ONLINE FIRST

Lifestyle Factors on the Risks of Ischemic and Hemorrhagic Stroke

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Background: The joint effects of different lifestyle factors on stroke risk are still to some extent unclear, especially regarding hemorrhagic stroke.

Methods: We prospectively investigated the association of different indicators of lifestyle (smoking, body mass index, physical activity, and vegetable and alcohol consumption) with total and type-specific stroke incidence among 36 686 Finnish participants who were 25 to 74 years old and free of coronary heart disease and stroke at baseline.

Results: During a mean follow-up period of 13.7 years, 1478 people developed an incident stroke event (1167 ischemic and 311 hemorrhagic). The multivariate-adjusted (age, sex, education, family history of stroke, history of diabetes mellitus, systolic blood pressure, and serum total cholesterol level) hazard ratios associated with adherence to 0 to 1 (reference group), 2, 3, 4, and 5 healthy lifestyle indicators were 1, 0.66, 0.57, 0.51, and 0.33 ($P<.001$ for trend) for total stroke; 1, 0.67, 0.60, 0.50, and 0.30 ($P<.001$ for trend) for ischemic stroke; and 1, 0.63, 0.49, 0.49, and 0.40 ($P<.001$ for trend) for hemorrhagic stroke, respectively. These inverse associations were similar in both men and women. The partial population attributable risk percentages associated with adherence to 3, 4, and 5 healthy lifestyle indicators were 26.3%, 43.8%, and 54.6% for total stroke; 22.7%, 45.3%, and 59.7% for ischemic stroke; and 35.0%, 35.0%, and 36.1% for hemorrhagic stroke, respectively.

Conclusion: Healthy lifestyle factors are associated with a lower risk of stroke, and there is a graded inverse association between the number of healthy lifestyle indicators and the risks of total, ischemic, and hemorrhagic stroke.

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STROKE IS ONE OF THE LEADING causes of death worldwide, and the quality-of-life decrements after stroke exceed that of myocardial infarction.[1-3] Many previous studies focused on the pharmacologic management and improved therapies for acute stroke. Although these treatments have been proven to be beneficial, they are costly, require medical intervention, and may have adverse effects. Moreover, the functional recovery is often incomplete.[4] Therefore, primary prevention of stroke is considered to be the most effective strategy in controlling stroke and its consequences.[5]

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There is good evidence that a healthy lifestyle can reduce the risk of cardiovascular disease and that patterns based on combinations of multiple of healthy lifestyle factors (HLFs) may be more effective than any single factor alone in lowering the risk of cardiovascular disease.[6,7] The associations of lifestyle factors (including physical activity[8,9]; smoking[10]; alcohol consumption[11]; body mass index [BMI], calculated as weight in kilograms divided by height in meters squared[12]; and dietary factors[13,14]) with the risk of stroke have been studied, but results are inconsistent. Furthermore, only a few studies have assessed the joint effects of lifestyle factors on stroke risk, especially regarding hemorrhagic stroke.[15,16]

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The aim of the present study is to assess the individual and joint associations of multiple lifestyle factors with the risks of ischemic and hemorrhagic stroke.

METHODS

PARTICIPANTS

Five independent cross-sectional population surveys were performed in 6 geographic areas of Finland in 1982, 1987, 1992, 1997, and 2002.[17] The sample was stratified by area, sex, and 10-year age group according to the World Health Organization (WHO) MONICA (MONItoring trends and determinants of CArdiovascular disease) protocol.[18] The participation rate varied by year from 65% to 88%.[17] The participants included in the 5 surveys were 25 to 64 years old, and the 1997 and 2002 surveys also included individuals 65 to 74 years old. People who participated in more than 1 survey were included only in the first survey cohort. The total sample size of the 5 surveys was 38 737. After excluding participants with a history of coronary heart disease (1090 persons) or stroke (775 persons) at baseline, and those with incomplete data for any required variables (186 persons), the present analyses include 17 287 men and 19 399 women. The participants gave an informed consent (verbal consents in 1982, 1987, and 1992, and signed consents in 1997 and 2002). These surveys were conducted according to the ethical rules of the National Public Health Institute, and the investigations were performed in accordance with the Declaration of Helsinki.

BASELINE MEASUREMENTS

A self-administered questionnaire was sent to the participants to be completed at home. The questionnaire included questions on medical history, socioeconomic factors, physical activity, smoking habits, alcohol consumption, and diet. Education level, measured as the total number of school years, was divided into birth cohort–specific tertiles. A family history of stroke was defined as a history of those whose mothers or fathers were once diagnosed as having stroke. History of myocardial infarction, stroke or diabetes mellitus (DM) at baseline was obtained from the questionnaire and collected by hospital discharge or National Social Insurance Institution's drug register (DM only).[19]

