Total Antioxidant Capacity of Diet and Risk of Stroke
A Population-Based Prospective Cohort of Women

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Background and Purpose—Consumption of antioxidant-rich foods may reduce the risk of stroke by inhibition of oxidative stress and inflammation. Total antioxidant capacity (TAC) takes into account all antioxidants and the synergistic effects between them. We examined the association between dietary TAC and stroke incidence in cardiovascular disease (CVD)-free women and in women with CVD history at baseline.

Methods—The study included women (31 035 CVD-free and 5680 with CVD history at baseline), aged 49 to 83 years, from the Swedish Mammography Cohort. Diet was assessed with a food frequency questionnaire. Dietary TAC was calculated using oxygen radical absorbance capacity values. Stroke cases were ascertained by linkage with the Swedish Hospital Discharge Registry.

Results—During follow-up (September 1997 to December 2009), we identified 1322 stroke cases (988 cerebral infarctions, 226 hemorrhagic strokes, and 108 unspecified strokes) among CVD-free women and 1007 stroke cases (796 cerebral infarctions, 100 hemorrhagic strokes, and 111 unspecified strokes) among women with a CVD history. The multivariable hazard ratio of total stroke comparing the highest with the lowest quintile of dietary TAC was 0.83 (95% CI, 0.70–0.99; *P* for trend=0.04) in CVD-free women. Among women with a CVD history, the hazard ratios for the highest versus lowest quartile of TAC were 0.90 (95% CI, 0.75–1.07; *P* for trend=0.30) for total stroke and 0.55 (95% CI, 0.32–0.95; *P* for trend=0.03) for hemorrhagic stroke.

Conclusions—These findings suggest that dietary TAC is inversely associated with total stroke among CVD-free women and hemorrhagic stroke among women with CVD history. **(*Stroke*. 2012;43:335-340.)**

Key Words: antioxidants ■ diet ■ stroke

Stroke is the leading cause of death after heart disease in the world.[1] Identification of modifiable risk factors for stroke is thus of great importance. Fruit and vegetable consumption has been inversely associated with risk of stroke.[2] Phytochemicals with antioxidant properties present in fruits and vegetables such as vitamin C, vitamin E, carotenoids, and flavonoids have been hypothesized to contribute to the protective effects associated with high fruit and vegetable consumption. Phytochemicals can inhibit oxidative stress and inflammation by scavenging reactive oxygen species and reactive nitrogen species.[3]

Because not only fruits and vegetables contribute to dietary antioxidants, it is important to study the overall effect from all antioxidants in the diet. The total antioxidant capacity (TAC) aims to measure the free radical-reducing capacity of all antioxidants in the diet and takes into account synergistic effects between substances. Fruits and vegetables are the major contributors (approximately 50%) of TAC.[4] Only 1 previous study has investigated TAC of diet in relation to stroke risk.[5] That study of Italian women and men included only 194 stroke cases and observed an inverse association between dietary TAC and risk of cerebral infarction.[5]

Given the limited data on TAC of diet in relation to stroke risk, we examined this association in cardiovascular disease (CVD)-free women as well as in women with a CVD history at baseline in a population-based prospective cohort of women with a large number of stroke cases.

Methods

The study was based on the Swedish Mammography Cohort, which was established between 1987 and 1990. All women born 1914 to 1948 residing in Uppsala and Västmanland counties received a questionnaire concerning diet, education, weight, and height; 74% completed the questionnaire. An expanded questionnaire was sent in 1997 to all 56 030 cohort members who were still alive and living in the study area. The questionnaire was completed by 38 984 women (70%). Because information on several potential risk factors for stroke (eg, vitamin supplement use, smoking, physical activity, aspirin use, and history of diabetes, hypertension, and hypercholesterolemia) was collected first in 1997, the 1997 questionnaire served as a baseline for the present analyses.

Women with a diagnosis of cancer (except nonmelanoma skin cancer, n=1756) and extreme total energy intake (±3 SD from the mean value for $\log_e$-transformed energy, n=513) were excluded. The remaining cohort of 36 715 women was followed from September 15, 1997, through December 31, 2009. The study was approved by

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the Regional Ethical Review Board at the Karolinska Institutet (Stockholm, Sweden).

