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ORIGINAL ARTICLE

Dietary fiber and fiber-rich food intake in relation to risk of stroke in male smokers

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Background/Objectives: There is convincing evidence that a high dietary fiber intake may lower the risk of coronary heart disease. However, the role of fiber in the prevention of stroke is unclear. We examined the associations of dietary fiber and fiber-rich food intake with risk of stroke within the Alpha-tocopherol, Beta-carotene Cancer Prevention Study.
Subjects/Methods: Between 1985 and 1988, 26 556 Finnish male smokers aged 50–69 years, who had no history of stroke, completed a dietary questionnaire. During a mean follow-up of 13.6 years, 2702 cerebral infarctions, 383 intracerebral hemorrhages and 196 subarachnoid hemorrhages were ascertained.
Results: After adjustment for cardiovascular risk factors and folate and magnesium intakes, there was no significant association between intake of total fiber, water-soluble fiber, water-insoluble fiber, or fiber derived from fruit or cereal sources and risk of any stroke subtype. Vegetable fiber intake, as well as the consumption of fruit, vegetables and cereals, was inversely associated with the risk of cerebral infarction; the multivariate relative risks for the highest quintile of intake as compared with the lowest were 0.86 (95% confidence interval (CI): 0.76–0.99) for vegetable fiber, 0.82 (95% CI: 0.73–0.93) for fruit, 0.75 (95% CI: 0.66–0.85) for vegetables and 0.87 (95% CI: 0.74–1.03) for cereals. Vegetable consumption was inversely associated with risk of subarachnoid hemorrhage (relative risk for highest versus lowest quintile: 0.62; 95% CI: 0.40–0.98), and cereal consumption was inversely associated with risk of intracerebral hemorrhage (relative risk: 0.64; 95% CI: 0.41–1.01).
Conclusions: These findings suggest a beneficial effect of the consumption of fruits, vegetables and cereals on stroke risk.
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Keywords: cereals; dietary fiber; fruits; prospective studies; stroke; vegetables

Introduction

Diets high in fiber may reduce the risk of cardiovascular disease through several mechanisms. Experimental studies in humans have shown that dietary fiber, especially water-soluble fiber, favorably affects blood pressure, serum lipid profile, insulin sensitivity and inflammation (Hallfrisch *et al.*, 1995; Brown *et al.*, 1999; Chandalia *et al.*, 2000; Whelton *et al.*, 2005; Weickert *et al.*, 2006; King *et al.*, 2007). Although compelling epidemiological evidence indicates that a high dietary fiber intake may decrease the risk of coronary heart disease (Pereira *et al.*, 2004), few studies have examined the role of dietary fiber in the prevention of stroke (Ascherio *et al.*, 1998; Mozaffarian *et al.*, 2003; Oh *et al.*, 2005). Furthermore, no study has, to our knowledge, examined water-soluble and water-insoluble fiber in relation to risk of stroke.

We had earlier found an inverse association between dietary fiber intake and risk of coronary heart disease among Finnish male smokers participating in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention(ATBC) Study cohort (Pietinen *et al.*, 1996). The purpose of this study was to examine whether dietary fiber intake is associated with risk of stroke in this cohort. Besides total fiber intake, we assessed intakes of water-soluble and water-insoluble fibers as well as the intake of fiber from fruit, vegetable and cereal sources. We also extended our earlier analysis (Hirvonen *et al.*, 2000) and examined the relationship between fruit and vegetable consumption and stroke risk.

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Subjects and methods

Study population

The ATBC Study was established between 1985 and 1988 when 29 133 male smokers, aged 50–69 years and residing in southwestern Finland, were recruited to participate in a prevention trial (ATBC Cancer Prevention Study Group, 1994). The study was a randomized, double-blinded, placebo-controlled primary prevention trial that was designed to determine whether supplementation with α-tocopherol, α-carotene or with both would reduce the incidence of lung or other cancers. The trial ended in 1993, with registry-based follow up thereafter. At baseline, men were excluded from the trial if they smoked fewer than five cigarettes per day; had a history of cancer, severe angina on exertion, chronic renal insufficiency, liver cirrhosis, chronic alcoholism or other medical conditions that might limit long-term participation; or if they received anticoagulant therapy or used supplements containing vitamin E, vitamin A or α-carotene in excess of predefined doses. Information on dietary intake was provided by 26 556 (93%) of the randomized men who had no history of stroke at baseline.

Written informed consent was obtained from each participant before randomization. The study was approved by the institutional review boards of the National Public Health Institute of Finland and by the US National Cancer Institute.

Baseline data collection

At baseline, participants provided information on background characteristics and medical, smoking and physical activity histories (ATBC Cancer Prevention Study Group, 1994). Body weight, height and blood pressure were measured using standard methods. Serum samples were collected and stored at $-70\,^{\circ}C$ for later analyses. Total serum cholesterol and HDLcholesterol concentrations were determined enzymatically (CHOD-PAP method, Boehringer Mannheim, Germany).

Dietary assessment

Diet was assessed at baseline with a validated self-administered food frequency questionnaire that included 276 food items and mixed dishes commonly consumed in Finland (Pietinen *et al.*, 1988). The questionnaire was used with a portion-size picture booklet of 122 photographs of foods, each with three to five different portion sizes. Each man was asked to indicate his usual frequency of consumption and usual portion size of foods during the past year. Frequencies were reported as the number of times per month, week or day. Dietary fiber and nutrient intakes were estimated using food-composition data obtained from the National Public Health Institute in Finland. Data on fiber content were based on analyses of Finnish foods (Varo *et al.*, 1984a, b).

