confidence intervals), based on the results presented for each category of fiber intake. To derive a study's dose–response curve, the distribution of cases and person-years, or

cases and noncases, with relative risks and estimates of uncertainty (eg, confidence interval) for at least 3 categories of quantified fiber intake must be presented in the reviewed publication. Where the total number of cases or person-years was presented, but not the distribution, we estimated this based on definitions of the quantiles. We then assigned the median or mean level of fiber intake to the corresponding relative risk for each study. Where medians and means were not presented, we used the category midpoint. Where the highest or lower category was unbounded, we assumed the width of the category to be the same as the next adjacent category, so that we could assign a midpoint. Where studies already reported a linear dose—response trend, with confidence interval or standard error, this was used directly.

Nonlinear dose–response curves were plotted using restricted cubic splines for each study, using knots fixed at percentiles 10%, 50%, and 90% through the distribution.²² These were combined using multivariate meta-analysis.²³ All analyses were performed in Stata 12.1.²⁴

To include results from 1 study in meta-analyses,¹⁷ the method of Hamling and colleagues was used to first combine data for stroke subtypes in a random effects meta-analysis.²⁵ Where results were only presented separately for men and women, separate dose–response curves were derived, and these were then combined into a single estimate for the study using a fixed effects meta-analysis, before combining with the other studies using a random effects meta-analysis. This maintained the correct degrees of freedom for tests of heterogeneity.

Heterogeneity between studies was tested using Cochran Q statistic, alongside the more useful proportion of total variation in study estimates explained by heterogeneity (I^2). Pooled estimates are only presented when I^2 did not exceed our prespecified cutpoint of 75%, and when studies had included appropriate adjustments. For comparability, fiber increments presented in the dose–response figures were chosen to be approximately 1 standard deviation of the mean, based on European population intakes from multiple sources $^{17,27-29}$ and are equivalent to Association of Official Analytical Chemist (AOAC) fiber values.

Metaregression of predefined study characteristics was also undertaken and the following were explored: fiber intake assessment method (AOAC/non-AOAC), inclusion of nonfatal events, follow-up length (<10 years/≥10 years), geographic location (Americas/EU/Other), and whether the results were adjusted for the following: age, alcohol, anthropometry, energy intake, physical activity, and sex.

The potential for small-study effects, such as publication bias, was explored using funnel plots with Egger's test of asymmetry,³⁰ where sufficient studies were included to allow the test.

Results

Eight cohort studies were identified^{12–19} (the online-only Data Supplemental Figure 1), 3 from the United States, ^{12,13,18} 2 were

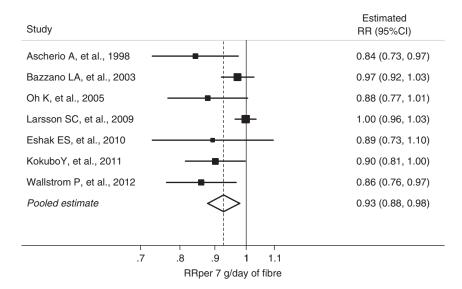


Figure 1. Relative risk (RR) plus 95% confidence intervals (CI) for stroke and each 7 g/day increase in total dietary fiber.

Japanese, 14,16 2 were from northern Europe, 17,19 and 1 from Australia.¹⁵ Study follow-up ranged from 8 to 19 years (see Table) and case numbers ranged from 95 fatal strokes¹⁵ to 2 781 incident events.¹⁷ Only fatal events were reported in 2 studies14,15 and another reported only ischemic stroke risk,19 but 5 publications reported stroke incidence data. 12,13,16–18 Fiber intakes were estimated using AOAC values, or equivalent, in all but the 2 northern European studies. 17,19

Total Fiber Intake and Stroke Risk

Seven studies reported total dietary fiber intake in relation to stroke risk, all of which were included in the dose-response meta-analysis (Figure 1). 12-14,16-19 The pooled relative risk (RR) per 7 g/day increase was 0.93 (95% confidence intervals [CI], 0.88-0.98). There was some evidence of heterogeneity between studies I2=59% (95% CI, 7%-82%). The doseresponse curve for total fiber intake and stroke (Figure 2) suggests that risk steadily reduces with increasing total fiber intake. Data points become especially sparse above intakes of 25 g/day and so extrapolation of risk at higher intakes should be undertaken with caution. There was evidence of a smallstudy effect (P=0.002).