Food Frequency Questionnaire-Based TAC Estimates and Covariates

Dietary data were collected with a 96-item food frequency questionnaire (FFQ). Participants were asked how often, on average, they had consumed each type of food or beverage during the last year. There were 8 predefined response categories, ranging from "never/seldom" to "≥3 times per day." The calculation of TAC estimates has been described in detail elsewhere.[4] Briefly, TAC from the diet was calculated by using a database of the most common foods analyzed with the oxygen radical absorbance capacity (ORAC) assay. ORAC measures the antioxidant capacity of the diet to reduce free radicals, taking into account the synergism between compounds. TAC from the diet was calculated by multiplying the average frequency of consumption of each food by ORAC value (μmol Trolox equivalents/100 g) of age-specific portion sizes. In the 96-item FFQ there were 30 items (including 17 fruit and vegetable items) with ORAC values. TAC from the diet was adjusted for total energy intake with the residual method.[6] The validity of FFQ-based TAC estimates, as compared with plasma TAC measures using the ORAC method, assessed with Pearson correlation coefficients was 0.3 for ORAC from all foods and 0.4 for ORAC from fruit and vegetable consumption.[4] The validity of food items contributing to TAC of the diet as compared with food records was reasonably good. Pearson correlation coefficients ranged from 0.4 to 0.7 for individual fruit and vegetable items, 0.8 for tea consumption, and 0.5 for dietary fiber (A. Wolk, unpublished data).

Body mass index was calculated by dividing reported weight (kg) by reported height (m^2). Physical activity was calculated by multiplying the reported duration of predefined activities by the intensity of these activities expressed as multiples of the metabolic equivalent per day ($kcal \times kg^{-1} \times h^{-1}$) of sitting quietly for 1 hour. History of hypertension, hypercholesterolemia, and diabetes was assessed from the questionnaire and through linkage to the Swedish Hospital Discharge Registry and the National Diabetes Registry.

Identification of Cases and Follow-Up of the Cohort

Separate analyses were performed among 31 035 women who were CVD-free (no history of stroke, myocardial infarction, angina pectoris, atrial fibrillation, or congestive heart failure) at baseline as well as among 5680 women with a CVD history. Information on CVD was obtained by linkage to the Swedish Hospital Discharge Registry (International Statistical Classification of Disease, 10th Revision, code I11.0, I20–25, I48, I50, and I60–69), which provides nearly complete coverage of the discharges. Incident cases of stroke were classified as cerebral infarction (International Statistical Classification of Disease, 10th Revision, code I63), intracerebral hemorrhage (I61), subarachnoid hemorrhage (I60), and unspecified stroke (I64). Information on dates of death was obtained from the Swedish Cause of Death Registry. The registries for 1987 and 1995 were thoroughly validated and revealed high sensitivity (94%) and positive predictive value (86%).[7]

Statistical Analysis

Participants were followed from September 15, 1997, until the date of first stroke, death, or December 31, 2009, whichever came first. Women were categorized into quintiles (CVD-free cohort) or quartiles (cohort with CVD history) of dietary TAC. Quartiles were used for the cohort with a CVD history because of a smaller sample size. We also performed analyses using ORAC as a continuous variable using the unit of 5000 ORAC Trolox equivalents corresponding to approximately 1 SD in the cohort. Cox proportional hazards models with age as the time scale were used to estimate hazard ratios (HRs) with 95% CIs using the PHREG procedure in SAS (Version 9.1; SAS Institute, Inc, Cary, NC). In the multivariable models, we adjusted for potential confounders including body mass index (<18.5, 18.5–24.9, 25–29.9, 30+ kg/m^2), smoking (never, past, current (≤10, >10 cigarettes/day), alcohol consumption (gram/day, continuous), physical activity (metabolic equivalent hours in quartiles), educational level (<10, 10–12, >12 years), hypertension (yes/no), hypercholesterolemia (yes/no), diabetes (yes/no), family history of myocardial infarction before age 60 years (yes/no), aspirin use (yes/no), dietary supplement use (never/ever), energy intake (kcal/day, continuous), and coffee consumption (quartiles). Among women with a CVD history, we further adjusted for history of stroke (yes/no), myocardial infarction (yes/no), angina pectoris (yes/no), and atrial fibrillation (yes/no) at baseline. To assess trends across quintiles, we used the median value of each category to create a single continuous variable. The proportional hazards assumption was assessed by calculating scaled Schoenfeld residuals. We did not find evidence of violation of the proportional hazards assumption. The HR of stroke per 5000 increment of ORAC Trolox equivalents was corrected for bias due to dietary measurement error using data from our validation study in a subgroup of 108 women from the cohort.[4] The correction was done using the regression calibration method.[8]