A detailed description of the questions on occupational and leisure-time physical activity has been presented elsewhere.[8,19-21] Since we found that moderate and high occupational or leisure-time physical activity independently and significantly reduced stroke risk,[8] these activities were merged into 3 categories: "low" when participants reported light levels of both occupational and leisure time physical activity, "moderate" when participants reported moderate or high level of either occupational or leisure time physical activity, and "high" when individuals reported a moderate or high level of both occupational and leisure-time physical activity. Based on the response, participants were classified as never, ever, and current smokers. Types of smoking included filter or nonfilter cigarettes, pipes, and cigars. Alcohol consumption was categorized into 4 groups: none, 1 to 34, 35 to 209, and 210 or more grams per week in men, and none, 1 to 34, 35 to 139, and 140 or more grams per week in women. The frequency of consumption of vegetables and fruits over the past week (<1 time/week, 1-2 times/week, 3-6 times/week, ≥7 times/week) was inquired.[22]

At the study center, specially trained nurses measured height, weight, and blood pressure using the standardized protocol as described in the WHO MONICA project.[18] Height and weight were measured without shoes and with light clothing. The measurements of height were rounded to the nearest centimeter and weight to the nearest 100 g. Blood pressure was measured from the right arm of the participant after 5 minutes of sitting using a mercury sphygmomanometer in each survey. After blood pressure measurement, venous blood specimen was taken. The serum total cholesterol level was determined by an enzymatic method (CHOD-PAP; Boehringer Mannheim, Mannheim, Germany). All samples were analyzed in the same central laboratory at the National Public Health Institute.[23]

DEFINITION OF HEALTHY LIFESTYLE

We considered 5 HLFs in our analyses, and fruit consumption was dropped from the analyses because no statistically significant association of fruit consumption with stroke risk was found (**Table 1**). Each lifestyle factor was dichotomized into unhealthy and healthy categories that were based mostly on total and ischemic stroke results (Table 1 and **Table 2**): smoking (current or ever vs never), BMI (≥25 vs <25), physical activity (low vs moderate or high), vegetable consumption (≤2 vs ≥3 times per week), and alcohol consumption (none or ≥210 g/week in men and ≥140 g/week in women vs 1-209 g/week in men and 1-139 g/week in women). Each person could have a minimum of 0 and maximum of 5 HLFs.

PROSPECTIVE FOLLOW-UP

The survey cohorts were followed until the end of 2007 through computerized register linkage by a unique personal identification number. Mortality data were obtained from Statistics Finland and data on nonfatal events from the National Hospital Discharge Register. Several editions of the *International Classification of Diseases* (*ICD*) were used to identify hemorrhagic stroke (*ICD 8* and *ICD 9*, codes 430-431; and *ICD 10*, codes I60-I62), ischemic stroke (*ICD 8* and *ICD 9*, codes 432-438; and *ICD 10*, codes I63-I66), and any stroke (*ICD 8* and *ICD 9*, codes 430-438; and *ICD 10*, code I60-I66) events. *ICD-9*, code 432, was classified as a hemorrhagic stroke. The stroke events occurred before the baseline survey were identified from the Hospital Discharge Register retrospectively and were excluded from the analyses. The validity of the diagnosis of acute stroke in Finland is good for hospital discharge register (agreement in 90% for all strokes, 82% for hemorrhage, and 90% for ischemic stroke) and death register (agreement in 97% for all strokes, 95% for hemorrhage, and 92% for ischemic stroke).[24] End points during follow-up were incident stroke events, defined as either the first nonfatal stroke event, or stroke death without a preceding nonfatal event.

STATISTICAL ANALYSIS

Differences in risk factors at different levels of HLFs were tested using analysis of variance or logistic regression after adjustment for age and study year. The Cox proportional hazards model was used to evaluate the association between each of the modifiable lifestyle factors and stroke risk. Then, the association between combinations of HLFs with stroke risk was analyzed using the Cox proportional hazards model. Because the interactions between sex and each of lifestyle factors with stroke risk were not statistically significant, men and women were combined in some analyses. The reference group, with an HLF ranging from 0 to 1, was chosen rather than the group with adherence to 0 HLF because stroke risk did not differ between groups with HLFs of 0 and 1 (hazard ratio [HR], 1), and the samples of the group with 0 HLF were small (487 persons). Thus, the reference group contained larger numbers of participants, making the statistical comparisons more