Hemorrhagic or Ischemic Stroke

Four studies reported ischemic stroke risk. A protective association for total dietary fiber was reported in both Japanese women, RR 0.73 (95% CI, 0.55-0.97),16 and Swedish men, RR 0.69 (95% CI, 0.49-0.96; the online-only Data Supplemental Table S1). 19 In the Nurses' Health Study, the risk estimate was <1, but the CIs were wide, RR 0.78 (95% CI, 0.56–1.09)¹⁸ reflecting greater uncertainty about the role of fiber in this cohort. In a cohort of male smokers, no association was apparent.¹⁷

Hemorrhagic stroke was reported in 3 studies and evidence of a protective association was only seen for intracerebral hemorrhagic stroke in women of a Japanese study16 and not in the 2 other cohorts. 17,18

Soluble Fiber Intake and Stroke Risk

Four studies presented stroke risk in relation to water-soluble fiber intake, 13,14,16,17 and all but one, which did not present an estimate of soluble fiber intake,16 were included in the meta-analysis (Figure 3). For each 4 g/day increase in soluble fiber, risk was reduced by 6%: RR 0.94 (95% CI, 0.88-1.01). Evidence of relatively low heterogeneity between studies was seen, $I^2=21\%$ (95% CI, 0%–92%), but as the pooled estimate was based on only 3 studies, it should be interpreted with care. In the study which was not included in the meta-analysis, there was an indication of a protective association for total stroke with greater soluble fiber intake (P-trend=0.031). However, the comparison of high to low consumers did not show strong evidence of an association, RR 0.78 (95% CI, 0.58–1.06), and the results for male participants were omitted from the article.16 There were too few studies to investigate any small-study effects.

Insoluble Fiber and Stroke Risk

Three cohorts reported an association between stroke risk and insoluble fiber intake,14,16,17 but a meta-analysis could not be conducted as 1 article did not provide an estimate for insoluble fiber intake in the cohort.¹⁶ A protective association for total stroke, RR 0.62 (95% CI, 0.45-0.85), and cerebral infarction, RR 0.62 (95% CI, 0.40-0.98), was reported in Japanese women in 1 study (results for men were not presented in the article), 16 but associations were not observed in another Japanese cohort¹⁴ or in the Finnish Alpha-Tocopherol Beta-Carotene study of male smokers.¹⁷

Cereal Fiber Intake and Stroke Risk

Three cohorts reported stroke risk in relation to cereal fiber intake (including fiber from breads, crackers, grains and pasta, etc.). 15,17,18 When pooled, there was evidence of high heterogeneity between studies, I²=90% (95% CI, 73-96%), and a pooled estimate is therefore not presented because this would be unreliable. The Nurses' Health Study reported evidence of an association when the highest cereal fiber consumers were compared with lowest (5.7 versus 1.4 g/day) for total stroke, RR 0.66 (95% CI, 0.52-0.83), and hemorrhagic stroke, RR 0.51 (95% CI, 0.33–0.78), but this was not apparent for ischemic stroke, RR 0.80 (95% CI, 0.57-1.12).18 Another study also saw a significant association with risk of total stroke when the lowest consumers were compared with highest (3 versus 11 g/day), RR 2.13 (95% CI, 1.19–3.80), 15 but in the Alpha-Tocopherol Beta-Carotene study, there was no evidence to support a significant association.¹⁷

Fruit and Vegetable Fiber and Stroke Risk

Two cohorts reported stroke risk and fruit or vegetable fiber intake. In the Nurses' Health Study, there was no strong evidence of an association for stroke and fruit fiber, RR 0.87 (95% CI, 0.70-1.09), and for vegetable fiber, RR 0.92 (95% CI, 0.74–1.14), for highest compared with lowest consumers.¹⁸ In the Alpha-Tocopherol Beta-Carotene study, no strong evidence of an association existed for fruit fiber, but vegetable fiber intake was significantly inversely associated with risk of ischemic stroke, RR 0.86 (95% CI, 0.76–0.99).¹⁷