The dietary method was validated in a pilot study carried out among 189 men before the ATBC study (Pietinen *et al.*, 1988). The men completed the food-frequency questionnaire at the beginning and at the end of a 6-month period, and they kept food-consumption records for 24 days (2×12 days) in the interim period. The correlation coefficients between the dietary questionnaire and food records were the following: total fiber 0.7, water-soluble fiber 0.7, water-insoluble fiber 0.7, fruit fiber 0.6, vegetable fiber 0.5, cereal fiber 0.7, fruits 0.6, vegetable 0.5 and cereals 0.7.

Ascertainment of end points

The endpoint was that point of time when the first-ever stroke occurred between the date of randomization and December 31, 2004. The strokes were further divided into cerebral infarction, intracerebral hemorrhage, subarachnoid hemorrhage and unspecified stroke. The end points were identified by record linkage with the National Hospital Discharge Register and the National Register of Causes of Death. Both registers used the codes of the *International Classification of Diseases* (ICD): the eighth edition was used until the end of 1986, the ninth edition through to the end of 1996 and the tenth edition thereafter. The end points comprised ICD-8 codes 430–434 and 436, ICD-9 codes 430-431, 433-434 and 436, and ICD-10 codes I60, I61, I63 and I64, excluding ICD-8 codes 431.01 and 431.91, representing subdural hemorrhage, and ICD-9 codes 4330X, 4331X, 4339X and 4349X, denoting cerebral or precerebral artery stenosis or occlusion without cerebral infarction. In a reviewed sample, the diagnoses of cerebral infarction, subarachnoid hemorrhage and intracerebral hemorrhage proved to be correct by strict preset criteria (Walker *et al.*, 1981) in 90, 79 and 82% of the discharge diagnoses and in 92, 95 and 91% of the causes of death (Leppälä *et al.*, 1999).

Statistical analysis

Person–time was calculated for each participant from the date of randomization until the date of occurrence of first stroke, death from any cause or until the end of follow-up (31 December, 2004), whichever occurred first. Dietary fiber intake was adjusted for total energy intake using the residual method (Willett and Stampfer, 1986). Participants were categorized into quintiles of energy-adjusted dietary fiber intake. We used Cox proportional hazards models (Cox, 1972) to estimate relative risks with 95% confidence intervals for different quintiles of fiber intake, with simultaneous adjustment for age at baseline and supplementation group. In the multivariate analysis, we additionally controlled for cardiovascular risk factors (BMI, total number of cigarettes smoked daily, systolic and diastolic blood pressure, total cholesterol and HDL cholesterol, histories of diabetes and coronary heart disease and alcohol intake) and energy intake. In a second multivariate model, we further adjusted for dietary folate and magnesium intakes because these nutrients have been found to be inversely associated with risk of cerebral infarction in the ATBC Study (Larsson *et al*., 2008a, b) and are correlated with fiber intake.

Tests of a linear trend across quintiles of fiber intake were conducted by assigning the median value for each quintile and treating this variable as a continuous variable. Effect modification was examined in stratified analyses and was statistically tested by including the cross-product term of fiber intake and the effect modifier. Statistical analyses were carried out using Stata software, version 9.2 (StataCorp, College Station, TX, USA). All statistical tests were two-sided and *P*-values less than 0.05 were considered statistically significant.

Results

Baseline characteristics of the study population according to quintiles of total fiber intake are shown in Table 1. There was more than a two-fold difference in the median fiber intake between the highest (35.8 g/day) and the lowest quintile (16.1 g/day) of the population. Men with a high fiber intake smoked slightly lesser number of cigarettes daily, were more likely to have a history of diabetes or coronary heart disease and to be physically active at leisure time compared with those with a low fiber intake. Moreover, men with a high fiber intake consumed less alcohol and had higher intakes of folate, magnesium, fruits, vegetables, cereals and rye products. The correlations between different types of fiber and foods rich in fiber showed that, in this population, water-soluble and water-insoluble fibers were highly correlated ($r = 0.89$) (Table 2). The main sources of fiber were cereals, particularly rye bread.

During a mean follow-up of 13.6 years (360 187 person-years), we identified 2702 cerebral infarctions, 383 intracerebral hemorrhages, 196 subarachnoid hemorrhages and 84 unspecified strokes. In analysis adjusted for age and supplementation group, total fiber, water-soluble fiber and water-insoluble fiber intakes were significantly inversely associated with the risk of cerebral infarction but not with the risk of intracerebral or subarachnoid hemorrhage (Table 3). The inverse associations were attenuated, but remained statistically significant after further adjustment for cardiovascular risk factors and total energy intake. However, neither total fiber, soluble fiber nor insoluble fiber remained significantly protective after additional adjustment for folate and magnesium intakes. The association between fiber intake and stroke was not significantly modified by age, cardiovascular risk factors (alcohol intake, cigarettes/day,

Table 1 Age-standardized baseline characteristics by quintiles of total dietary fiber intake among 26 556 men in the ATBC Study[a]