To evaluate whether the effect of dietary TAC on stroke risk varied by potential risk factors, we performed subgroup analyses by age (<65/≥65 years), body mass index (≤25/>25 kg/m^2), high blood pressure (no/yes), alcohol consumption (nondrinkers/current drinkers), and smoking (nonsmokers/current smokers). The log likelihood ratio test was used to test statistical significance of interaction. All probability values shown are 2-sided. P values <0.05 were considered statistically significant.

Results

CVD-Free Cohort

The CVD-free cohort was followed up during a mean of 11.5 years (360 080 person-years) and a total of 1322 stroke cases (988 cerebral infarctions, 226 hemorrhagic strokes, 108 unspecified strokes) were identified. Compared with women in the lowest quintile of dietary TAC, those in the highest quintile were more likely to be nonsmokers, have higher education, have hypercholesterolemia, and to use dietary supplements (Table 1). Women with a high TAC consumed more fruits and vegetables (>2-fold) and tea (17-fold) but less coffee (38%). The major contributors to TAC of diet were fruit and vegetables, which contributed 50% of total TAC. The Pearson correlation coefficient between TAC of diet and fruit and vegetable consumption was 0.55. Other contributors were whole grains (18%), tea (16%) and chocolate (5%). We further investigated the changes in dietary TAC over time by comparing baseline intake (1997) with dietary TAC estimated in 1987 and observed a Pearson correlation coefficient of 0.5.

The HR of total stroke, cerebral infarction, and hemorrhagic stroke by quintiles of TAC of diet is presented in Table 2. In the multivariable-adjusted analyses, women in the highest quintile of dietary TAC had a significant 17% (95% CI, 1%–30%) lower risk of total stroke compared with women in the lowest quintile. Further adjustment for consumption of red meat and fish did not alter the results. The association was attenuated and not statistically significant after adjustment for fruit and vegetable consumption (as a continuous variable), which is the major contributor of dietary TAC (HR, 0.89; 95% CI, 0.71–1.11). Dietary TAC was inversely associated with both cerebral infarction and hemorrhagic stroke but results were not statistically significant.

The multivariable-adjusted HR of total stroke for an increment of 5000 ORAC Trolox equivalents units/day was

Table 1. Age-Standardized Baseline Characteristics of Women in the Swedish Mammography Cohort

