Depression as a Risk Factor for the Incidence of First-Ever Stroke in 85-Year-Olds

Martin Liebetrau, MD; Bertil Steen, MD, PhD; Ingmar Skoog, MD, PhD

Background and Purpose—Depression may increase the risk for stroke. Few studies have examined whether depression increases the risk for stroke in the very old and among the demented. We examined the relation between depression in 85-year-olds and the 3-year incidence of first-ever stroke.

Methods—A representative sample of 494 85-year-olds (147 demented, 347 nondemented) in Gothenburg, Sweden, was examined with psychiatric examinations and key informant interviews. Diagnoses of depression and dementia were made according to the Diagnostic and Statistical Manual of Mental Disorders, Third Revision. The sample was followed for 3 years regarding the incidence of stroke. Information on stroke was obtained from the Swedish Hospital Discharge Register, death certificates, self-reports, and key informants. Those with known stroke history at baseline (n=93) were excluded from the incidence study.

Results—The prevalence of depression at age 85 was 19%. Depression at baseline (hazard ratio, 2.7; 95% CI, 1.5 to 4.7; $P=0.0006$) and systolic blood pressure (hazard ratio, 1.014 per 1 mm Hg; 95% CI, 1.00 to 1.03; $P=0.019$) were related to increased incidence of first-ever stroke during follow-up. Depression increased stroke risk both among demented and nondemented individuals. Among the symptoms of depression, only depressed mood was an independent predictor of incidence first-ever stroke in multivariate analyses. Stroke history at age 85 was not associated with clinical depression.

Conclusions—Depression and stroke are both common in elderly populations. The finding that depression increases risk for first-ever stroke indicates that detection and treatment of depression may have implications for stroke prevention. **(*Stroke*. 2008;39:1960-1965.)**

Key Words: dementia ■ depression ■ elderly ■ epidemiology ■ stroke

The prevalence of depression and stroke is high in the elderly.[1,2] It has long been noted that depression is common after stroke[3] and that depression is associated with increased mortality in patients with stroke.[4] During the last decade, results from animal studies and from prospective population-based studies suggest that depression may also increase the risk for cardiovascular accidents or stroke.[5–11] The population-based studies were based on relatively young populations, and only one study[11] excluded stroke at baseline. In some studies, the depressed had elevated blood pressure at baseline[9,10] or had more vascular risk factors than nondepressed individuals.[11] The Framingham Study[11] recently reported a more than 4-fold increased risk of stroke in those with depressive symptoms, but this relation was only found among individuals younger than age 65 and not in older individuals, in whom stroke prevalence and incidence is highest. In this age group, stroke is an important contributor to dementia and other disabilities.[12,13] Furthermore, it is not known if depression increases risk for first-ever stroke among the demented. Hypotheses why depression may increase stroke risk include that depression exerts large stress on the individual and that depression is often related to silent cerebrovascular diseases, which may increase the risk of further strokes. Depression as a risk factor for stroke may have important implications for stroke prevention because it is both treatable and common.

We have previously reported that 19% of 85 year olds had depression[14] and that the 3-year cumulative incidence of first-ever stroke was 14% between ages 85 and 88.[2]

The aim of this study was to examine the relation between depression and the incidence of first-ever stroke in a population-based sample of stroke-free 85-year-olds. The present study is part of the Longitudinal Gerontological and Geriatric Population Studies (H70) in Göteborg, Sweden.[15,16]

Methods

Subjects

All 85-year-olds born between July 1, 1901, and June 30, 1902, and registered for census purposes in Göteborg, Sweden, were invited to take part in a health survey in 1986 to 1987. People living in the community and at institutions were included. Every second person (n=784) was systematically selected for a neuropsychiatric examination and 494 accepted (response rate, 63%; 144 men, 350 women).

Received April 9, 2007; final revision received November 5, 2007; accepted December 10, 2007.