Table 1. Hazard Ratios (HRs) for Stroke According to Different Lifestyle Factors

Lifestyle Factors	Participants, No.	Total Stroke		Ischemic Stroke		Hemorrhagic Stroke	
		Cases, No.	HR (95% CI)[a]	Cases, No.	HR (95% CI)[a]	Cases, No.	HR (95% CI)[a]
Physical activity							
Light	4887	297	1 [Reference]	241	1 [Reference]	56	1 [Reference]
Moderate	17 463	750	0.84 (0.73-0.96)	604	0.85 (0.73-0.99)	149	0.82 (0.60-1.13)
High	14 336	431	0.73 (0.65-0.89)	323	0.74 (0.62-0.88)	106	0.84 (0.60-1.19)
P value for trend			.003		.004		.47
Smoking status							
Never	19 712	722	1 [Reference]	596	1 [Reference]	126	1 [Reference]
Ever	6662	303	1.19 (1.02-1.38)	242	1.11 (0.94-1.31)	61	1.55 (1.11-2.17)
Current	10 312	453	1.79 (1.56-2.05)	330	1.62 (1.39-1.90)	124	2.56 (1.92-3.41)
P value for trend			<.001		<.001		<.001
Alcohol consumption, g/wk							
0	16 381	832	1 [Reference]	691	1 [Reference]	141	1 [Reference]
1-35	5921	186	0.85 (0.73-1.00)	142	0.80 (0.66-0.96)	44	1.11 (0.79-1.57)
<210 in men, <140 in women	12 138	366	0.98 (0.86-1.12)	279	0.94 (0.80-1.09)	88	1.21 (0.90-1.63)
≥210 in men, ≥140 in women	2246	94	1.43 (1.14-1.80)	56	1.10 (0.83-1.47)	38	2.73 (1.83-4.07)
P value for trend			.001		.07		<.001
BMI							
<25.0	15 481	399	1 [Reference]	296	1 [Reference]	102	1 [Reference]
25.0-29.9	14 468	645	1.11 (0.98-1.26)	511	1.15 (0.99-1.33)	137	1.04 (0.80-1.35)
≥30.0	6737	434	1.33 (1.15-1.53)	361	1.45 (1.23-1.70)	72	0.97 (0.70-1.34)
P value for trend			<.001		<.001		.90
Fruit consumption, times/wk							
<1	3751	203	1 [Reference]	165	1 [Reference]	38	1 [Reference]
1-2	11 046	490	0.93 (0.79-1.11)	387	0.90 (0.74-1.08)	102	1.07 (0.73-1.58)
3-6	11 108	402	0.95 (0.80-1.14)	307	0.89 (0.73-1.09)	95	1.21 (0.81-1.81)
≥7	10 781	383	0.99 (0.82-1.20)	309	0.99 (0.80-1.22)	76	1.04 (0.67-1.59)
P value for trend			.80		.42		.69
Vegetable consumption, times/wk							
<1	3885	278	1 [Reference]	224	1 [Reference]	54	1 [Reference]
1-2	11 195	541	0.96 (0.82-1.11)	434	0.98 (0.83-1.16)	107	0.86 (0.61-1.21)
3-6	12 926	422	0.83 (0.71-0.98)	326	0.84 (0.70-1.01)	98	0.80 (0.55-1.15)
≥ 7	8680	237	0.82 (0.67-1.00)	184	0.84 (0.67-1.04)	52	0.71 (0.46-1.09)
P value for trend			.06		.11		.45

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).
[a]Adjusted for age, study year, sex, smoking, physical activity, vegetable consumption, fruit consumption, education, alcohol consumption, family history of stroke, history of diabetes mellitus, BMI, systolic blood pressure, and total cholesterol level, other than the variable in the analytic model.

Table 2. Hazard Ratios (HRs) for Stroke According to Different Lifestyle Factors by 2 Categories (Healthy vs Nonhealthy)

Lifestyle Factors	Participants, No.	Total Stroke		Ischemic Stroke		Hemorrhagic Stroke	
		Cases, No.	HR (95% CI)[a]	Cases, No.	HR (95% CI)[a]	Cases, No.	HR (95% CI)[a]
Physical activity							
Light	4887	297	1 [Reference]	241	1 [Reference]	56	1 [Reference]
Moderate or high	31 799	1181	0.78 (0.68-0.89)	927	0.77 (0.67-0.90)	255	0.81 (0.60-1.08)
Smoking status							
Current or ever	16 974	756	1 [Reference]	572	1 [Reference]	185	1 [Reference]
Never	19 712	722	0.64 (0.57-0.73)	596	0.72 (0.63-0.82)	126	0.43 (0.33-0.56)
Alcohol consumption, g/wk							
None or ≥210 in men, ≥140 in women	18 627	926	1 [Reference]	747	1 [Reference]	179	1 [Reference]
1-209 In men, 1-139 In women	18 059	552	0.88 (0.79-0.99)	421	0.87 (0.76-0.98)	132	0.96 (0.76-1.21)
BMI							
≥25	21 205	1079	1 [Reference]	872	1 [Reference]	209	1 [Reference]
<25	15 481	399	0.88 (0.78-0.99)	296	0.83 (0.73-0.95)	102	1.02 (0.80-1.31)
Vegetable consumption, times/wk							
≤2	15 080	819	1 [Reference]	658	1 [Reference]	161	1 [Reference]
≥3	21 606	659	0.83 (0.75-0.93)	510	0.83 (0.73-0.94)	150	0.85 (0.67-1.07)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HR, hazard ratio.
[a]Adjusted for age, study year, sex, smoking, physical activity, education, vegetable consumption, alcohol consumption, family history of stroke, history of diabetes mellitus, BMI, systolic blood pressure, and total cholesterol level, other than the variable in the analytic model.