	Total Antioxidant Capacity of the Diet*				
	CVD-Free†			CVD History‡	
Characteristics	Q1 (n=6207)	Q3 (n=6207)	Q5 (n=6207)	Q1 (n=1420)	Q4 (n=1420)
Median ORAC, μmol Trolox equivalents/d	7444	12 214	19 197	7670	18 370
Nondietary factors					
Age, y, mean (SD)	60.6 (9.0)	60.5 (8.6)	60.3 (8.7)	69.1 (8.5)	68.7 (8.2)
>12 y of education, %	11.9	19.4	30.0	4.7	16.8
Current smokers, %	36.8	20.9	16.3	26.1	13.9
Body mass index, mean kg/m^2 (SD)	25.0 (4.0)	24.9 (3.7)	24.7 (3.7)	25.8 (4.3)	25.5 (4.2)
Current total physical activity score (MET×h/d), mean (SD)	42.4 (4.3)	42.6 (4.1)	42.6 (4.1)	41.6 (4.4)	42.2 (4.2)
Stroke, %				11.5	7.9
Myocardial infarction, %				15.8	18.7
Angina pectoris, %				31.4	33.6
Atrial fibrillation, %				60.4	61.4
Hypertension, %	17.5	18.4	18.5	39.1	38.0
Hypercholesterolemia, %	6.5	7.3	7.7	13.5	17.0
Diabetes, %	3.2	3.3	3.6	10.0	10.9
Family history of myocardial infarction, %	12.5	13.1	12.6	16.3	19.6
Aspirin use, %	43.0	42.0	42.6	51.1	53.4
Dietary supplement use, %	50.7	58.1	61.0	49.5	57.9
Alcohol, g/d (SD)	5.3 (12.1)	5.7 (7.2)	5.6 (8.8)	3.3 (6.8)	3.8 (7.2)
Total energy intake, kcal/d (SD)	1754 (590)	1753 (498)	1720 (507)	1681 (592)	1640 (534)
Foods, mean (SD)					
Fruits and vegetables, servings/d	3.4 (1.6)	5.4 (2.0)	7.7 (3.5)	3.4 (1.8)	7.1 (3.5)
Whole grains, servings/d	3.4 (2.1)	3.8 (2.0)	3.7 (1.9)	3.6 (2.3)	3.8 (2.0)
Tea, servings/wk	0.7 (1.9)	3.5 (4.4)	12.0 (12.9)	0.8 (2.1)	10.0 (11.6)
Chocolate, servings/wk	0.8 (1.0)	1.0 (1.4)	1.1 (1.8)	0.7 (1.0)	1.1 (1.7)
Coffee, servings/d	3.6 (2.0)	3.0 (1.7)	2.3 (1.8)	3.2 (1.9)	2.1 (1.6)
Red meat, servings/wk	7.8 (5.8)	7.8 (4.9)	7.0 (4.8)	8.1 (7.1)	7.2 (5.6)
Fish, servings/wk	2.1 (2.9)	2.1 (1.9)	2.2 (1.8)	2.4 (3.4)	2.5 (2.3)

CVD indicates cardiovascular disease; Q, quartile; ORAC, oxygen radical absorbance capacity; MET, metabolic equivalents.
*Total antioxidant capacity intake (μmol Trolox equivalents/d) was measured with the oxygen radical absorbance capacity assay.
†Women (n=31 035) were categorized into quintiles of total antioxidant capacity of diet.
‡Women (n=5680) were categorized into quartiles of total antioxidant capacity of diet.

0.94 (95% CI, 0.89–1.00). After correction for measurement error in dietary TAC, the corresponding HR was 0.81 (95% CI, 0.67–1.00). An increase of 5000 ORAC units is equivalent to approximately 1 or 2 apples, 2 oranges, or 2 cups of tea.

To investigate potential reversed causality, we excluded all stroke cases that occurred in the first 3 years of follow-up. In this analysis, women in the highest quintile of dietary TAC had a 16% (95% CI, 0%–30%) lower risk of total stroke, indicating that our results were unlikely due to reversed causality. The association between TAC of the diet and total stroke was not modified by age, body mass index, high blood pressure, alcohol consumption, or smoking (all *P* for interaction >0.14).

Cohort With a CVD History

During an average follow-up of 9.6 years (57 124 person-years) of the cohort with a CVD history, we identified 1007 stroke cases (796 cerebral infarctions and 100 hemorrhagic strokes, 111 unspecified strokes). Characteristics of the cohort with a CVD history are shown in Table 1.

There was no statistical significant association between TAC of the diet and risk of total stroke or cerebral infarction among women with a CVD history (Table 3). However, in the multivariable-adjusted analysis, women in the highest 3 quartiles of dietary TAC had a statistically significant 46% to 57% lower risk of hemorrhagic stroke compared with those in the lowest quintile. After adjustment for fruit and vegetable consumption, the inverse association was not statistically

Table 2. Relative Risk of Stroke by Quintiles of Total Antioxidant Capacity of the Diet Among Cardiovascular Disease-Free Women in the Swedish Mammography Cohort (n=31 035)