	Quintiles of fiber intake				
	1	*2*	*3*	*4*	*5*
Median fiber intake, g/d	16.1	20.9	24.7	28.9	35.8
Age, yr	57.4	57.6	57.7	57.7	57.8
Smoking, cigarettes/d	22.8	21.0	20.1	19.4	18.9
Body mass index, kg/m^2	26.0	26.2	26.3	26.3	26.4
Systolic blood pressure, mm Hg	142.0	142.5	142.7	142.6	142.8
Diastolic blood pressure, mm Hg	88.3	87.8	87.4	87.2	87.3
Serum total cholesterol, mmol/l	6.20	6.25	6.27	6.24	6.25
Serum HDL cholesterol, mmol/l	1.24	1.20	1.19	1.18	1.16
Diabetes, %	4.9	4.9	5.7	5.9	7.6
History of coronary heart disease, %	10.0	10.8	11.2	10.8	12.1
Physically active, %[b]	56.9	57.6	60.4	63.5	66.9
Daily intake					
Energy, kcal	2656	2723	2716	2711	2651
Alcohol, g	29.3	19.6	16.4	13.9	11.1
Folate, g	288	314	333	350	384
Magnesium, g	411	442	469	498	558
Water-soluble fiber, g	3.7	4.8	5.6	6.3	7.8
Water-insoluble fiber, g	11.8	16.0	19.1	22.6	29.5
Fruit fiber, g	2.0	2.8	3.3	3.6	4.3
Vegetable fiber, g	4.1	4.7	5.2	5.2	5.4
Cereal fiber, g	9.2	13.4	16.5	20.4	28.2
Fruits, g	59.1	84.4	96.5	104.2	119.5
Vegetables, g	64.1	77.7	85.0	89.3	94.7
Cereals, g	158	193	214	237	277
Rye products, g	30.2	60.4	85.0	89.3	94.7

Abbreviations: HDL, high-density lipoprotein; yr, year.
[a]Values are means unless otherwise indicated.
[b]Moderate or heavy activity at leisure time.

Table 2 Correlations among different fiber types and foods rich in fiber[a]

Variable	*Correlation*									
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
Total fiber (1)	1.00	0.93	0.99	0.33	0.27	0.91	0.26	0.19	0.50	0.77
Water-soluble fiber (2)	...	1.00	0.89	0.56	0.39	0.73	0.49	0.35	0.45	0.61
Water-insoluble fiber (3)	...	...	1.00	0.26	0.23	0.94	0.19	0.15	0.50	0.81
Fruit fiber (4)	...	...	...	1.00	0.23	0.04	0.81	0.37	0.05	0.01
Vegetable fiber (5)	...	...	...	...	1.00	0.00	0.19	0.55	−0.01	0.03
Cereal fiber (6)	...	...	...	...	...	1.00	0.02	−0.02	0.51	0.85
Fruits (7)	...	...	...	...	...	...	1.00	0.40	0.19	0.09
Vegetables (8)	...	...	...	...	...	...	...	1.00	0.17	0.06
Cereals (9)	...	...	...	...	...	...	...	...	1.00	0.57
Rye products (10)	...	...	...	...	...	...	...	...	...	1.00

[a]Dietary fiber variables are adjusted for total energy intake.

smoking years, BMI, hypertension, serum total cholesterol, serum HDL cholesterol, physical activity) or by the supplementation group (data not shown).

We also evaluated the associations of fiber derived from fruit, vegetable and cereal sources with stroke risk (Table 4). After adjustment for age, supplementation group, cardiovascular risk factors and intakes of total energy, folate and magnesium, only the intake of vegetable fiber was statistically significantly inversely associated with the risk of cerebral infarction; the multivariate relative risk for the highest compared with the lowest quintile was 0.86 (95% CI: 0.76–0.99). When vegetable intake was included in the model, in place of folate and magnesium intakes, the corresponding relative risks were 0.90 (95% CI: 0.78–1.04).

We considered the possibility that the effect of fiber intake on stroke risk may be mediated through reductions in the total serum cholesterol levels and blood pressure, and that adjustment for these factors in our multivariate models may minimize potential associations. The results were similar when we excluded serum cholesterol and systolic and diastolic blood pressure from the multivariate model (data not shown).

To address the potential for increased exposure misclassification over time, we divided the follow-time into less than 10 years and 10 or more years of follow-up. The association between fiber intake and stroke did not differ appreciably by follow-up time.

We further examined the food sources of fiber in relation to risk of stroke (Table 5). Intakes of fruit and vegetables were statistically significantly inversely associated with risk of cerebral infarction after adjustment for age, supplementation group and cardiovascular risk factors. The multivariate relative risk of cerebral infarction for the highest quintile of combined fruit and vegetable intake (median, 321 g/d) compared with that for the lowest quintile (median, 53 g/d) was 0.77 (95% CI: 0.68–0.87; P for trend <0.001). Vegetable consumption was inversely associated with risk of intracerebral and subarachnoid hemorrhage, but the association with intracerebral hemorrhage was not statistically significant in multivariate analysis. In multivariate analysis, cereal consumption was statistically significantly inversely associated with risk of intracerebral hemorrhage (P for trend $=0.04$) and nonsignificantly inversely associated with risk of cerebral infarction (P for trend $=0.08$). We observed no statistically significant association between intake of rye products and risk of any subtype of stroke; the multivariate relative risks for the highest quintile of rye product intake (172.7 g/d) compared with those for the lowest quintile (16.0 g/d) were 0.98 (95% CI: 0.86–1.11) for cerebral infarction, 0.82 (95% CI: 0.57–1.17) for intracerebral hemorrhage and 0.98 (95% CI: 0.63–1.52) for subarachnoid hemorrhage.