From the Department of Neurology (M.L.), Dr Horst Schmidt Klinik, Wiesbaden, Germany; and the Department of Geriatric Medicine (B.S.) and Institute of Neuroscience and Physiology, Neuroepidemiology Unit (M.L., I.S.), Sahlgrenska Academy, Göteborg University, Göteborg, Sweden.

Correspondence to Ingmar Skoog, MD, PhD, Institute of Neuroscience and Physiology, Department of Psychiatry, Neuropsychiatric Epidemiology Unit, Sahlgrenska University Hospital/Mölndal, Wallinsgatan 6, SE-431 41 Mölndal, Sweden. E-mail ingmar.skoog@neuro.gu.se

Stroke **is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.107.490797**

Nonparticipants and participants did not differ regarding gender, marital status, 3-year mortality rate, and registration as psychiatric outpatients or inpatients in Göteborg.[13]

We excluded 93 individuals with stroke history at baseline (age 85) for the follow-up analyses. Information on new strokes during follow-up was derived from the Swedish Hospital Discharge Register and death certificates on all 401 individuals,[2] and from self-reports (n=235) and key informant interviews (n=190) during a follow-up examination at age 88 (performed 1989 to 1990). Among 401 stroke-free individuals at age 85, 104 had died and 62 refused the follow-up examination at age 88.

Informed consent was obtained from all participants and/or their relatives. The study was approved by the Ethics Committee for Medical Research at Göteborg University.

Methods

The study included home visits by a nurse, physical examinations by geriatricians (including assessment of physical disorders), neuropsychiatric examinations and key informant interviews by a psychiatrist, and extensive laboratory examinations, including blood and serum samples, electrocardiograms, chest x-rays, and CT of the head. Casual blood pressure was measured in the right arm in the seated position after 5 minutes of rest using a mercury manometer. Systolic and diastolic blood pressure were registered to the nearest 5 mm Hg. Hypertension was defined as blood pressure above 160/90 mm Hg or antihypertensive treatment. Myocardial infarction and atrial fibrillation were defined as a history or electrocardiographic manifestations. Diabetes was defined as a history of diabetes told by a doctor. Hypercholesterolemia was defined as cholesterol above 6.22 mmol/L. Overweight was defined as a body mass index above 25 kg/m^2. Education was defined as 6 years of compulsory education or more. Alcohol consumption was defined as weekly use of any alcoholic beverage. The neuropsychiatric examination was performed by an experienced psychiatrist in the subject's place of residence and included questions about social factors, psychiatric and stroke symptoms, cognitive measures (eg, memory, language, visuospatial ability), and observed variables (eg, psychiatric symptoms, neurological symptoms) as described previously.[13,14] The key informant telephone interview (performed by a neuropsychiatrist in 451 participants at age 85 and in 190 at age 88) included questions about cognitive, psychiatric, and stroke symptoms. Both examinations were semistructured allowing clarifying questions, eg, in the questions about history of stroke, several synonyms for stroke were given to the participant.

Diagnostic Procedures

Dementia

A diagnosis of dementia and its severity was made according to the Diagnostic and Statistical Manual of Mental Disorders, Third Revision as previously described.[13]

Depression

The diagnosis of depression at age 85 was made according to the Diagnostic and Statistical Manual of Mental Disorders, Third Revision criteria using a symptom algorithm based on the assessments of symptoms made by a psychiatrist during an examination with a mean length of 83 minutes (range, 20 to 191 minutes), as described previously,[17] and included the categories major depression, dysthymia, and depression not otherwise specified. The diagnoses were based on symptoms during the month preceding the examination and observed symptoms during the psychiatric examination. Symptoms included in the diagnoses are depressed mood, diminished interest or pleasure, decreased appetite, sleep problems, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness and guilt, diminished ability to think or concentrate or indecisiveness, and thoughts of death or suicidal feelings. Interrater reliability between psychiatrists for the assessment of these symptoms using Spearman rank order correlations ranged from 0.87 (insomnia) to 1.00 (decreased appetite). For observed signs of depression, the rank order correlations ranged from 0.55 (inability to think or concentrate) to 0.88 (decreased amount of speech). For reported symptoms of depressed mood, it was 0.98, and for observed depressed mood, it was 0.81.