Table 3. General Characteristics of Study Participants at Baseline[a]

Characteristic	Healthy Lifestyle Factors, No.				
	0-1	2	3	4	5
Participants, No.	3976	9161	12,093	8713	2743
Age at baseline, y	48.7	47.4	46.1	43.8	41.4
BMI	29.3	28.0	26.5	24.4	22.5
Diastolic BP, mm Hg	85.9	84.1	82.1	79.6	77.9
Systolic BP, mm Hg	143	141	140	133	130
Serum cholesterol level, mg/dL	235.5	230.5	222.8	214.3	204.6
Education, y	9.2	9.7	10.8	12.1	13.6
Alcohol consumption, g/wk	73.2	57.2	46.6	44.3	48.9
Moderate or high physical activity, %	48.4	81.8	92.6	96.8	100
Vegetable consumption ≥3 times/wk, %	8.0	32.1	64.9	88.9	100
Ever or current smoker, %	51.5	38.8	27.8	15.5	0
History of DM, %	3.6	2.9	2.2	1.3	1.2

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; DM, diabetes mellitus.
SI conversion factor: To convert serum cholesterol to millimoles per liter, multiply by 0.0259.
[a]Values represent mean or percentage; adjusted for age and study year. Healthy lifestyle factors are defined as a moderate or high level of physical activity; never smoking; alcohol consumption, none or 1 to 209 g/week in men, and 1 to 139 g/week in women; a BMI lower than 25; and vegetable consumption at least 3 times/week. $P < .001$ for all comparisons.

stable. All the analyses were performed first adjusting for age and baseline study year and further adjusting for education and family history of stroke (multivariate model 1), and for potential intermediate factors (systolic blood pressure, total serum cholesterol level, and history of DM) on the causal pathway of lifestyle factor with stroke risk (multivariate model 2). To avoid a potential bias due to severe or subclinical diseases at baseline, additional analyses were performed, excluding participants who were subsequently diagnosed as having stroke (107 participants) or who died during the first 2 years of follow-up after baseline survey (181 participants). To estimate the proportion of new stroke cases occurring in this population that hypothetically could have been prevented if all participants had been in healthy lifestyle group, the partial population attributable risk percentage (PAR%) and 95% CIs were calculated by using SAS statistical software for Windows (version 9.12; SAS Institute Inc, Cary, North Carolina).[25] Statistical significance was considered to be $P < .05$. All statistical analyses were performed with PASW for Windows (version 18.0; SPSS Inc, Chicago, Illinois) and SAS software for Windows, version 9.12.

RESULTS

During a mean follow-up period of 13.7 years, we identified 1478 stroke events (1167 ischemic and 311 hemorrhagic) in the study cohort. General characteristics of the study population at baseline are presented in **Table 3**.

Physical activity and vegetable consumption were inversely associated with, whereas smoking and BMI were directly associated with, total and ischemic stroke risk in multivariate-adjusted (model 2) analyses (Table 1). Only smoking was significantly and directly associated with hemorrhagic stroke risk. There was no apparent association between fruit consumption and stroke risk. Alcohol drinking showed a J-shaped association with total and ischemic stroke risk (ie, people with light to moderate alcohol drinking had the lowest risk).

The association between each dichotomized variable and stroke risk is presented in Table 2. Each of the HLFs (never smoking, maintaining normal BMI, moderate or high level of physical activity, vegetable consumption ≥3 times per week, and light or moderate alcohol drinking) was significantly associated with a reduced risk of total and ischemic stroke and was associated with a reduced trend of hemorrhagic stroke risk.

The multivariate-adjusted (model 1) HRs associated with adherence to 0 to 1 (reference group), 2, 3, 4, and 5 HLFs were 1, 0.68, 0.60, 0.59, and 0.35 ($P < .001$ for trend) for total stroke; 1, 0.72, 0.62, 0.59, and 0.32 ($P < .001$ for trend) for ischemic stroke; and 1, 0.55, 0.51, 0.54, and 0.39 ($P = .01$ for trend) for hemorrhagic stroke in men; and 1, 0.61, 0.50, 0.38, and 0.26 ($P < .001$ for trend) for total stroke; 1, 0.59, 0.52, 0.37, and 0.23 ($P < .001$ for trend) for ischemic stroke; and 1, 0.71, 0.45, 0.41, and 0.35 ($P = .004$ for trend) for hemorrhagic stroke in women, respectively (**Table 4**). Further adjustment for systolic blood pressure, total cholesterol level, and history of DM affected the results slightly.

The inverse associations between the number of HLFs and the risks of total, ischemic, and hemorrhagic stroke were present in participants in both age groups (25-49 years and 50-74 years), both those with and those without hypertension, both with and without a history of DM, and of total cholesterol levels lower than 251.0 mg/dL and 251.0 mg/dL or greater at baseline (**Table 5**) (to convert cholesterol to millimoles per liter, multiply by 0.0259). Exclusion of the persons who were diagnosed as having stroke (107 participants) or died during the first 2 years of follow-up (181 participants) did not affect the associations between the number of HLFs and stroke risk (data not shown).