Cereals are sources of dietary magnesium, folate and vitamin E. To evaluate whether the observed inverse association of cereal intake with risk of cerebral infarction and intracerebral hemorrhage could be attributed to increased intakes of dietary magnesium, folate and vitamin E, we added these nutrients (contributions from food sources) to the multivariate model. When these nutrients were simultaneously included in the model, the relative risks for the highest versus the lowest quintile of cereal intake were 0.98 (95% CI: 0.82–1.18) for cerebral infarction and 0.67 (95% CI: 0.41–1.09) for intracerebral hemorrhage.

Discussion

In this prospective study of male smokers, we found no significant association between intake of total fiber, water-soluble fiber, water-insoluble fiber or fiber derived from fruit or cereal sources with risk of stroke after adjustment for cardiovascular risk factors and other dietary variables including folate and magnesium intakes. Nevertheless, vegetable fiber intake, as well as fruit and vegetable consumption, was significantly inversely associated with risk of cerebral infarction. Vegetable consumption was inversely related to risk of subarachnoid hemorrhage and cereal consumption to risk of intracerebral hemorrhage.

Table 3 Relative risks (95% confidence intervals) of stroke subtypes by quintiles of total fiber and water-soluble and water-insoluble fiber intake among 26 556 men in the ATBC Study, 1985–2004

	Quintiles of fiber intake					P *for trend*
	1	*2*	*3*	*4*	*5*	
Total fiber						
Median, g/d	16.1	20.9	24.7	28.9	35.8	
Cerebral infarction						
Cases, *n*	578	524	560	523	517	
Age-adjusted RR (95% CI)[a]	1.00	0.85 (0.75–0.95)	0.88 (0.79–0.99)	0.80 (0.71–0.90)	0.80 (0.71–0.90)	<0.001
Multivariate RR 1 (95% CI)[b]	1.00	0.89 (0.79–1.00)	0.95 (0.84–1.07)	0.87 (0.77–0.98)	0.86 (0.76–0.98)	0.03
Multivariate RR 2 (95% CI)[c]	1.00	0.92 (0.82–1.04)	1.01 (0.89–1.15)	0.95 (0.83–1.10)	1.01 (0.85–1.19)	0.83
Intracerebral hemorrhage						
Cases, *n*	68	86	87	77	65	
Age-adjusted RR (95% CI)[a]	1.00	1.19 (0.86–1.63)	1.17 (0.85–1.60)	1.00 (0.72–1.38)	0.85 (0.61–1.20)	0.15
Multivariate RR 1 (95% CI)[b]	1.00	1.27 (0.92–1.76)	1.30 (0.94–1.80)	1.11 (0.79–1.56)	0.94 (0.66–1.35)	0.37
Multivariate RR 2 (95% CI)[c]	1.00	1.29 (0.92–1.79)	1.32 (0.93–1.87)	1.13 (0.77–1.63)	0.97 (0.61–1.54)	0.63
Subarachnoid hemorrhage						
Cases, *n*	39	41	37	35	44	
Age-adjusted RR (95% CI)[a]	1.00	1.02 (0.66–1.58)	0.91 (0.58–1.43)	0.84 (0.53–1.33)	1.07 (0.70–1.65)	0.95
Multivariate RR 1 (95% CI)[b]	1.00	1.02 (0.65–1.59)	0.92 (0.58–1.46)	0.85 (0.53–1.37)	1.09 (0.69–1.71)	0.87
