

Prospective Study of Depressive Symptoms and Risk of Stroke Among Japanese

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Background and Purpose—We sought to examine the relationship between depressive symptoms and the incidence of stroke among Japanese men and women.

Methods—A 10.3-year prospective study on the relationship between depressive symptoms and the incidence of stroke was conducted with 901 men and women aged 40 to 78 years in a rural Japanese community. Depressive symptoms were measured at baseline with the use of the Zung Self-Rating Depression Scale (SDS). The incidence of stroke was ascertained under systematic surveillance.

Results—During the 10-year follow-up, 69 strokes (39 ischemic strokes, 10 intracerebral hemorrhages, 10 subarachnoid hemorrhages, and 10 unclassified strokes) occurred. Age- and sex-adjusted prevalence of mild depression (SDS scores ≥ 40) at baseline was 25% among subjects with incident stroke and 12% among subjects without stroke ($P < 0.01$). Persons with SDS scores in the high tertile had twice the age- and sex-adjusted relative risk of total stroke as those with scores in the low tertile. The excess risk was confined to ischemic stroke. After we adjusted for body mass index, systolic blood pressure level, serum total cholesterol level, cigarette smoking, current treatment with antihypertensive medication, and history of diabetes mellitus, these relative risks remained statistically significant for total stroke (1.9; 95% CI, 1.1 to 3.5) and ischemic stroke (2.7; 95% CI, 1.2 to 6.0).

Conclusions—Depressive symptoms predict the risk of stroke, specifically ischemic stroke among Japanese. (*Stroke*. 2001;32:903-908.)

Key Words: cerebral infarction ■ depression ■ population ■ risk factors

It is well known that depression, a common psychiatric disease, occurs frequently after stroke.¹⁻⁴ However, whether depression or depressive scores predict the risk of stroke remains inconclusive. Higher depression scores estimated by the Center for Epidemiological Studies Depression Scale (CES-D) were associated with the increased risk of stroke in the elderly, aged ≥ 65 years; however, the association did not remain statistically significant after adjustment for known risk factors.⁵ More recent studies have shown significant relations between depression and stroke even after adjustment for known risk factors. Persons who reported ≥ 5 depressive symptoms had higher stroke mortality than did those with fewer symptoms.⁶ Depressive symptoms predicted the incidence of ischemic stroke in the Australian elderly, aged ≥ 60 years.⁷

Japan has a higher mortality from stroke than the United States and Europe.⁸ No prospective study, however, has been conducted to examine the relation between depression and the incidence of stroke among Japanese. In the present study, to examine the relation between depression and the incidence of

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stroke, we used the data from a 10.3-year follow-up study of men and women in a rural Japanese community.

Subjects and Methods

The population surveyed included 901 men and women aged 40 to 78 years who were examined in October 1985 in a rural community, Kyowa, Ibaraki prefecture. In this community, surveillance of stroke and coronary heart disease has been conducted since 1981.⁹ Persons with a history of stroke ($n = 14$) or coronary heart disease ($n = 8$) were excluded, and the data of 311 men and 568 women were used in the analyses.

Subjects were followed up to determine the incidence of stroke by the end of 1996. Only 20 persons (2%) moved out of the community during the follow-up, and 100 persons (11%) died. They were censored at the date of moving out or the date of death. The average follow-up for the participants was 10.3 years. Stroke incidence were ascertained by 6 overlapping methods¹⁰: (1) national insurance claims, (2) reports by local physicians, (3) ambulance records, (4) death certificates, (5) reports by public health nurses and health volunteers, and (6) cardiovascular risk surveys. From death certificates, cases with underlying cause of death of stroke (*International*

Received October 1, 2000; final revision received December 14, 2000; accepted January 10, 2001.

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TABLE 1. Age- and Sex-Adjusted Values or Proportions of Risk Characteristics at Baseline Among Persons With Stroke and Those Without Stroke

	Subjects With Stroke	Subjects Without Stroke (n=810)	P*
Age, y	62 (8)	56 (9)	...
Men, %	51	34	...
SDS score	35 (0.7)	33 (0.2)	0.02
High SDS score (≥ 40), %	25	12	0.002
Systolic blood pressure, mm Hg	148 (2.6)	140 (0.8)	0.01
Diastolic blood pressure, mm Hg	84 (1.5)	82 (0.4)	0.30
Antihypertensive medication, %	42	21	0.001
Hypertensive subjects, %	47	33	0.04
Body mass index, kg/m ²	23.9 (0.4)	23.9 (0.1)	0.89
Serum total cholesterol, mmol/L	5.11 (0.12)	5.05 (0.03)	0.61
Alcohol intake, g/d	13 (2.3)	11 (0.7)	0.27
Heavy drinker (≥ 46 g/d), %	10	12	0.13
Current smoker, %	30	25	0.33
Diabetes mellitus, %	5	8	0.56

Values are mean (SE).