A total of 64.2% of participants had at least 3 HLFs, 31.2% had at least 4 HLFs, and 7.5% had all 5 HLFs (Table 3). We also estimated the reduction in total and type-specific stroke risk for participants with 3 (never smoking, moderate or high level of physical activity, and vegetable consumption ≥3 times per week), 4 (these 3 factors plus maintaining normal BMI) and all 5 HLFs. The partial PAR% associated with adherence to 3, 4, and 5 HLFs, respectively, were 26.3% (95% CI, 17.7%-

Table 4. Hazard Ratios (HRs) of Stroke According to Number of Healthy Lifestyle Factors

Characteristic	Healthy Lifestyle Factors, No. 0-1	2	3	4	5	*P* Value for Trend
Men						
Total stroke						
Participants, No.	2256	5082	5594	3165	890	
Incidence cases, No.	203	259	215	92	11	
Person-years, No.	32 846	69 692	76 911	42 366	12 024	
Age and study years, adjusted HR (95% CI)	1 [Reference]	0.67 (0.56-0.81)	0.57 (0.47-0.70)	0.55 (0.43-0.71)	0.32 (0.17-0.58)	<.001
Model 1, HR (95% CI)[a]	1 [Reference]	0.68 (0.57-0.82)	0.60 (0.49-0.72)	0.59 (0.46-0.76)	0.35 (0.19-0.65)	<.001
Model 2, HR (95% CI)[b]	1 [Reference]	0.70 (0.58-0.84)	0.62 (0.51-0.76)	0.64 (0.50-0.83)	0.40 (0.22-0.74)	<.001
Ischemic stroke						
Incidence case, No.	161	214	172	68	7	
Age and study years, adjusted HR (95% CI)	1 [Reference]	0.70 (0.57-0.86)	0.59 (0.48-0.73)	0.54 (0.41-0.72)	0.28 (0.13-0.60)	<.001
Model 1, HR (95% CI)[a]	1 [Reference]	0.72 (0.59-0.88)	0.62 (0.50-0.77)	0.59 (0.44-0.79)	0.32 (0.15-0.68)	<.001
Model 2, HR (95% CI)[b]	1 [Reference]	0.73 (0.60-0.90)	0.65 (0.52-0.80)	0.64 (0.48-0.86)	0.36 (0.17-0.77)	<.001
Hemorrhagic stroke						
Incidence cases	42	45	43	23	4	
Age and study years, adjusted HR (95% CI)	1 [Reference]	0.55 (0.36-0.84)	0.51 (0.33-0.78)	0.55 (0.33-0.92)	0.40 (0.14-1.13)	.01
Model 1, HR (95% CI)[a]	1 [Reference]	0.55 (0.36-0.84)	0.51 (0.33-0.78)	0.54 (0.32-0.90)	0.39 (0.14-1.11)	.01
Model 2, HR (95% CI)[b]	1 [Reference]	0.57 (0.37-0.87)	0.54 (0.35-0.84)	0.61 (0.36-1.04)	0.47 (0.16-1.34)	.04
Women						
Total stroke						
Participants, No.	1420	4079	6499	5548	1853	
Incidence cases, No.	123	221	234	103	17	
Person-years, No.	19 666	58 813	91 538	75 283	24 095	
Age and study years, adjusted HR (95% CI)	1 [Reference]	0.62 (0.50-0.77)	0.51 (0.41-0.63)	0.37 (0.29-0.49)	0.25 (0.15-0.42)	<.001
Model 1, HR (95% CI)[a]	1 [Reference]	0.61 (0.49-0.77)	0.50 (0.40-0.63)	0.38 (0.29-0.50)	0.26 (0.15-0.43)	<.001