Total Antioxidant Capacity of the Diet*						
CVD-Free Cohort	Q1	Q2	Q3	Q4	Q5	*P* for Trend
Total stroke						
No. of cases	299	273	259	255	236	
Person-time, y	70 829	72 208	72 066	72 158	72 819	
Age-adjusted HR	1.00	0.88 (0.75–1.05)	0.86 (0.72–1.01)	0.83 (0.70–0.98)	0.78 (0.66–0.98)	0.004
Multivariable HR†	1.00	0.92 (0.78–1.09)	0.90 (0.76–1.07)	0.88 (0.74–1.04)	0.83 (0.70–0.99)	0.04
Cerebral infarction						
No. of cases	222	207	189	188	182	
Age-adjusted HR	1.00	0.91 (0.75–1.10)	0.84 (0.69–1.02)	0.82 (0.68–1.00)	0.81 (0.67–0.99)	0.03
Multivariable HR†	1.00	0.94 (0.78–1.14)	0.88 (0.73–1.08)	0.87 (0.71–1.06)	0.87 (0.71–1.07)	0.14
Hemorrhagic stroke						
No. of cases	50	44	49	48	35	
Age-adjusted HR	1.00	0.86 (0.57–1.29)	0.96 (0.65–1.43)	0.94 (0.63–1.39)	0.69 (0.45–1.06)	0.14
Multivariable HR†	1.00	0.90 (0.60–1.35)	1.04 (0.70–1.55)	1.02 (0.68–1.54)	0.74 (0.47–1.17)	0.30

CVD indicates cardiovascular disease; Q, quartile; HR, hazard ratio.

*Total antioxidant capacity intake (μmol Trolox equivalents/d) was measured with the oxygen radical capacity absorbance assay.

†Adjusted for age, education, smoking, body mass index, physical activity, hypertension, hypercholesterolemia, diabetes, family history of myocardial infarction, aspirin use, dietary supplement use, and intakes of total energy, alcohol, and coffee.

significant (HR, 0.59; 95% CI, 0.30–1.17). Among the hemorrhagic stroke cases, compared with women in the highest 3 quartiles of dietary TAC, those in the lowest quartile were more likely to have a history of stroke (Quartile 1: 30%, Quartile 2: 18%, Quartile 3: 23%, Quartile 4: 9%).

Discussion

In this large prospective population-based cohort, TAC of the diet was statistically significantly inversely associated with risk of total stroke among women who were CVD-free at baseline. Among women with a CVD history, those in the highest 3 quartiles of dietary TAC had a lower risk of hemorrhagic stroke but not total stroke or cerebral infarction.

There is only 1 previous prospective study that has examined the association between TAC of the diet and stroke risk in CVD-free men and women. That study included 112 cerebral infarctions and 48 hemorrhagic stroke cases and found an inverse association between dietary TAC and risk of

Table 3. Relative Risk of Stroke by Quartiles of Total Antioxidant Capacity of Diet Among Women With a Cardiovascular Disease History at Baseline in the Swedish Mammography Cohort (n=5680)

Total Antioxidant Capacity of the Diet*					
Cohort With a CVD History	Q1	Q2	Q3	Q4	*P* for Trend
Total stroke					
No. of cases	272	248	233	245	
Person-time, y	13 780	14 370	14 445	14 529	
Age-adjusted HR	1.00	0.85 (0.71–1.00)	0.81 (0.68–0.97)	0.90 (0.76–1.07)	0.31
Multivariable HR†	1.00	0.86 (0.72–1.02)	0.82 (0.68–0.98)	0.90 (0.75–1.07)	0.30
Cerebral infarction					
No. of cases	206	197	188	205	
Age-adjusted HR	1.00	0.88 (0.73–1.08)	0.87 (0.71–1.06)	0.96 (0.79–1.17)	0.80
Multivariable HR†	1.00	0.90 (0.74–1.10)	0.87 (0.71–1.06)	0.96 (0.79–1.18)	0.82
Hemorrhagic stroke					
No. of cases	39	20	18	23	
Age-adjusted HR	1.00	0.48 (0.28–0.82)	0.44 (0.25–0.76)	0.56 (0.34–0.94)	0.03
Multivariable HR†	1.00	0.47 (0.27–0.82)	0.43 (0.25–0.76)	0.54 (0.32–0.93)	0.03

CVD indicates cardiovascular disease; Q, quartile; HR, hazard ratio.

*Total antioxidant capacity intake (μmol Trolox equivalents/d) was measured with the oxygen radical absorbance capacity assay.