*Differences tested by ANCOVA or χ^2 test.

Classification of Diseases, Ninth Revision codes 430 to 438) were selected.

To confirm the diagnosis, all living patients were visited or invited to complete risk factor surveys. Study physicians obtained a medical history and a history and neurological examination from stroke patients. For deaths, histories were obtained from the families, and medical records were reviewed.

Stroke was defined as a focal neurological disorder with rapid onset that persists ≥ 24 hours. Thus, transient ischemic attack was not included. Determination of type of stroke (ie, intracerebral hemorrhage, subarachnoid hemorrhage, and ischemic stroke) was done primarily by CT in a standardized way.¹¹ Stroke cases that were diagnosed clinically but showed no lesion on CT were regarded as unclassified stroke. CT films were available for 90% of the stroke cases. Stroke cases without CT films were classified according to clinical criteria¹² based on Millikan.¹³

Depressive symptoms were measured at the baseline examinations with the Zung Self-Rating Depression Scale (SDS).¹⁴ The original English scale was translated into Japanese, and the Japanese version has been well validated.¹⁵ The 20 items of SDS are scored on a standard 4-point scale (1 to 4) for each item, with a potential range of 20 to 80. A previous study showed that a score ≥ 40 was regarded as a mild depressive disorder.¹⁶

Cardiovascular disease risk factors were also measured at baseline. Detailed methods of risk factor surveys were described elsewhere.¹⁰ Briefly, systolic and diastolic blood pressures were measured by trained observers using a standard mercury sphygmomanometer on the right arm of seated participants after at least a 5-minute rest.¹⁷ Readings were made to the nearest 2 mm Hg, and diastolic blood pressure was taken as phase V Korotkoff sound. Hypertension was defined as systolic blood pressure of ≥ 160 mm Hg, diastolic blood pressure of ≥ 95 mm Hg, and/or current treatment with antihypertensive medication. Height in stockinged feet and weight in light clothing were measured. Body mass index was calculated as weight (kg)/height (m)². An interview was conducted to ascertain alcohol intake per day, the number of cigarettes smoked per day, and use of medication for diabetes mellitus. Amount of alcohol intake was measured as corresponding grams of ethanol. Persons who smoked ≥ 1 cigarette per day were defined as current smokers. Diabetes mellitus was defined as fasting glucose level of ≥ 7.8 mmol/L, nonfasting glucose level of ≥ 11.1 mmol/L, and/or use of medication for diabetes. Serum total cholesterol level was measured by the Liebermann-Burchard direct

method with the Autoanalyzer II (Technicon).¹⁸ The laboratory had been standardized by the Lipid Standardization Program, Centers for Disease Control and Prevention, Atlanta, Ga, and successfully met the criteria of precision and accuracy of cholesterol measurements.¹⁹

Incidence rates were calculated according to the tertile of SDS scores (score ranges: low, ≤ 30 ; medium, 31 to 34; high, ≥ 35). For statistical analyses, differences in mean values and the prevalence of potential confounding factors at baseline between stroke and free of stroke were tested by *t* test or the χ^2 test adjusted for age and sex. The relations between SDS scores and cardiovascular risk factors were examined by the Pearson correlation coefficient with adjustment for age and sex. The relative risks and 95% CIs relative to the low tertile of SDS were calculated with adjustment for age, sex, and other potential confounding factors using the Cox proportional hazards model. The relative risk was also estimated with the use of continuous SDS scores. Potential confounding factors were systolic blood pressure level (mm Hg), serum total cholesterol level (mmol/L), body mass index (kg/m²), alcohol category (never-drinkers, current drinkers of ethanol 1 to 22, 23 to 45, or >45 g/d), smoking category (never-smoker, current smokers of <20 or ≥ 20 cigarettes per day), current treatment with antihypertensive medication (yes or no), and a history of diabetes mellitus (yes or no). The analyses were also tested stratified by stroke subtype: ischemic and hemorrhagic stroke. All probability values were tested with the 2-tailed test, and $P<0.05$ was the cutoff indicating statistical significance.

Results

Among 879 men and women followed for 10.3 years, 69 incident strokes occurred. These cases included 39 ischemic strokes, 20 hemorrhagic strokes (10 intracerebral and 10 subarachnoid hemorrhages), and 10 unclassified strokes.