Model 2, HR (95% CI)[b]	1 [Reference]	0.62 (0.50-0.78)	0.52 (0.42-0.65)	0.40 (0.31-0.52)	0.28 (0.16-0.46)	<.001
Ischemic stroke						
Incidence cases, No.	99	170	189	77	11	
Age and study years, adjusted HR (95% CI)	1 [Reference]	0.60 (0.47-0.76)	0.52 (0.41-0.67)	0.37 (0.28-0.51)	0.23 (0.12-0.42)	<.001
Model 1, HR (95% CI)[a]	1 [Reference]	0.59 (0.46-0.76)	0.52 (0.41-0.67)	0.37 (0.28-0.51)	0.23 (0.12-0.43)	<.001
Model 2, HR (95% CI)[b]	1 [Reference]	0.60 (0.47-0.77)	0.54 (0.42-0.69)	0.40 (0.29-0.54)	0.24 (0.13-0.46)	<.001
Hemorrhagic stroke						
Incidence cases, No.	24	52	45	27	6	
Age and study years, adjusted HR (95% CI)	1 [Reference]	0.73 (0.45-1.18)	0.45 (0.27-0.74)	0.40 (0.23-0.71)	0.33 (0.13-0.82)	.002
Model 1, HR (95% CI)[a]	1 [Reference]	0.71 (0.44-1.16)	0.45 (0.27-0.74)	0.41 (0.23-0.73)	0.35 (0.14-0.87)	.004
Model 2, HR (95% CI)[b]	1 [Reference]	0.72 (0.44-1.17)	0.46 (0.28-0.76)	0.43 (0.24-0.76)	0.37 (0.15-0.93)	.007
Men and Women Combined[c]						
Total stroke						
Patients, No.	3976	9161	12 093	8713	2743	
Incidence cases, No.	326	480	449	195	28	
Person-years, No.	52 512	128 505	168 449	117 650	36 119	
Age and study years, adjusted HR (95% CI)	1 [Reference]	0.63 (0.55-0.73)	0.52 (0.45-0.60)	0.42 (0.35-0.50)	0.26 (0.18-0.38)	<.001
Model 1, HR (95% CI)[a]	1 [Reference]	0.65 (0.57-0.75)	0.56 (0.48-0.65)	0.47 (0.39-0.57)	0.30 (0.20-0.45)	<.001
Model 2, HR (95% CI)[b]	1 [Reference]	0.66 (0.58-0.76)	0.57 (0.50-0.66)	0.51 (0.42-0.61)	0.33 (0.23-0.50)	<.001
Ischemic stroke						
Incidence cases, No.	260	384	361	145	18	
Age and study years, adjusted HR (95% CI)	1 [Reference]	0.64 (0.55-0.75)	0.54 (0.46-0.63)	0.42 (0.34-0.51)	0.23 (0.14-0.37)	<.001
Model 1, HR (95% CI)[a]	1 [Reference]	0.66 (0.57-0.78)	0.58 (0.49-0.68)	0.47 (0.38-0.58)	0.27 (0.17-0.44)	<.001
Model 2, HR (95% CI)[b]	1 [Reference]	0.67 (0.57-0.79)	0.60 (0.51-0.70)	0.50 (0.41-0.62)	0.30 (0.18-0.49)	<.001
Hemorrhagic stroke						
Incidence cases, No.	66	97	88	50	10	
Age and study years, adjusted HR (95% CI)	1 [Reference]	0.62 (0.45-0.84)	0.46 (0.34-0.64)	0.44 (0.30-0.64)	0.34 (0.17-0.66)	<.001
Model 1, HR (95% CI)[a]	1 [Reference]	0.62 (0.46-0.85)	0.48 (0.34-0.66)	0.46 (0.31-0.67)	0.36 (0.18-0.71)	<.001
Model 2, HR (95% CI)[b]	1 [Reference]	0.63 (0.46-0.87)	0.49 (0.35-0.68)	0.49 (0.34-0.73)	0.40 (0.20-0.79)	<.001