Stroke

The diagnosis of stroke has been described in detail previously[2] and was based on information from 3 sources (self-reports, key informants, and Swedish Hospital Discharge Register). Participants and key informants (eg, spouse or child) were interviewed by a neuropsychiatrist regarding stroke symptoms. The participants were also interviewed by a geriatrician. The interviews included questions about sudden onset of focal symptoms or acute aphasia and admission to the hospital due to stroke. All side notes and answers to these questions were examined by a stroke neurologist and a neuropsychiatrist. Only stroke cases with a definite history of acute focal symptoms (hemiparesis or acute aphasia) were included (as an example, stroke was self-reported in 98 cases at age 85 but only 53 were accepted after review of side notes).

The diagnosis of stroke was also derived from the computerized Swedish Hospital Discharge Register, in which all hospital admissions in Sweden have been registered and classified according to the International Classification of Diseases, Ninth Edition (codes 430 to 438 for stroke) since 1978. In addition, strokes were identified by death certificates.

Calculation of stroke incidence was based on person-years at risk and computed as subjects affected in the interval divided by sum of person-years at risk. The risk time was calculated as the time from the examination at age 85 to time of stroke, death, or 36 months, whichever came first. In cases of missing information about onset, the assumption was made that onset occurred in the middle of the follow-up period and risk time was calculated as time between the examinations divided by 2.

Statistical Methods

The associations between depression and stroke at age 85 were tested for significance with Fisher exact test, and OR were calculated with logistic regression analyses.

The associations between depression or depressive symptoms at age 85 and incidence of first-ever stroke between age 85 and 88 were tested with Cox proportional hazards regression analyses. The risks were calculated as number of incidence cases divided by the number of person-years. Hazard ratios were calculated for factors related to the incidence and risk time of stroke and the relation between baseline depression and depression symptoms and the incidence and risk time of stroke.

Potential confounders considered were sex, education, smoking, hypertension, systolic and diastolic blood pressure, cholesterol levels, body mass index, diabetes mellitus, myocardial infarction, and treatment with anxiolytics, antidepressants or antihypertensives. Those variables that were significant at $P<0.10$ in these models (depression, systolic blood pressure) were then entered into a Cox regression analysis together with sex. The final model included depression at baseline, sex, and systolic blood pressure.

Because the significance of the Cox regression model parameter rests on large sample approximations, we also used these risk estimates to compare the significance level of the Cox models with a nonparametric exact test of the difference between 2 Poisson rates.[18] Because the results always agreed, we only report the results from the Cox models.

We also validated the Cox proportional model by including an interaction term with risk time. This did not improve the explanatory power of the model (change in χ^2 631.2 to 630.8).

Results

Depression at Age 85 in Relation to Stroke History at Age 85

Among all 85-year-olds, 93 had a history of stroke, 93 (18.8%; 67 of 351 women, 26 of 143 men) were diagnosed with depression (58 had major depression, 25 dysthymia, and

Table 1. Demographic Factors in Relation to Depression in 85-Year-Olds Without Previous Stroke