Table 1 shows age- and sex-adjusted mean values or proportions of risk characteristics at baseline for incident cases of stroke and for those who remained free of stroke. For men and women, mean values of SDS scores and systolic blood pressure were higher among subjects with stroke than among subjects without stroke. Age- and sex-adjusted prevalence of mild depression (SDS score ≥ 40) was 2 times higher among subjects with stroke than among subjects

TABLE 2. Age- and Sex-Adjusted Values or Proportions of Risk Characteristics at Baseline According to Tertiles of SDS Scores

	Tertile of SDS Scores			<i>P</i> *
	≤30 (n=332)	31–34 (n=257)	≥35 (n=294)	
Systolic blood pressure, mm Hg	142 (1.2)	141 (1.3)	139 (1.3)	0.29
Diastolic blood pressure, mm Hg	83 (0.7)	82 (0.8)	82 (0.7)	0.30
Antihypertensive medication, %	21	25	23	0.53
Hypertensive subjects, %	33	36	32	0.75
Body mass index, kg/m ²	24.2 (0.2)	23.7 (0.2)	23.8 (0.2)	0.13
Serum total cholesterol, mmol/L	5.06 (0.05)	5.01 (0.06)	5.08 (0.06)	0.61
Alcohol intake, g/d	10 (1.0)	11 (1.2)	12 (1.1)	0.60
Heavy drinker (≥46 g/d), %	11	13	13	0.25
Current smoking, %	25	22	28	0.23
Diabetes mellitus, %	8	6	9	0.89

Values are mean (SE).

*Differences tested by ANCOVA or χ^2 test.

without stroke. Subjects with stroke were more likely to be hypertensive than subjects without stroke.

As shown in Table 2, none of the selected cardiovascular risk characteristics at baseline varied significantly among the tertiles of SDS scores for men and women. There was only a weak inverse correlation of SDS scores with blood pressures ($r=-0.09$, $P<0.01$ for systolic and $r=-0.07$, $P<0.05$ for diastolic blood pressure levels) and body mass index ($r=-0.09$, $P<0.01$) at baseline (not shown).

Table 3 presents the relative risk of stroke relative to the low tertile of SDS scores. The age- and sex-adjusted relative risk of total stroke was 2.0 (95% CI, 1.1 to 3.6) for the high

tertile of SDS scores. Further adjustment for body mass index, systolic blood pressure levels, serum total cholesterol levels, alcohol intake, cigarette smoking, use of antihypertensive medication, and history of diabetes mellitus reduced the relative risk to 1.9, but it remained statistically significant. These excess risks were confined to ischemic stroke. SDS scores were not related to the risk of hemorrhagic strokes. Furthermore, when we divided the highest tertile into 2 subgroups (35 to 39 and ≥40), the multivariate-adjusted relative risks of total stroke were 1.1 (95% CI, 0.5 to 2.3) for the score 35 to 39 and 3.5 (95% CI, 1.8 to 6.9) for the score ≥40. The respective relative risks of ischemic stroke were 1.4 (95% CI, 0.5 to 3.7) and 6.4 (95% CI, 2.5 to 16.1). The multivariate-adjusted relative risks associated with 1-SD (6 points) increment in the SDS scores were 1.4 (95% CI, 1.1 to 1.7) for total stroke and 1.8 (95% CI, 1.3 to 2.5) for ischemic stroke.

The relations between SDS scores and the risk of ischemic stroke were similar between men and women (not shown). The multivariate relative risks of ischemic stroke for the high tertile of SDS scores were 2.5 (95% CI, 0.8 to 7.9) for men and 2.3 (95% CI, 0.7 to 7.4) for women.

Discussion

The present prospective study showed a significant relation between depressive symptoms and the risk of stroke among Japanese men and women. Persons with depressive symptoms in the high tertile had approximately 2 times the excess risk of total stroke than did those with scores in the low tertile, and this excess risk was confined to ischemic stroke. Our results were consistent with the results of an Australian study that showed that the elderly with depressive symptoms in the high tertile, measured by CES-D, had 41% higher risk for ischemic stroke than those in the low tertile.⁷

The mechanisms by which depressive symptoms may increase the risk of stroke were not fully elucidated. Since depressive symptoms predicted later hypertension inci-

TABLE 3. Relative Risks and 95% CIs of Stroke and Stroke Subtypes According to SDS Scores