[a] Model 1: adjusted for age, study year, education, and family history of stroke.
[b] Model 2: adjusted for age, study year, education, family history of stroke, history of diabetes mellitus, systolic blood pressure, and total cholesterol level.
[c] Adjusted also for sex.

34.6%), 43.8% (95% CI, 28.6%-56.9%), and 54.6% (95% CI, 31.5%-71.6%) for total stroke; 22.7% (95% CI, 12.8%-32.2%), 45.3% (95% CI, 28.1%-59.7%), and 59.7% (95% CI, 33.7%-77.3%) for ischemic stroke; and 35.0% (95% CI, 17.4%-50.5%), 35.0% (95% CI, 0.5%-62.1%), and 36.1% (95% CI, –17.3% to 73.1%) for hemorrhagic stroke, suggesting that 17.7% to 71.6%, 12.8% to 77.3%, and 17.4% to 73.1% of new cases of total, ischemic, and hem-

Table 5. Hazard Ratios (HRs) of Stroke According to Number of Healthy Lifestyle Factors Stratified by the Status of Hypertension, Diabetes Mellitus (DM), and Hyperlipidemia at Baseline[a]

Characteristic	Healthy Lifestyle Factors, No.					*P* Value for Trend	*P* Value for Interaction
	0-1	2	3	4	5		
Total Stroke							
Age, y							
25-49	1 [Reference]	0.68 (0.50-0.93)	0.71 (0.52-0.96)	0.57 (0.40-0.82)	0.31 (0.17-0.58)	.001	>.25
≥50	1 [Reference]	0.65 (0.56-0.76)	0.52 (0.44-0.61)	0.45 (0.36-0.56)	0.33 (0.20-0.55)	<.001	
Hypertension[b]							
No	1 [Reference]	0.63 (0.46-0.87)	0.51 (0.37-0.70)	0.38 (0.26-0.56)	0.14 (0.06-0.34)	<.001	<.05
Yes	1 [Reference]	0.67 (0.57-0.78)	0.59 (0.50-0.70)	0.56 (0.45-0.69)	0.49 (0.32-0.77)	<.001	
History of DM							
No	1 [Reference]	0.65 (0.56-0.76)	0.58 (0.50-0.67)	0.49 (0.40-0.59)	0.31 (0.21-0.46)	<.001	>.25
Yes	1 [Reference]	0.68 (0.41-1.14)	0.35 (0.19-0.64)	0.38 (0.17-0.87)	0.27 (0.04-2.05)	.008	
Total cholesterol level, mg/dL							
<251.0	1 [Reference]	0.64 (0.53-0.78)	0.59 (0.49-0.71)	0.44 (0.35-0.56)	0.24 (0.15-0.39)	<.001	>.10
≥251.0	1 [Reference]	0.67 (0.54-0.83)	0.49 (0.39-0.63)	0.52 (0.39-0.70)	0.50 (0.26-0.96)	<.001	
Ischemic Stroke							
Age, y							
25-49	1 [Reference]	0.78 (0.53-1.14)	0.80 (0.55-1.15)	0.62 (0.41-0.96)	0.29 (0.13-0.66)	.03	>.25
≥50	1 [Reference]	0.64 (0.54-0.77)	0.54 (0.45-0.64)	0.44 (0.34-0.56)	0.29 (0.16-0.54)	<.001	
Hypertension[b]							
No	1 [Reference]	0.63 (0.44-0.90)	0.50 (0.34-0.71)	0.42 (0.27-0.63)	0.17 (0.07-0.44)	<.001	>.25
Yes	1 [Reference]	0.68 (0.57-0.81)	0.63 (0.52-0.75)	0.54 (0.42-0.69)	0.40 (0.22-0.70)	<.001	
A history of DM							
No	1 [Reference]	0.66 (0.56-0.77)	0.60 (0.51-0.71)	0.48 (0.39-0.60)	0.28 (0.17-0.46)	<.001	>.25
Yes	1 [Reference]	0.77 (0.44-1.33)	0.37 (0.19-0.72)	0.47 (0.20-1.09)	0.35 (0.05-2.71)	.03	
Total cholesterol level, mg/dL							
<251.0	1 [Reference]	0.63 (0.51-0.77)	0.59 (0.48-0.73)	0.42 (0.32-0.56)	0.18 (0.10-0.35)	<.001	>.10
≥251.0	1 [Reference]	0.72 (0.57-0.91)	0.56 (0.43-0.72)	0.56 (0.40-0.78)	0.57 (0.27-1.17)	<.001	
Hemorrhagic Stroke							
Age, y							
25-49	1 [Reference]	0.47 (0.26-0.84)	0.53 (0.31-0.91)	0.47 (0.26-0.87)	0.32 (0.12-0.86)	.045	>.50
≥50	1 [Reference]	0.71 (0.49-1.03)	0.44 (0.29-0.66)	0.46 (0.28-0.75)	0.45 (0.18-1.15)	.001	
Hypertension[b]							
No	1 [Reference]	0.65 (0.33-1.28)	0.55 (0.29-1.07)	0.31 (0.14-0.68)	0.08 (0.01-0.59)	.01	>.05
Yes	1 [Reference]	0.63 (0.44-0.89)	0.46 (0.32-0.68)	0.60 (0.39-0.93)	0.73 (0.35-1.51)	.003	
History of DM							
No	1 [Reference]	0.65 (0.47-0.89)	0.49 (0.35-0.68)	0.48 (0.33-0.71)	0.37 (0.19-0.74)	<.001	>.50
Yes	1 [Reference]	0.23 (0.04-1.28)	0.20 (0.03-1.17)	NA[c]	NA[c]	.35	
Total cholesterol level, mg/dL							
<251.0	1 [Reference]	0.72 (0.48-1.08)	0.58 (0.38-0.88)	0.50 (0.31-0.80)	0.40 (0.18-0.89)	.02	>.50
≥251.0	1 [Reference]	0.49 (0.30-0.80)	0.31 (0.18-0.54)	0.40 (0.21-0.77)	0.30 (0.07-1.28)	.001	

Abbreviation: NA, not applicable.
SI conversion factor: To convert serum cholesterol to millimoles per liter, multiply by 0.0259.
[a] Adjusting for age, sex, study year, education, and family history of stroke.
[b] Hypertension was defined as an average baseline blood pressure of at least 140/90 mm Hg.
[c] There were no incident cases in this group.

orrhagic strokes, respectively, could be prevented if people would have kept 3 to 5 HLFs.

COMMENT

In this large prospective study, a combination of HLFs—maintaining normal BMI, eating vegetables regularly (≥3 times per week), practicing a moderate or high level of physical activity, never smoking, and having light to moderate alcohol consumption—was associated with a substantially reduced risk of stroke. These 5 HLFs were significantly associated with a decreased risk of total, ischemic, and hemorrhagic stroke, and the stroke risk progressively decreased as the number of HLFs increased. These results also suggest that in this population, most cases of stroke could be avoided by practicing a healthy lifestyle.