Metaregression

When study subgroups were pooled, the results largely offered similar estimates (the online-only Data Supplemental Table S2), however, it should be recognized that because of small numbers of included studies, analyses may have a limited capacity to fully explain potential sources of heterogeniety. Different results were observed when data from the 2 European studies, which did not assess fiber intake using AOAC methods, were pooled, RR 0.94 (95% CI, 0.81-1.08; I²=82%).^{17,19} A nonsignificant association was also reported in 1 study, which presented only fatal stroke data and total fiber intake, RR 0.89 (95% CI, 0.73-1.10).14 Studies were also grouped on the basis of included adjustments, but as all 7 studies adjusted for each of the variables listed in the method section, no additional pooled values are presented.

Discussion

The results of this meta-analysis indicate that greater total dietary fiber intake is associated with a significantly reduced risk of primary stroke occurrence. Our findings

Table. Details of Cohort Studies Reporting Stroke Risk and Dietary Fiber Intake

P Trend Model Adjustments	O.028 Age, total energy intake, smoking, alcohol, history of hypertension or hypercholesterolemia, parental MI before 65 yr, profession, BMI, physical activity	Hay ex, race, education, SBP, serum total cholesterol, DM, physical activity, alcohol, smoking, BMI, saturated fat intake	14	0.555 Age, BMI, history of hypertension or DM, alcohol, smoking, education, physical activity, mental stress, sleep, fish intake, saturated fat, n-3 fatty acids, sodium, folate, Vitamin E	0.775	0.790 0.643 0.715 0.128	antihypertensive medication, BMI, smoking, education, self-rated health, history of MI, stroke or DM	(Continued)
	0.0	0.44	0.14				0.65	
Relative Risk (95% Confidence Intervals)	TF: 0.70 (0.48, 1.00)	TF: 0.95 (0.78, 1.16)	SF: 0.88 (0.73, 1.06)	TF(M): 1.09 (0.75, 1.58)	TF(F): 1.05 (0.73, 1.51)	SF(M): 0.90 (0.61, 1.31) SF(P): 1.02 (0.73, 1.42) IF(M): 0.96 (0.64, 1.45) IF(F): 0.90 (0.63, 1.28)	CF: 0.94 (0.73, 1.22)	
Case Numbers	328	928		883			95	
Outcomes Examined	Total stroke incidence	Total stroke incidence		Total stroke mortality			Total stroke mortality	
Fiber Estimation Method	AOAC High vs Iow consumers	Method not reported, likely AOAC.	High vs low consumers for all exposures	Assessment similar to AOAC	High vs low consumers for all exposures		AOAC CF (energy adjusted) low vs high consumers	
Initial Cohort Size, (Eligible After Exclusions)	51 529 (43 738)	14 407 (9 776)		110 792 (58 730)			3 654 (2 897)	
Follow-Up Duration, Years	ω	19		14.3			13	
Age at Recruitment, Years	40–75	25–74 (mean 49)		40–79			Median 65	
Country/ Sex of Participants	United States Men	United States	Men/women	Japan	Men/women		Australia Men/ women	
Authors, Cohort Name	Ascherio et al ¹² Heatth-Professionals Follow-up Study	Bazzano et a ¹³ National Health and Nutrition Examination Survey I		Eshak et al ¹⁴ Japan Collaborative Cohort Study			Kaushik et al ¹⁵ Blue Mountains Eye Study	

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Continued

Table.