	Tertile of SDS Scores		
	≤30	31–34	≥35
No. at risk	332	257	295
Person-years of follow-up	3481	2684	2925
Total stroke			
No. of cases	19	20	30
Age/sex-adjusted RR (95% CI)	1.0	1.3 (0.7–2.4)	2.0 (1.1–3.6)
Multivariate-adjusted* RR (95% CI)	1.0	1.2 (0.6–2.2)	1.9 (1.1–3.5)
Ischemic stroke			
No. of cases	9	10	20
Age/sex-adjusted RR (95% CI)	1.0	1.4 (0.6–3.4)	3.0 (1.3–6.6)
Multivariate-adjusted* RR (95% CI)	1.0	1.1 (0.4–2.7)	2.7 (1.2–6.0)
Hemorrhagic stroke			
No. of cases	6	9	5
Age/sex-adjusted RR (95% CI)	1.0	1.8 (0.6–5.0)	0.9 (0.3–3.1)
Multivariate-adjusted* RR (95% CI)	1.0	1.7 (0.6–4.8)	0.9 (0.3–3.1)

RR indicates relative risk.

*Adjusted for age, sex, body mass index, systolic blood pressure levels, serum total cholesterol levels, alcohol intake, cigarette smoking, antihypertensive medication, and diabetes mellitus.

dence,^{20,21} it is possible that depressive symptoms may be associated with incident stroke through the development of hypertension. However, this mechanism does not explain why the excess risk was confined to ischemic stroke.

Previous studies showed that deep white matter lesions detected by MRI were more frequently observed in patients with senile depression than in controls.^{22,23} Patients with presenile-onset depression had a higher prevalence of silent cerebral infarction than those with juvenile-onset depression, regardless of the 2 subtypes of presenile and senile depression.²⁴ Thus, depressive symptoms during or after the presenile period are associated with silent cerebral infarction, which may raise the risk of clinical stroke.²⁵ This inference was also supported by our findings that the relations between SDS scores and the risk of stroke were confined to ischemic stroke. These findings suggested that depression is a marker of cerebral atheroarteriosclerosis or silent cerebral infarction, which predict the clinical onset of ischemic stroke.

Recent reports suggested that depressive symptoms may increase the risk of stroke by increased platelet activity due to sympathoadrenal hyperactivity.²⁶ Depressed patients exhibited greater platelet activation, demonstrated by increased binding of monoclonal antibody, ie, annexin V protein, than did healthy controls.²⁷ Mean plasma levels of platelet factor 4 and β -thromboglobulin were higher in depressed patients with ischemic heart disease than in nondepressed patients with ischemic heart disease and healthy controls.²⁸ Platelet 5-hydroxytryptamine₂ binding density, one of the useful indices of serotonin-mediated platelet activation, was higher in depressed patients than in controls.^{29,30} Furthermore, platelet secretion in response to collagen was significantly reduced among depressive patients after treatment with sertraline, an agent widely used for depression.³¹ These findings support the possibility that depression per se increases the risk of ischemic stroke through increased platelet aggregation.

The strengths of the present study are a high precision of stroke classification with the use of CT and the examination of known risk factors by standard methods, which are likely to provide reliable epidemiological data. In the present study >90% of stroke cases were confirmed by CT, compared with 70% for the Australian study.⁷

Several limitations of our study warrant discussion. First, we assessed depression scores but not clinical depression. The high tertile of SDS score (≥ 35) may be below what is considered a mild depressive disorder. Then we divided the high tertile of SDS scores into 2 subgroups (35 to 39 and ≥ 40) and found a dose-response relation between the SDS scores and risk of ischemic stroke. This result indicates a correlation between the severity of depressive symptoms and the likelihood of ischemic stroke.

Second, since depressive symptoms were measured only once at baseline, we have no data regarding whether the subjects in the high tertile of SDS scores may have developed depression at some later date. However, an earlier study showed that persons scoring high on a depression inventory at baseline have 4 times higher prevalence of depression at 9-year follow-up.³² Third, the number of incident stroke cases was small. The sex-specific analysis did not show significant relations between depression scores and the risk of stroke,

although the relations were similar between the sexes. Since depressive scores and prevalence of depression were generally higher in women than in men,³³ it is interesting to examine the sex-specific relations. Further follow-up of this cohort may allow us to conduct a reliable sex-specific analysis. Finally, we did not examine any psychosocial factors other than depressive scores. It is possible that social network, psychological status, and personal characteristics may confound the relation between depressive scores and risk of stroke. However, a previous study of white elderly persons showed that psychosocial factors did not predict the risk of stroke after adjustment for known risk factors.⁵

In conclusion, depressive scores are useful to predict the risk of ischemic stroke among the Japanese elderly. Further study is warranted to examine the sex-related difference in the relation between depressive scores and risk of stroke.