	Depression			
	Yes	No	OR (95% CI)	All, % (n/all)
Female gender, % (n/all)	69.4 (50/72)	70.5 (232/329)	1.0 (0.5–1.7)	70.3 (282/401)
High education, % (n/all)	26.1 (18/69)	25.3 (77/304)	1.2 (0.6–2.3)	25.5 (95/373)
Antidepressants, % (n/all)	9.7 (7/72)	4.0 (13/329)	2.6 (1.0–6.8)	5.0 (20/401)
Hypertension, % (n/all)	47.9 (34/71)	50.0 (163/326)	0.9 (0.6–1.5)	49.6 (197/397)
Systolic blood pressure, mean±SD	156±25	159±24	(*P*=0.383)	159±24
Diastolic blood pressure, mean±SD	75±15	80±12	(*P*=0.007)	79±12
Hypercholesterolemia, % (n/all)	18.3 (11/60)	24.1 (70/291)	0.7 (0.3–1.4)	23.1 (81/351)
Cholesterol, mean±SD	5.3±1.0	5.4±1.2	(*P*=0.611)	5.4±1.1
Diabetes mellitus, % (n/all)	7.2 (5/69)	7.5 (24/321)	1.0 (0.4–2.6)	7.4 (29/390)
Current smoker, % (n/all)	7.2 (5/69)	6.6 (21/319)	1.1 (0.4–3.1)	6.7 (26/388)
Past smoker, % (n/all)	26.1 (18/69)	24.1 (77/319)	1.1 (0.6–2.0)	24.5 (95/388)
Alcohol consumption, % (n/all)	41.4 (29/70)	38.6 (114/295)	1.1 (0.6–1.9)	39.2 (143/365)
Overweight (body mass index >25 kg/m^2), % (n/all)	43.1 (22/51)	47.6 (117/246)	0.8 (0.5–1.5)	46.8 (139/297)
Body mass index, mean±SD, % (n/all)	27.1±3.8	26.5±3.5	(*P*=0.560)	26.6±3.6
Atrial fibrillation, % (n/all)	9.7 (6/62)	10.8 (31/288)	0.9 (0.4–2.2)	10.6 (37/350)
Myocardial infarction, % (n/all)	13.0 (9/69)	10.8 (34/316)	1.3 (0.6–3.1)	11.1 (43/385)
3-year mortality rate, % (n/all)	36.1 (26/72)	26.4 (87/329)	1.9 (1.0–3.6)	28.1 (113/401)

10 depression not otherwise specified), and 147 (108 women, 39 men) were diagnosed with dementia. The prevalence of depression was similar in those with and without stroke at age 85 (22.6% [N=21 of 93] versus 18.0% [N=72 of 401]; OR, 1.3; 95% CI, 0.8 to 2.3).

Among the 85-year-olds, 8.6% used antidepressants (N=8 of 93) among those with a stroke history and 5.0% (N=20 of 401) among those without (OR, 1.8; 95% CI, 0.8 to 4.2), 23.7% used neuroleptics (N=22 of 93) among those with stroke history and 11.7% (N=47 of 401) among those without (OR, 2.3; 95% CI, 1.3 to 4.1), and 35.5% used any anxiolytic drugs (N=33 of 93) in those with known stroke and 33.9% (N=136 of 401) in those without (OR, 1.1; 95% CI, 0.7 to 1.7). The significant association for neuroleptics disappeared completely when controlling for dementia, because those who were demented more often had previous stroke and more often had been receiving neuroleptics.

We also made separate analyses with the demented individuals excluded (N=147), leaving 347 nondemented 85-year-olds for analyses. Among these, 40 had a history of stroke, and 62 (17.9%; 45 of 243 women, 17 of 104 men) were diagnosed with depression (38 had major depression, 22 dysthymia, and 2 depression not otherwise specified). The prevalence of depression was similar in those with and without stroke at age 85 (15.0% [N=6 of 40] versus 18.2% [N=56 of 307]; OR, 0.8; 95% CI, 0.3 to 2.0).

Depression at Age 85 in Relation to 3-Year Incidence of Stroke

Demographic factors in relation to depression among stroke-free 85-year-olds are described in Table 1. Those with depression had a lower diastolic blood pressure, more often used antidepressants, and had a higher 3-year mortality rate than those without depression. These results were similar when demented individuals were excluded from the analyses.