Multivariate RR 2 (95% CI)[c]	1.00	0.97 (0.62–1.53)	0.84 (0.51–1.37)	0.74 (0.44–1.26)	0.86 (0.47–1.59)	0.49
Water-soluble fiber						
Median, g/d	3.8	4.8	5.5	6.3	7.7	
Cerebral infarction						
Cases, *n*	590	530	549	547	484	
Age-adjusted RR (95% CI)[a]	1.00	0.85 (0.76–0.96)	0.86 (0.76–0.96)	0.83 (0.74–0.93)	0.73 (0.64–0.82)	<0.001
Multivariate RR 1 (95% CI)[b]	1.00	0.91 (0.81–1.03)	0.93 (0.82–1.04)	0.91 (0.80–1.02)	0.79 (0.69–0.89)	0.001
Multivariate RR 2 (95% CI)[c]	1.00	0.93 (0.82–1.05)	0.96 (0.85–1.10)	0.96 (0.83–1.10)	0.86 (0.73–1.02)	0.17
Intracerebral hemorrhage						
Cases, *n*	66	98	88	65	66	
Age-adjusted RR (95% CI)[a]	1.00	1.40 (1.03–1.92)	1.23 (0.89–1.69)	0.88 (0.62–1.24)	0.89 (0.63–1.25)	0.06
Multivariate RR 1 (95% CI)[b]	1.00	1.55 (1.12–2.13)	1.38 (0.99–1.92)	0.98 (0.68–1.39)	0.99 (0.69–1.42)	0.35
Multivariate RR 2 (95% CI)[c]	1.00	1.55 (1.12–2.15)	1.38 (0.97–1.97)	0.98 (0.65–1.46)	0.99 (0.62–1.59)	0.60
Subarachnoid hemorrhage						
Cases, *n*	37	37	41	38	43	
Age-adjusted RR (95% CI)[a]	1.00	0.96 (0.61–1.52)	1.05 (0.67–1.63)	0.96 (0.61–1.51)	1.07 (0.69–1.67)	0.75
Multivariate RR 1 (95% CI)[b]	1.00	0.97 (0.61–1.55)	1.06 (0.67–1.68)	0.98 (0.61–1.58)	1.11 (0.69–1.77)	0.66
Multivariate RR 2 (95% CI)[c]	1.00	0.94 (0.59–1.51)	1.00 (0.61–1.63)	0.90 (0.53–1.54)	0.95 (0.51–1.79)	0.86
Water-insoluble fiber						
Median, g/d	12.2	16.0	19.1	22.6	28.3	
Cerebral infarction						
Cases, *n*	577	537	534	528	526	
Age-adjusted RR (95% CI)[a]	1.00	0.86 (0.76–0.97)	0.84 (0.74–0.94)	0.81 (0.72–0.91)	0.81 (0.72–0.91)	0.001
Multivariate RR 1 (95% CI)[b]	1.00	0.90 (0.80–1.02)	0.90 (0.80–1.02)	0.88 (0.78–0.99)	0.88 (0.76–0.99)	0.06
Multivariate RR 2 (95% CI)[c]	1.00	0.94 (0.80–1.03)	0.97 (0.85–1.10)	0.97 (0.84–1.11)	1.03 (0.87–1.21)	0.61
Intracerebral hemorrhage						
Cases, *n*	72	89	76	80	66	
Age-adjusted RR (95% CI)[a]	1.00	1.14 (0.84–1.56)	0.95 (0.69–1.32)	0.98 (0.71–1.34)	0.81 (0.58–1.14)	0.11
Multivariate RR 1 (95% CI)[b]	1.00	1.22 (0.89–1.68)	1.05 (0.75–1.46)	1.08 (0.78–1.51)	0.89 (0.63–1.26)	0.29
Multivariate RR 2 (95% CI)[c]	1.00	1.22 (0.89–1.69)	1.05 (0.74–1.50)	1.08 (0.74–1.57)	0.88 (0.56–1.39)	0.43
Subarachnoid hemorrhage						
Cases, *n*	38	39	41	35	43	
Age-adjusted RR (95% CI)[a]	1.00	0.99 (0.63–1.55)	1.04 (0.67–1.61)	0.86 (0.55–1.37)	1.08 (0.70–1.67)	0.89
Multivariate RR 1 (95% CI)[b]	1.00	1.02 (0.64–1.58)	1.06 (0.67–1.66)	0.88 (0.55–1.42)	1.10 (0.70–1.75)	0.80
Multivariate RR 2 (95% CI)[c]	1.00	0.96 (0.60–1.52)	0.97 (0.60–1.57)	0.78 (0.46–1.32)	0.89 (0.49–1.64)	0.58