†Adjusted for age, education, smoking, body mass index, physical activity, stroke, myocardial infarction, angina pectoris, atrial fibrillation, hypertension, hypercholesterolemia, diabetes, family history of myocardial infarction, aspirin use, dietary supplement use, and intakes of total energy, alcohol, and coffee.

cerebral infarction (HR, 0.41; 95% CI, 0.23–0.74 for highest versus lowest category) and a nonsignificant positive association with hemorrhagic stroke.[5] To the best of our knowledge, no study has assessed the relation between TAC of diet and stroke risk in participants with a CVD history at baseline. Previous studies have found inverse associations between consumption of major contributors of TAC such as fruit and vegetables,[2] cereals,[9–11] tea,[12] and chocolate[13,14] and risk of stroke.

Antioxidants are hypothesized to inhibit the atherosclerotic process by reducing reactive oxygen species and reactive nitrogen species.[15] Other potential mechanisms whereby antioxidants, especially flavonoids, may affect the atherosclerotic process include improved endothelial function, reduced platelet aggregation, lowered blood pressure, and anti-inflammatory effects.[16]

It may seem contradicting that randomized controlled trials have failed to show beneficial effects of antioxidant supplementation on stroke risk. A meta-analysis of randomized controlled trials on vitamin E supplementation and risk of stroke reported decreased risk of cerebral infarction but increased risk of hemorrhagic stroke.[17] Other randomized controlled trials on high-dose antioxidants supplements of 1 to 3 compounds[18,19] and randomized controlled trials on low-dose antioxidant supplements of 2 compounds have reported no effect on stroke risk.[20] In contrast to randomized controlled trials of a limited number of antioxidants, we aimed to examine antioxidant intake by taking into account all antioxidants present in the diet, including thousands of compounds, in doses obtained from a usual diet.

In the cohort of women with a CVD history at baseline, we observed a reduced risk of hemorrhagic stroke among women in the highest 3 quartiles of dietary TAC. The observed association may be explained by the fact that women in the lowest quartile were more likely to have a history of stroke and thus may be more likely to get hemorrhagic stroke.[21] However, the inverse association remained when we adjusted for a history of stroke. Women with a CVD history may control their blood pressure or change their lifestyles because of knowledge of their disease. This might have produced a spurious inverse association between TAC of the diet and risk of hemorrhagic stroke.

There are several strengths with our study including the prospective and population-based design, detailed data on diet and other potential risk factors for stroke, the almost complete follow-up of the cohort, and the large number of stroke cases. Our study also has some limitations. First, in the present study, we only used dietary information from 1 FFQ, which was administered at baseline (in 1997) because of more information on potential confounders compared with the 1987 questionnaire. However, the correlation between TAC of the diet between the 1997 FFQ and the FFQ administered in 1987 was 0.5. The FFQ assessed frequency of consumption but not the exact amount (in grams) of food consumption, which is also a limitation because of individual variations in portion sizes. In addition, we did not have ORAC values for Swedish foods. We therefore used the American ORAC database. Geographic location and growing conditions can affect the antioxidant content in foods. Our results may also have been affected by measurement error of self-reported dietary intake. Because of the prospective design, any measurement error and resulting misclassification of exposure is most likely to be nondifferential and would tend to attenuate the true association. We were able to correct for measurement error in TAC of the diet and found an even stronger inverse association after this correction. The correlation between TAC of the diet and plasma TAC was somewhat weak,[4] which can be partly explained by that plasma TAC values are influenced by many factors such as endogenous antioxidants, homeostatic control mechanisms of plasma antioxidants, absorption, and the extent of the metabolism of dietary antioxidants.[22] Another limitation is that blood pressure and serum cholesterol concentrations were not measured at baseline. Finally, women with a high antioxidant intake may be more health-conscious and have other healthy behaviors, which may have influenced our results. However, the observed inverse association between dietary TAC and stroke persisted after further adjustments for potential confounders related to healthy behavior such as smoking, physical activity, and education.

In conclusion, our results suggest that TAC of the diet may be of importance for the prevention of total stroke among CVD-free women and hemorrhagic stroke among women with a CVD history. Additional studies of the association between TAC of diet and stroke are needed. Future studies should assess whether the association between TAC and stroke varies for different stroke subtypes and between CVD-free populations and populations with a CVD history.

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Disclosures

None.

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