Among 85-year-olds without stroke (n=401), 56 individuals had their first-ever stroke between ages 85 and 88 (according to self-reports in 19 cases, key informants in 19 cases, hospital linkage system and death certificates in 45 cases). The incidence of first-ever stroke was higher in those with depression at age 85 (116.5 of 1000 person-years) than in the rest of the sample (46.1 of 1000 person-years; relative risk [RR], 2.6; 95% CI, 1.5 to 4.6; *P*=0.0009). Depression at baseline was related to an increased incidence of stroke both among the demented (RR, 3.8; 95% CI, 1.2 to 9.8) and the nondemented (RR, 2.4; 95% CI, 1.2 to 4.6; Table 2). The risk of incident stroke was similar in those with major depression (RR, 1.9; 95% CI, 0.9 to 3.9) and those with dysthymic disorder (RR, 2.5; 95% CI, 0.9 to 5.8) at baseline.

A multivariate model, including depression at age 85, sex, and systolic blood pressure, found that depression at baseline (hazard ratio, 2.7; 95% CI, 1.5 to 4.7; *P*=0.0006) and systolic blood pressure (HR, 1.014 per 1 mm Hg; 95% CI, 1.00 to 1.03; *P*=0.019) were independently related to the incidence of first-ever stroke. The results were similar when demented and nondemented individuals were analyzed separately.

We then examined whether the 9 specific symptom clusters included in the Diagnostic and Statistical Manual of Mental Disorders, Third Revision criteria were related to the incidence of stroke in the whole sample. We also examined whether anxiety, common in depression but not included in the criteria, was related to the incidence of stroke in the whole sample. Among these 10 symptoms, only depressed mood and loss of interest or pleasure were related to an increased incidence of stroke in univariate analyses considering each symptom separately (Table 3). A Cox regression multivariable model including all 10 symptoms showed that only

Table 2. Three-Year Incidence of Stroke in Relation to Depression in 85-Year-Olds Without Stroke at Baseline

	N	Stroke Events	Risk-Years	Stroke per 1000 Years (95% CI)	RR (95% CI)
All participants	401	56	979.1	57.2 (43.2–74.3)	
No depression	329	38	824.5	46.1 (32.6–63.3)	
Women	232	31	593.1	52.3 (35.5–74.2)	
Men	97	7	231.4	30.3 (12.2–62.3)	
Depression	72	18	154.6	116.5 (69.0–184.0)	2.6 (1.5–4.6)*
Women	50	16	109.2	146.6 (83.8–238.0)	2.9 (1.6–5.3)*
Men	22	2	45.4	44.1 (5.3–159.1)	1.4 (0.3–6.8)*
No dementia	307	43	777.6	55.3 (40.0–74.5)	
No depression	251	30	655.5	45.8 (30.9–65.3)	
Women	176	23	467.1	49.2 (32.2–74.1)	
Men	75	7	188.5	37.1 (14.9–76.5)	
Depression	56	13	122.0	106.5 (56.7–182.2)	2.4 (1.2–4.6)*
Women	40	12	89.4	134.3 (74.6–227.5)	2.8 (1.4–5.7)*
Men	16	1	32.7	30.6 (0.8–170.6)	0.8 (0.1–6.5)*
Demented	94	13	201.5	64.5 (34.3–110.4)	
No depression	78	8	168.9	47.4 (20.4–93.3)	
Women	56	8	126.0	63.5 (27.4–125.1)	
Men	22	0	42.9		
Depression	16	5	32.5	153.7 (49.9–358.7)	3.8 (1.2–9.8)*
Women	10	4	19.8	202.1 (55.1–517.6)	3.2 (1.0–11.6)*
Men	6	1	12.7	78.5 (2.0–437.4)	...

*Compared with no depression. Sex is controlled for in all analyses in which men and women are analyzed together.

depressed mood was independently related to an increased risk for stroke. The findings were similar when demented individuals were excluded.

Use of Psychotropic Drugs at Age 85 in Relation to the Incidence of Stroke

Use of psychotropic drugs at age 85 was not related to stroke incidence at follow-up (Table 4). These results did not change after controlling for depression at age 85 and excluding demented individuals.