Abbreviations: RR, relative risk; CI, confidence interval.
[a]Adjusted for age and supplementation group.
[b]Adjusted further for number of cigarettes smoked daily, BMI, systolic and diastolic blood pressures, total serum cholesterol, serum high-density lipoprotein cholesterol, histories of diabetes and coronary heart disease, leisure-time physical activity, and intakes of alcohol and total energy.
[c]Adjusted further for intakes of folate and magnesium.

Table 4 Relative risks (95% confidence intervals) of stroke subtypes by quintiles of fruit, vegetable and cereal fiber intake among 26 556 men in the ATBC Study, 1985–2004

	Quintiles of fiber intake					P *for trend*
	1	*2*	*3*	*4*	*5*	
Fruit fiber						
Median, g/d	0.7	1.8	2.7	3.9	6.2	
Cerebral infarction						
Cases, *n*	590	521	521	555	515	
Age-adjusted RR (95% CI)[a]	1.00	0.85 (0.75–0.95)	0.82 (0.73–0.92)	0.86 (0.77–0.97)	0.78 (0.69–0.88)	0.001
Multivariate RR 1 (95% CI)[b]	1.00	0.90 (0.80–1.01)	0.88 (0.78–0.99)	0.93 (0.83–1.05)	0.86 (0.76–0.97)	0.05
Multivariate RR 2 (95% CI)[c]	1.00	0.91 (0.81–1.03)	0.90 (0.80–1.02)	0.96 (0.85–1.09)	0.91 (0.80–1.04)	0.83
Intracerebral hemorrhage						
Cases, *n*	77	78	78	84	66	
Age-adjusted RR (95% CI)[a]	1.00	0.97 (0.71–1.33)	0.93 (0.68–1.28)	1.00 (0.73–1.36)	0.76 (0.55–1.06)	0.12
Multivariate RR 1 (95% CI)[b]	1.00	1.06 (0.77–1.45)	1.00 (0.73–1.38)	1.06 (0.78–1.46)	0.82 (0.58–1.15)	0.21
Multivariate RR 2 (95% CI)[c]	1.00	1.07 (0.78–1.48)	1.04 (0.75–1.43)	1.11 (0.80–1.55)	0.88 (0.61–1.26)	0.44
Subarachnoid hemorrhage						
Cases, *n*	39	35	32	42	48	
Age-adjusted RR (95% CI)[a]	1.00	0.88 (0.56–1.39)	0.79 (0.49–1.25)	1.03 (0.67–1.60)	1.18 (0.77–1.80)	0.20
Multivariate RR 1 (95% CI)[b]	1.00	0.90 (0.57–1.42)	0.79 (0.49–1.27)	1.05 (0.67–1.64)	1.23 (0.80–1.91)	0.15
Multivariate RR 2 (95% CI)[c]	1.00	0.91 (0.57–1.45)	0.81 (0.50–1.31)	1.08 (0.68–1.71)	1.28 (0.80–2.06)	0.14
Vegetable fiber						
Median, g/d	2.9	3.9	4.7	5.6	7.1	
Cerebral infarction						
Cases, *n*	571	621	533	493	484	
Age-adjusted RR (95% CI)[a]	1.00	1.04 (0.93–1.17)	0.89 (0.79–1.01)	0.81 (0.72–0.92)	0.79 (0.70–0.89)	<0.001
Multivariate RR 1 (95% CI)[b]	1.00	1.06 (0.94–1.18)	0.92 (0.82–104)	0.84 (0.74–095)	0.82 (0.73–0.93)	<0.001
Multivariate RR 2 (95% CI)[c]	1.00	1.07 (0.95–1.20)	0.94 (0.83–1.06)	0.86 (0.76–0.98)	0.86 (0.76–0.99)[d]	0.001
Intracerebral hemorrhage						
Cases, *n*	88	73	63	91	68	
Age-adjusted RR (95% CI)[a]	1.00	0.80 (0.58–1.08)	0.69 (0.50–0.95)	0.98 (0.73–1.31)	0.73 (0.53–1.00)	0.21
Multivariate RR 1 (95% CI)[b]	1.00	0.81 (0.59–1.10)	0.70 (0.51–0.98)	1.00 (0.74–1.35)	0.76 (0.55–1.05)	0.35
Multivariate RR 2 (95% CI)[c]	1.00	0.82 (0.60–1.11)	0.72 (0.52–1.00)	1.04 (0.76–1.41)	0.81 (0.57–1.14)	0.62
Subarachnoid hemorrhage						
Cases, *n*	47	40	38	32	39	
Age-adjusted RR (95% CI)[a]	1.00	0.81 (0.53–1.23)	0.76 (0.49–1.16)	0.62 (0.40–0.97)	0.74 (0.48–1.13)	0.11
Multivariate RR 1 (95% CI)[b]	1.00	0.81 (0.53–1.23)	0.77 (0.50–1.18)	0.62 (0.39–0.97)	0.74 (0.48–1.14)	0.12
Multivariate RR 2 (95% CI)[c]	1.00	0.79 (0.52–1.20)	0.73 (0.47–1.13)	0.59 (0.37–0.93)	0.63 (0.43–1.07)[d]	0.06
Cereal fiber						
Median, g/d	8.9	13.1	16.5	20.6	27.5	
Cerebral infarction						
Cases, *n*	563	531	525	549	534	
Age-adjusted RR (95% CI)[a]	1.00	0.87 (0.78–0.98)	0.85 (0.76–0.96)	0.87 (0.77–0.98)	0.86 (0.77–0.97)	0.04
Multivariate RR 1 (95% CI)[b]	1.00	0.93 (0.82–1.05)	0.91 (0.80–1.02)	0.95 (0.84–1.07)	0.92 (0.82–1.04)	0.36
Multivariate RR 2 (95% CI)[c]	1.00	0.95 (0.84–1.08)	0.95 (0.84–1.08)	1.03 (0.90–1.17)	1.06 (0.91–1.23)	0.25
Intracerebral hemorrhage						
Cases, *n*	74	89	64	85	71	
Age-adjusted RR (95% CI)[a]	1.00	1.11 (0.82–1.51)	0.79 (0.56–1.10)	1.02 (0.75–1.39)	0.87 (0.63–1.20)	0.31
Multivariate RR 1 (95% CI)[b]	1.00	1.18 (0.86–1.61)	0.85 (0.61–1.20)	1.12 (0.81–1.54)	0.93 (0.66–1.30)	0.55
Multivariate RR 2 (95% CI)[c]	1.00	1.18 (0.86–1.62)	0.86 (0.60–1.22)	1.13 (0.80–1.59)	0.94 (0.63–1.42)	0.71
Subarachnoid hemorrhage						
Cases, *n*	44	35	39	33	45	
Age-adjusted RR (95% CI)[a]	1.00	0.77 (0.50–1.20)	0.86 (0.56–1.32)	0.72 (0.46–1.13)	1.00 (0.66–1.52)	0.93
Multivariate RR 1 (95% CI)[b]	1.00	0.77 (0.49–1.21)	0.87 (0.56–1.34)	0.73 (0.46–1.15)	1.02 (0.66–1.57)	0.84
Multivariate RR 2 (95% CI)[c]	1.00	0.75 (0.47–1.17)	0.81 (0.52–1.28)	0.66 (0.40–1.08)	0.86 (0.50–1.46)	0.60

Abbreviations: RR, relative risk; CI, confidence interval.
[a]Adjusted for age and supplementation group.
[b]Adjusted further for number of cigarettes smoked daily, BMI, systolic and diastolic blood pressures, serum total cholesterol, serum high-density lipoprotein cholesterol, histories of diabetes and coronary heart disease, leisure-time physical activity, and intakes of alcohol and total energy.
[c]Adjusted further for intakes of folate and magnesium.
[d]When adjusting for vegetable intake in place of folate and magnesium intakes, the RR was 0.90 (95% CI, 0.78–1.04) for cerebral infarction and 0.91 (95% CI, 0.55–1.51) for subarachnoid hemorrhage.