Acknowledgment

The authors thank Dr Todd Horowitz for valuable advice on the manuscript.

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Editorial Comment

Is Depression a Risk Factor for Ischemic Stroke?

Current treatment for patients with established stroke is relatively ineffective. More than 50% of stroke survivors have severe and permanent disability.¹ Despite the advent of thrombolytic therapy for selected patients with ischemic stroke, the best approach to reducing the burden of stroke remains prevention.²

Hemorrhagic stroke is closely related to hypertension, among other causes, and its prevention rests with adequate blood pressure control.³ But ischemic stroke constitutes the major portion of the stroke burden, and its prevention is more complex. The American Heart Association recently published a statement on the primary prevention of ischemic stroke.² The following risk factors were described as being well-documented and modifiable: hypertension, smoking, diabetes, asymptomatic carotid stenosis, sickle cell disease, hyperlipidemia, and nonvalvular atrial fibrillation. Risk factors with the highest population attributable risk were hypertension, hyperlipidemia, diabetes and smoking. The AHA statement also refers to less well-documented or “potentially modifiable” risk factors, including lifestyle factors.² But there is no specific mention of depression as a risk factor for future stroke.

Depression is a common event that may influence functional recovery and possibly mortality after a stroke.⁴ However, I would like to focus attention on late-life depression that has preceded clinically manifested cerebrovascular disease. Early work in this field suggested that higher depression scores⁵ or depression symptoms⁶ may be predictive of later

stroke. Subsequent studies have been more definitive. Simons et al⁷ followed an Australian cohort of 2805 men and women 60 years and older for more than 8 years and identified 306 incident ischemic stroke cases. Self-reported depression score significantly predicted stroke (hazard ratio in tertile III versus tertile I was 1.41 for all ischemic strokes and 2.30 for fatal strokes). Jonas and Mussolino,⁸ using the NHANES I Epidemiologic Study, followed 6095 stroke-free men and women aged 25 to 74 years for an average of 16 years and identified 483 stroke cases. Self-reported depression symptomatology was significantly predictive of stroke (hazard ratio 1.73). These studies adjusted for other baseline risk factors or confounders. In the accompanying article, Ohira et al report that symptoms measured on the Zung Self-Rating Depression Scale predicted the later onset of ischemic stroke in Japanese men and women aged 40 to 78 years (hazard ratio 2.7 in a multivariate model). This was a study of 879 subjects producing only 39 ischemic strokes. Nevertheless, the findings are confirmatory of results in Western populations.

A growing body of evidence^{9–11} suggests that depressive symptoms also constitute a risk factor for coronary heart disease. This gives added plausibility to the notion that depressive symptoms are indeed a true precursor of ischemic stroke. What might be the pathway(s) to the ultimate event? Subjects with depressive symptoms have been reported to manifest increased platelet activity,¹² related to increased autonomic sympathetic activity. Serotonin-mediated platelet activation is increased in depressed patients.¹³ But depressive

symptoms have also been shown to predict later hypertension incidence,¹⁴ and this may be a pathway to a stroke event. In the presence of depressive symptoms, there may be other subtle lifestyle changes that impact on conventional risk factors.

It is also plausible that the association of depressive symptoms and later onset of ischemic stroke is an "epiphenomenon." Late-life depression may have a vascular basis. The vascular depression hypothesis links small-vessel disease and/or preclinical disease, secondary to factors such as hypertension or diabetes, with disruption of frontal-subcortical circuits.¹⁵ There is evidence from MRI studies that changes in the brain (deep white matter hyperintensities and reduction in basal ganglia volumes) are associated with onset of depression in later life.^{16,17} The vascular depression hypothesis needs further evidence of an association between risk factors and depression scores. In unpublished analyses from the Australian longitudinal study, we found no significant association between depressive symptom scores and the presence of hypertension or diabetes at study entry.

There does seem to be a consistent association between depressive symptoms and later development of ischemic stroke. If the symptoms relate to underlying vascular risk factors, then we may ultimately obtain new treatments to prevent the onset of depression. This would be fairly amenable to testing. Prevention of ischemic stroke through intervention on depression would be much more difficult to evaluate. Perhaps we will ultimately gain a better understanding of relationships between risk factors, depressive symptoms, and stroke risk from ongoing neuroimaging linked to epidemiological studies.

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Stroke. 2001;32:903-908

doi: 10.1161/01.STR.32.4.903

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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