Table 3. Three-Year Incidence of Stroke in Relation to Specific Symptoms of Depression in All 85-Year-Olds Considering Each Symptom Separately

	Stroke Events (N=56)	RR (95% CI)
Depressed mood (N=108)	24	2.4 (1.4–4.2)
Loss of interest and pleasure (N=73)	15	2.0 (1.0–3.7)
Decreased appetite (N=76)	14	1.6 (0.8–3.0)
Sleep problems (N=80)	14	1.3 (0.7–2.5)
Psychomotor retardation/agitation (N=112)	16	1.2 (0.6–2.2)
Loss of energy, fatigue (N=174)	23	0.9 (0.5–1.7)
Feelings of worthlessness (N=30)	7	2.1 (0.8–4.6)
Cognitive symptoms (N=72)	15	1.7 (0.9–3.1)
Suicidal feelings (N=56)	9	1.3 (0.6–2.6)
Anxiety (N=37)	5	1.0 (0.3–2.4)

Discussion

We found that depression was associated with an increased incidence of first-ever stroke in a representative population of 85-year-olds followed for 3 years. The increased risk was found both among the demented and the nondemented. Our results are in accordance with recent studies in younger, nondemented age groups and further support the hypothesis that depression may be a risk factor, or prodrome, for stroke.[6–8,11] The relative risk (2.6) in our study is similar to that reported by Larson et al (2.7),[7] Jonas and colleagues (RR, 1.7),[8] and Ohira et al (RR, 1.9).[6] These studies were, however, conducted in younger samples, in which the incidence of stroke was relatively low, and individuals with stroke at baseline were not excluded. Interestingly, Salaycik et al found an increased stroke incidence in those with depressive symptoms only in individuals aged younger than 65.[11] Our findings are also in accordance with data from the Women's Health Initiative based on 94 000 younger women indicating that depression is a risk factor for stroke incidence.[10] The current data provide evidence that in women, this effect persists even among the very old.

The prevalence of depression in our study was 19% among nondemented 85-year-olds compared with 7.5% to 13.0% in the other studies. The incidence of stroke in our study was 57.2 per 1000 person-years compared with 7.6 per 1000 person-years in the study by Ohira et al.[6] The frequency of both depression and stroke is high in very old individuals. Thus, population-attributable risk of depression for stroke

Table 4. Three-Year Incidence of Stroke in Relation to the Use of Psychotropic Drugs in 85-Year-Olds Without Stroke at Baseline

	N	Stroke Events	Risk-Years	Stroke per 1000 Years (95% CI)	RR (95% CI)*
All participants	401	56	979.1	57.2 (43.2–74.3)	
No psychotropic drug	234	29	586.9	49.4 (33.1–71.0)	
Any psychotropics	167	27	392.1	68.9 (45.4–100.2)	1.4 (0.8–2.4)
Antidepressants	20	5	50.0	100.0 (32.5–233.3)	2.0 (0.6–5.3)
Neuroleptics	47	7	102.0	68.6 (27.6–141.3)	1.4 (0.5–3.2)
Anxiolytics	136	23	319.6	72.0 (45.6–108.0)	1.5 (0.8–2.6)

*Compared with those without psychotropic drugs.

risk is considerable, which is important in relation to prevention. We further found that depressed mood, which was found in 27% of the 85-year-olds, was the only individual symptom in the depression syndrome that was independently related to increased risk of first-ever stroke. Our findings suggest that detection of depression, and even milder forms of depressed mood, may be important for stroke prevention in the elderly.

Another interesting finding, which we are the first to report, was that depression increased risk for first-ever stroke also among demented individuals. One third of the 85-year-olds in our study had dementia,[13] and 57% of the demented had a stroke history already at baseline.[2] Dementia was not related to incidence of first-ever stroke in our study, but some other studies have reported an increased incidence of stroke in demented individuals.[19,20] Our finding is remarkable because depression is difficult to assess in demented individuals. Support for the validity of the diagnosis is that all individuals were assessed by a psychiatrist during a 1.5-hour examination.