Table 5 Relative risks (95% confidence intervals) of stroke subtypes by quintiles of fruit, vegetable and cereal intake among 26 556 men in the ATBC Study, 1985–2004

	Quintiles of intake					P for trend
	1	2	3	4	5	
Fruits						
Median, g/d	11.6	40.7	74.0	113.5	192.9	
Cerebral infarction						
Cases, *n*	603	547	543	515	494	
Age-adjusted RR (95% CI)[a]	1.00	0.88 (0.78–0.98)	0.86 (0.77–0.97)	0.81 (0.72–0.91)	0.78 (0.69–0.88)	<0.001
Multivariate RR (95% CI)[b]	1.00	0.90 (0.80–1.02)	0.91 (0.81–1.02)	0.85 (0.76–0.96)	0.82 (0.73–0.93)	0.003
Intracerebral hemorrhage						
Cases, *n*	76	86	77	84	60	
Age-adjusted RR (95% CI)[a]	1.00	1.09 (0.80–1.49)	0.97 (0.71–1.33)	1.05 (0.77–1.44)	0.75 (0.54–1.06)	0.07
Multivariate RR (95% CI)[b]	1.00	1.14 (0.84–1.55)	1.04 (0.75–1.43)	1.14 (0.83–1.57)	0.84 (0.59–1.20)	0.26
Subarachnoid hemorrhage						
Cases, *n*	41	28	43	45	39	
Age-adjusted RR (95% CI)[a]	1.00	0.65 (0.40–1.06)	1.00 (0.65–1.54)	1.03 (0.67–1.60)	0.88 (0.57–1.36)	0.85
Multivariate RR (95% CI)[b]	1.00	0.64 (0.40–1.04)	0.98 (0.63–1.50)	0.98 (0.64–1.51)	0.80 (0.51–1.26)	0.79
Vegetables						
Median, g/d	25.4	47.9	70.3	98.6	153.7	
Cerebral infarction						
Cases, *n*	593	570	534	549	456	
Age-adjusted RR (95% CI)[a]	1.00	0.94 (0.84–1.05)	0.88 (0.78–0.99)	0.89 (0.80–1.01)	0.74 (0.65–0.83)	<0.001
Multivariate RR (95% CI)[b]	1.00	0.94 (0.84–1.06)	0.90 (0.80–1.01)	0.91 (0.81–1.02)	0.75 (0.66–0.85)	<0.001
Intracerebral hemorrhage						
Cases, *n*	88	81	84	63	67	
Age-adjusted RR (95% CI)[a]	1.00	0.90 (0.67–1.22)	0.94 (0.69–1.26)	0.70 (0.50–0.97)	0.74 (0.54–1.02)	0.03
Multivariate RR (95% CI)[b]	1.00	0.91 (0.67–1.23)	0.97 (0.72–1.32)	0.73 (0.53–1.02)	0.80 (0.58–1.11)	0.10
Subarachnoid hemorrhage						
Cases, *n*	45	38	43	33	37	
Age-adjusted RR (95% CI)[a]	1.00	0.80 (0.52–1.24)	0.88 (0.58–1.34)	0.65 (0.42–1.02)	0.70 (0.45–1.08)	0.09
Multivariate RR (95% CI)[b]	1.00	0.76 (0.49–1.17)	0.83 (0.54–1.26)	0.60 (0.38–0.95)	0.62 (0.40–0.98)	0.04
Cereals						
Median, g/d	116.4	165.6	205.2	249.9	327.4	
Cerebral infarction						
Cases, *n*	569	561	553	530	489	
Age-adjusted RR (95% CI)[a]	1.00	0.92 (0.82–1.03)	0.89 (0.79–1.00)	0.85 (0.75–0.95)	0.78 (0.69–0.88)	<0.001
Multivariate RR (95% CI)[b]	1.00	0.98 (0.87–1.10)	0.97 (0.85–1.10)	0.93 (0.81–1.07)	0.87 (0.74–1.03)	0.08
Intracerebral hemorrhage						
Cases, *n*	94	82	84	65	58	
Age-adjusted RR (95% CI)[a]	1.00	0.81 (0.60–1.09)	0.82 (0.61–1.10)	0.63 (0.46–0.86)	0.56 (0.41–0.78)	<0.001
Multivariate RR (95% CI)[b]	1.00	0.85 (0.63–1.16)	0.88 (0.64–1.22)	0.70 (0.48–1.01)	0.64 (0.41–1.01)	0.04
Subarachnoid hemorrhage						
Cases, *n*	32	39	31	49	45	
Age-adjusted RR (95% CI)[a]	1.00	1.16 (0.73–1.85)	0.91 (0.55–1.49)	1.40 (0.90–2.19)	1.27 (0.81–2.00)	0.19
Multivariate RR (95% CI)[b]	1.00	1.12 (0.69–1.81)	0.84 (0.50–1.42)	1.24 (0.74–2.07)	1.00 (0.54–1.84)	0.91

Abbreviations: RR, relative risk; CI, confidence interval.
[a]Adjusted for age and supplementation group.
[b]Adjusted further for number of cigarettes smoked daily, body mass index, systolic and diastolic blood pressures, serum total cholesterol, serum high-density lipoprotein cholesterol, histories of diabetes and coronary heart disease, leisure-time physical activity, and intakes of alcohol and total energy.