Each HLF has been found to be associated with a lower risk of stroke in most studies, although some conflicting results exist. Overweight and obesity have been found to increase the risk of stroke in various observational studies.[12,26,27] For example, obese women (BMI ≥30.0) had 1.5-fold higher risk for total stroke and 1.7-fold higher risk for ischemic stroke compared with normal-weight women (BMI <25.0) in a large cohort of a US study.[26] Physical activity has been associated inconsistently with a decreased risk of stroke. A meta-analysis of observational studies showed that moderately intense physical activity had a protective ef-

fect for total, ischemic, and hemorrhagic stroke.[28] In the Women's Health Study,[16] vigorous physical activity was not strongly associated with a lower stroke risk. In our study, a single type or combination of occupational and leisure-time physical activity was associated with a decreased risk of stroke.[8] Previous reports by us and others have indicated that smoking is an independent risk factor for both ischemic[16,29,30] and hemorrhagic stroke.[31,32] Two meta-analyses of cohort studies suggest that fruit and vegetable consumption decreases stroke risk.[33,34] Our results provide evidence that vegetable consumption decreases stroke risk, but we did not find an association between fruit consumption and stroke risk. The inconsistency might partly be the result of the different questionnaires used to assess fruit consumption, and the differences in dietary habits between different populations.

The association between alcohol consumption and stroke risk has been described as J-shaped in most studies, with the lowest risk among those consuming light to moderate amount of alcohol.[11] In the Health Professionals Follow-up Study and the Nurses' Health Study, Chiuve et al[15] found a J-shaped association with a lower risk of ischemic and hemorrhagic stroke among light drinkers. In our study, we merged the groups of people with light to moderate alcohol intake as a healthy lifestyle for alcohol consumption because we found that alcohol drinking had a J-shaped association with ischemic stroke risk.

Thus far, only a few studies have assessed the association of combined lifestyle factors and stroke risk. In the Women's Health Study,[16] a healthy lifestyle consisting of never smoking, low BMI, moderate alcohol consumption, regular physical activity, and healthy diet score was associated with a significantly reduced risk of total and ischemic stroke but not of hemorrhage stroke. In the Health Professionals Follow-up Study and the Nurses' Health Study,[15] a low-risk lifestyle including no smoking, a healthy weight (BMI <25), moderate alcohol consumption, at least 30 minutes of moderate physical activity daily, and a healthy diet score showed substantial reductions in the risk of ischemic stroke among men and women but not of hemorrhagic stroke. The present study found a graded inverse association between the number of HLFs and the risks of total, ischemic, and hemorrhagic stroke among both men and women. The inconsistency might partly lie in fewer hemorrhagic stroke cases and a lower incident rate of hemorrhagic stroke in these studies. In addition, the participants in these studies were healthy professionals and had a better health awareness than the general population.

Hypertension, DM, and hyperlipidemia have been found to be important vascular risk factors for ischemic stroke.[35-37] The EPIC Potsdam Study[38] indicated that almost 60% of ischemic stroke risk could be attributed to hypertension, DM, hypercholesterolemia, smoking, and heavy alcohol consumption. It could be hypothesized that the protective effects of a healthy lifestyle on stroke may have a direct biological basis and also partly mediate through its effect on those vascular risk factors of stroke. For example, an individual HLF, such as physical activity, has a favorable effect on blood pressure, lipid profile, insulin sensitivity, and body weight, and also reduces the risk of incident hypertension and DM.[8,39-41] A combination of several lifestyle factors decreases the risks of incident hypertension and type 2 DM.[42,43] In our study, the inverse association between physical activity and stroke risk remained significant even after controlling for the major cardiovascular risk factors, including blood pressure, total cholesterol level, and history of DM.

There are several strengths in our study. First, a large number of both men and women from a relatively homogeneous population participated in the study. Second, the mean follow-up period was sufficiently long to ascertain a large number of stroke events that were classified into stroke subtypes using validated diagnostic methods. Several limitations should be considered. First, information on self-reported physical activity, smoking, and vegetable and alcohol consumptions was recorded only once at baseline. We have no data on possible changes in the lifestyle factors described herein during the follow-up period, as is typical in large prospective epidemiological studies. Second, vegetable consumption alone was included in our analysis because dietary patterns based on the food frequency questionnaires could not be derived from the data available in our study. Third, each HLF was weighted the same, which implies that each of them was equally important. This may lead to heterogeneity among people being classified in the same category. Fourth, the potential interaction between each individual lifestyle factor and stroke risk was not assessed. Fifth, we cannot completely either exclude the effects of residual confounding due to measurement error in assessment of confounding factors or of some unmeasured lifestyle, socioeconomic, or health-related covariates (eg, stress and depression) that may be associated with stroke risk.

In conclusion, our study demonstrates a graded inverse association between the number of HLFs and the risks of total, ischemic, and hemorrhagic stroke in both men and women. Our findings suggest the important role of promoting a healthy lifestyle in the primary prevention of both ischemic and hemorrhagic stroke.

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