The association between depression and first-ever stroke may have several explanations. First, depression has been associated with myocardial arrhythmia,[21] increased platelet activation,[22] and increased insulin resistance.[23] These changes in the vascular system might increase the risk of stroke. Second, depression has been associated with several risk factors for stroke, eg, smoking, high body mass index, and increased blood pressure. However, none of these factors were related to depression in our study. Instead, lower diastolic blood pressure was associated with depression at baseline, especially among the nondemented. Besides depression, only higher systolic blood pressure at baseline was related to increased incidence of stroke, but increased blood pressure did not affect the relation between depression at baseline and stroke incidence. Third, late-life depression has been suggested to be related to silent cerebrovascular diseases such as ischemic white matter lesions, which are related to an increased incidence of stroke.[24] Although depression was not related to ischemic white matter lesions on CT in this sample,[25] it is possible that the use of MRI would have detected more cases of mild white matter lesions. Fourth, depression exerts large stress on the individual, which might increase the risk of stroke. Finally, depression might lead to lower drug compliance, including antihypertensive drugs, which may increase the risk of stroke.

In contrast to numerous clinical studies,[3] a history of stroke was not related to depression at baseline. Survival effect may be one reason because both stroke and depression are related to an increased mortality rate, and depression is related to increased mortality in patients with stroke. This may attenuate a relation between stroke and depression in cross-sectional studies.

Among the strengths of the study are that the diagnosis of depression was based on an interview conducted by a psychiatrist, the extensive data-gathering, that the sample was representative of the general population in this age group and included both individuals living in the community as well as in institutions,[13] and that dementia and stroke were diagnosed with comprehensive assessments. As reported previously, the detection of stroke in the elderly depends on the number of information sources.[2] We used 3 sources of information (self-report, hospital register, key informants). Using several information sources to detect stroke was especially important regarding exclusion of stroke at baseline because unreported strokes probably are related to an increased risk for stroke at follow-up. There are also some limitations. First, 20% of the sample did not have key informant interviews, which may have underestimated the frequency of stroke. The frequency of stroke might also be underestimated by the fact that silent strokes identified by imaging were not included in this study. Second, some subgroups in this study included small numbers, yielding low statistical power. It is possible that a larger sample might have revealed significant associations between depression and incidence of stroke also in men. Third, in contrast to other studies,[7] we also included dysthymia for the diagnosis of depression, which might result in an overestimation of depressive disorders. Fourth, it has to be emphasized that a study on 85-year-olds includes the possibility of survival effects. However, both depression and stroke are related to an increased mortality rate, and survival effects should rather decrease the possibility to find associations between these factors.

In conclusion, the findings from this study may have clinical implications because depression and stroke are common in the elderly. The possible risk reduction of stroke is thus one more reason why individuals with depression should be diagnosed and adequately treated. However, randomized, controlled trials are needed before any conclusions can be made regarding the effect of antidepressants for stroke prevention. Most epidemiological studies report that only a small minority of all individuals with depression are detected and treated.[1] Depressive disorders disrupt social function and reduce quality of life for both patients and their relatives and

cause excess disability and mortality in the elderly. It is also the most important factor for suicide in the elderly. Our findings further emphasize that even mild depression is a serious disorder with serious consequences. The SADHART study found that treatment of depression with sertraline in patients with acute myocardial infarction or unstable angina decreased platelet activation[26] and cardiovascular events.[27] Whether successful treatment of depression may reduce the incidence of first-ever stroke needs to be further elucidated. Even if depression treatment does not reduce stroke incidence,[11] patients with depression may be an important target for control and optimizing of other vascular risk factors.

Acknowledgments

We thank Valter Sundh for his technical assistance.

Sources of Funding

This project was supported by grants from the European Neurological Society, the Swedish Research Council (No. 11267 and 825-2007-7462), Swedish Council for Working Life and Social Research (No. 1154), Stiftelsen Söderström-Königska Sjukhemmet, Stiftelsen för Gamla Tjänarinnor, Handlanden Hjalmar Svenssons Forskningsfond, The Swedish Society of Medicine, The Göteborg Medical Society, and the Fredrik and Rosa von Malmborgs Foundation for Brain Research.