Three earlier prospective studies have examined the association between fiber intake and risk of stroke. In Nurses' Health Study, with 18 years of follow-up and 1020 stroke cases, a high intake of cereal fiber was associated with a statistically significant 34 and 49% lower risk of total stroke and hemorrhagic stroke, respectively (Oh *et al.*, 2005). No association was observed for total fiber or vegetable or fruit fiber intake (Oh *et al*., 2005). In the Cardiovascular Health Study among 3588 elderly men and women, with 8.6 years of follow-up and 392 stroke cases, those in the 80th percentile of cereal fiber intake had a statistically significant 22 and 24% lower risk of total stroke and ischemic stroke, respectively, compared with those in the 20th percentile of intake (Mozaffarian *et al*., 2003). Results from the Health Professionals Follow-up Study, with 8 years of follow-up and 328 stroke cases, also indicated an inverse association between intake of cereal fiber, but not fruit or vegetable fiber, and risk of total stroke, but only among hypertensive men (Ascherio *et al*., 1998).

The discrepant findings for cereal fiber between our results and those of other studies may be because of different study populations. Cereal fiber intake in this population of Finnish men was substantially higher (median intake, 16.5 g/d) than in the three earlier cohorts of US men and women (median intake ranging from about 3 to 5 g/d) (Ascherio *et al*., 1998; Mozaffarian *et al*., 2003; Oh *et al*., 2005). The possibility of a threshold value so that cereal fiber intakes above a certain level do not provide any additional protective effect may explain our failure to detect an association between cereal fiber intake and stroke.

Our findings for fruit and vegetable consumption are consistent with results from earlier prospective studies. In a meta-analysis of nine prospective studies (with a total of 4917 stroke events), compared with those who consumed less than three servings of fruit and vegetables per day, the relative risk of stroke was 0.74 (95% CI 0.69–0.79) for those who consumed more than five servings per day (He *et al*., 2006).

Fruits and vegetables are one of the main components of the Dietary Approaches to Stop Hypertension (DASH) diet, which has been shown to substantially lower blood pressure (Appel *et al*., 1997). Raised blood pressure is a potent risk factor for stroke (Lewington *et al*., 2002). In our study, systolic and diastolic blood pressures were similar at all levels of fruit and vegetable intake, and removing blood pressure from the multivariate model did not appreciably change the results for fruit and vegetable intake (data not shown). Hence, blood pressure may not explain the observed inverse association between fruit and vegetable intake and stroke risk in our study. Fruits and vegetables are rich sources of many potentially protective compounds such as folate, which is a determinant of blood homocysteine concentrations. There is ample evidence linking elevated blood homocysteine concentrations to increased risk of stroke (Homocysteine Studies Collaboration, 2002b). Elevated homocysteine concentrations affect both the vascular wall structure and the blood coagulation system (Selhub, 1999). Fruits and vegetables are also rich in antioxidants. However, intervention studies of vitamin C, vitamin E and α-carotene have not shown a beneficial effect on stroke incidence or mortality (Leppälä *et al*., 2000; Heart Protection Study Collaborative Group, 2002a).

Although we observed no independent association between cereal fiber intake and risk of stroke, cereal consumption was significantly inversely associated with risk of intracerebral hemorrhage and nonsignificantly inversely associated with risk of cerebral infarction. This may suggest that factors other than fiber in cereals may be beneficial. Cereals are an important source of dietary magnesium and folate; one-third of magnesium and one-fifth of folate were derived from cereals in the ATBC Study population. We have earlier found that high intakes of magnesium and folate are associated with a lower risk of cerebral infarction in the ATBC Study (Larsson *et al*., 2008a, b). In addition, cereals contain many other compounds that may play a role in reducing the risk of stroke (Slavin *et al*., 1999). In our secondary analyses, we investigated whether the observed inverse association between cereal intake and risk of stroke could be attributed to magnesium, folate and vitamin E. After adjustment for these nutrients, the inverse association between cereal intake and intracerebral infarction remained (although it was not statistically significant), but not the inverse association between cereal intake and cerebral infarction.

Our study has certain strengths and limitations. Strengths include its prospective design and the large number of stroke cases, which provided a high statistical power to detect associations. Furthermore, we had detailed information on cardiovascular risk factors, including BMI, smoking, blood pressure and serum cholesterol, which enabled us to comprehensively control the potential confounding by these factors. A limitation of this study is that diet was assessed with a self-administered dietary questionnaire and at baseline only. Therefore, some measurement error leading to misclassification of dietary fiber intake was inevitable, and this tended to attenuate any true association between fiber intake and stroke risk. On the other hand, the correlation coefficient between total fiber intake based on the dietary questionnaire and the food records was 0.7 in the validation study. With this degree of validity, along with the size of the study, we should have been able to detect important associations. Another limitation is that our study population consists entirely of male smokers. Smokers tend to have a slightly lower blood pressure (Omvik, 1996) as well as increased serum total cholesterol and reduced HDL (Krupski, 1991) than nonsmokers. The associations of fiber and fiber-rich food intake with stroke risk could therefore differ in nonsmoking populations. There are, however, no studies to show different associations between intakes of fiber and risk of stroke in different smoking categories.

In summary, findings from this prospective study do not support the hypothesis that a high intake of dietary fiber is independently inversely associated with the risk of stroke. However, our results indicate that high consumption of fruits, vegetables and cereals may reduce the risk of stroke.

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