Authors Cohort Name	Country/ Sex of Participants	Age at Recruitment, Years	Follow-Up Duration, Years	Initial Cohort Size, (Eligible After Exclusions)	Fiber Estimation Method	Outcomes Examined	Case Numbers	Relative Risk (95% Confidence Intervals)	PTrend	Model Adjustments
								SF: 0.79 (0.69, 0.89)	0.001	
								IF: 0.88 (0.76, 0.99)	90.0	
								CF: 0.92 (0.82, 1.04)	0.36	
								FF: 0.86 (0.76, 0.97)	0.05	
								VF: 0.82 (0.73, 0.93)	<0.001	
Oh et al ¹⁸ Nurses'	United	30-22	18	121 700 (78 779)	AOAC High vs low	Total stroke incidence	1020	TF: 0.83 (0.66, 1.04)	0.07	Age, BMI, smoking,
Health Study	States Women				consumers for all			CF: 0.66 (0.52, 0.83)	0.001	alcohol, parental MI,
					exposures			FF: 0.87 (0.70, 1.09)	0.28	nistory of nypertension, hypercholesterolemia or
								VF: 0.92 (0.74, 1.14)	0.14	DM, menopausal status
						Ischemic stroke incidence	515	TF: 0.78 (0.56, 1.09)	0.09	and postmenopausal
								CF: 0.80 (0.57, 1.12)	0.23	hormone use, aspirin use,
								FF: 0.87 (0.63, 1.21)	0.22	E, physical activity, energy
								VF: 1.01 (0.74, 1.38)	0.48	intake, and carbohydrate
						Hemorrhagic stroke	279	TF: 0.84 (0.54,1.30)	0.34	intake
								CF: 0.51 (0.33.0.78)	0.01	
								FF: 0.86 (0.57, 1.29)	0.64	
								VF: 0.76 (0.51, 1.13)	0.18	
Wallstrom et	Sweden Men/	58 yr	13	28 098 (20 674)	Nonstarch	Ischemic stroke incidence	743	TF(M): 0.69 (0.49, 0.96)	0.050	Age, total energy intake,
ar maine blet and Cancer Cohort	in i				polysacoratine nigit					season, plwi, sinoking, education, alcohol, SBP, antihypertensive treatment, physical activity
								TF(F): 0.73 (0.52, 1.04)	0.18	

AOAC indicates Association of Official Analytical Chemists; BMI, body mass index; CF, cereal fiber; CHD, coronary heart disease; DBP, diastolic blood pressure; DM, diabetes mellitus; F, female; FF, fruit fiber; HDL, high-density lipoprotein; IF, water-insoluble fiber; M, male; MI, myocardial infarction; SBP, systolic blood pressure; SF, water-soluble fiber; TF, total fiber; and VF, vegetable fiber.

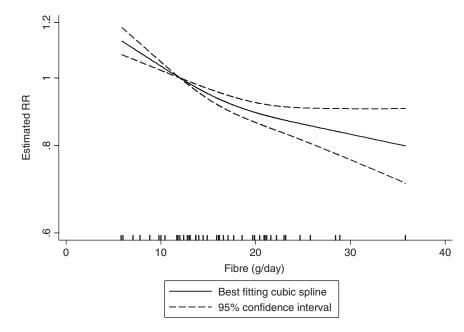


Figure 2. Restricted cubic spline displaying relative risk (RR) for stroke with increasing total dietary fiber intake levels.

support recommendations to increase fiber content of the diet. Notably, an increase of 7 g/day of total dietary fiber, equivalent to the standard deviation of European population level fiber intakes, was associated with a significant 7% reduction in stroke risk. To place this in context, increasing dietary fiber intake (AOAC) by 7 g/day is achievable, and it is equivalent to fiber within a portion of whole-meal pasta (70 g), a piece of fruit (apple/pear/orange) plus a serving of tomatoes each day.¹⁰

Average fiber intakes in the United States are estimated to be around 13 g/day in women and 17 g/day in men.³¹ These values are estimated to be around 5 g lower than actual consumption, as inulin and oligosaccharides were not included in values.³¹ Increasing fiber by 7 g/day would bring intakes close to current recommended levels in the United States of around 21 to 25 g/day for women of different ages and 30 to 38 g/day for men.³¹

Biologically plausible mechanisms exist for fiber and key risk factors for stroke, such as overweight and high cholesterol levels. Soluble types of fiber form gels in the stomach and small intestine, slowing the rate of nutrient absorption and slowing gastric emptying, which increases satiety and influences the overall amount of food eaten, resulting in lower levels of overweight. 10,111 Bacterial fermentation of resistant starch and soluble fibers in the large intestine produces shortchain fatty acids which inhibit cholesterol synthesis by the liver, consequently lowering serum levels. 10 Bile acid reabsorption is also slowed through physically binding to insoluble fiber molecules and the presence of soluble fiber gels. Bile acids contain cholesterol, and when absorption is slowed, blood cholesterol is shunted into bile acid production, thus lowering circulating levels. 10,111

Physiological effects of high-fiber diets may depend on the food sources and types of fiber consumed, ³² and so examining risk associations with different foods is potentially important. As studies focusing on cereal, fruit, or vegetable sources of fiber were too few or too heterogeneous to pool, conclusions cannot be made and future studies should explore risk with food sources of fiber and also with fractions (soluble/insoluble) to fill this research gap.

Although no previous reviews were identified, which examined fiber and stroke risk, one review on whole-grains found a similar lack of published data relating to stroke risk.³³ The review presented mixed findings in the few studies identified,

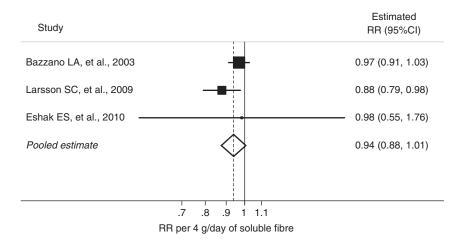


Figure 3. Relative risk (RR) plus 95% confidence intervals (CI) for stroke risk with each 4 g/day increase in soluble dietary fiber.

but concluded there was a strong suggestion of a protective effect of whole-grain on stroke risk.³³ Our findings are aligned with this observation for whole-grain diets, but whole grains contain many other potentially protective components aside from having a high fiber content.³⁴ Other protective components of whole grains include plant stannols and sterols, found in oilseeds, grains, nuts, and legumes, which are associated with reducing both biliary and dietary cholesterol absorption and also unsaturated fatty acids, found in whole-grain wheat and oats which additionally contribute toward lowering cholesterol levels.³⁵

Differing results seen in the 2 northern European studies, not using AOAC methods to estimate fiber intake, may not simply reflect heterogeneity between assessment methods because population characteristics and main sources of fiber within the diet are likely to also differ when compared with United States or Japanese studies. Additionally, there was strong evidence of between-study heterogeneity, and the associations reported in the Finnish study of male smokers pull the pooled result for the 2 European studies toward the null. The different observations from this study suggest that beneficial effects of fiber on stroke risk differ from nonsmoking populations.¹⁷

The contrasting results for the studies reporting incident events and the 1 study reporting mortality data suggest that protective associations may be best explained with the inclusion of nonfatal events. This is unsurprising as the addition of cases will increase statistical power and reduce misclassification of the nonfatal events, which are not identified and are combined with noncases in analyses.

A potential source of heterogeneity in the total fiber metaanalysis was small-study effects, with some evidence of asymmetry in the funnel plots. This could be because of publication bias, or possibly better dietary assessment in the smaller studies.

A key strength of this work is the inclusion of large cohort studies with long follow-up durations, and therefore many case observations. The prospective nature of the included studies also substantially reduces recall bias. A limitation in observational cohort studies is the inherent problem of unadjusted confounding, which remains when data are pooled and means that fiber may be acting as a surrogate for another healthy lifestyle factor. Greater intakes of fiber are associated with other healthy behaviors such as lower smoking rates and increased physical activity, 14,16 both of which may independently influence stroke occurrence, so it is particularly important that these factors are taken into account. It is difficult to estimate the extent to which other behaviors are accurately controlled for when used as adjustments in models, and therefore we cannot ascribe causality to the associations from observational studies. These weaknesses of observational studies therefore apply equally to meta-analysis of such studies. All of the pooled studies did, however, include adjustment for potentially important confounding variables such as age, body mass index, blood pressure or history of hypertension, smoking status, alcohol intake, physical activity, and sex (where applicable), and also a variety of other health and lifestyle variables (see Table).

Conclusion

Findings for this meta-analysis suggest that dietary fiber significantly protects against the risk of stroke. Our study supports current guidelines to increase fiber consumption. The identification of potentially protective food sources of fiber may help tailor recommendations for at-risk populations. To achieve this, further work is needed to explore the relationship between the various fiber types and stroke types.

Summary

Higher total dietary fiber intake is significantly associated with lower risk of first stroke. Overall, findings support dietary recommendations to increase intake of total dietary fiber. However, a paucity of data on fiber from different foods precludes conclusions regarding the association between fiber type and stroke. There is a need for future studies to focus on fiber type and to examine risk for ischemic and hemorrhagic strokes separately.

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