Disclosures

None.

References

1. Palsson S, Skoog I. The epidemiology of affective disorders in the elderly: a review. *Int Clin Psychopharmacol*. 1997;12(suppl 7):S3–13.
2. Liebetrau M, Steen B, Skoog I. Stroke in 85-year-olds. Prevalence, incidence, risk factors and relation to mortality and dementia. *Stroke*. 2003;34:2617–2622.
3. Desmond DW, Remien RH, Moroney JT, Stern Y, Sano M, Williams JB. Ischemic stroke and depression. *J Int Neuropsychol Soc*. 2003;9:429–439.
4. Morris PL, Robinson RG, Andrzejewski P, Samuels J, Price TR. Association of depression with 10-year poststroke mortality. *Am J Psychiatry*. 1993;150:124–129.
5. Grippo AJ, Beltz TG, Johnson AK. Behavioral and cardiovascular changes in the chronic mild stress model of depression. *Physiol Behav*. 2003;78:703–710.
6. Ohira T, Iso H, Satoh S, Sankai T, Tanigawa T, Ogawa Y, Imano H, Sato S, Kitamura A, Shimamoto T. Prospective study of depressive symptoms and risk of stroke among Japanese. *Stroke*. 2001;32:903–908.
7. Larson SL, Owens PL, Ford D, Eaton W. Depressive disorder, dysthymia, and risk of stroke: thirteen-year follow-up from the Baltimore Epidemiologic Catchment Area Study. *Stroke*. 2001;32:1979–1983.
8. Jonas BS, Mussolino ME. Symptoms of depression as a prospective risk factor for stroke. *Psychosom Med*. 2000;62:463–471.
9. Simonsick EM, Wallace RB, Blazer DG, Berkman LF. Depressive symptomatology and hypertension-associated morbidity and mortality in older adults. *Psychosom Med*. 1995;57:427–435.
10. Wassertheil-Smoller S, Shumaker S, Ockene J, Talavera GA, Greenland P, Cochrane B, Robbins J, Aragaki A, Dunbar-Jacob J. Depression and cardiovascular sequelae in postmenopausal women. The Women's Health Initiative (WHI). *Arch Intern Med*. 2004;164:289–298.
11. Salaycik KJ, Kelly-Hayes M, Beiser A, Nguyen AH, Brady SM, Kase CS, Wolf PA. Depressive symptoms and risk of stroke. *Stroke*. 2007;38:16–21.
12. Henon H, Pasquier F, Durieu I, Godefroy O, Lucas C, Lebert F, Leys D. Preexisting dementia in stroke patients. Baseline frequency, associated factors, and outcome. *Stroke*. 1997;28:2429–2436.
13. Skoog I, Nilsson L, Palmertz B, Andreasson LA, Svanborg A. A population-based study of dementia in 85-year-olds. *N Engl J Med*. 1993;328:153–158.
14. Skoog I. The prevalence of psychotic, depressive and anxiety syndromes in demented and non-demented 85-year-olds. *Int J Geriatric Psychiatry*. 1983;8:247–253.
15. Rinder L, Roupe S, Steen B, Svanborg A. Seventy-year-old people in Gothenburg. A population study in an industrialized Swedish city. *Acta Med Scand*. 1975;198:397–407.
16. Svanborg A. Seventy-year-old people in Gothenburg a population study in an industrialized Swedish city. II. General presentation of social and medical conditions. *Acta Med Scand Suppl*. 1977;611:5–37.
17. Skoog I, Nilsson L, Landahl S, Steen B. Mental disorders and the use of psychotropic drugs in an 85-year-old urban population. *Int Psychogeriatr*. 1993;5:33–48.
18. Cox DR, Hinkley DV. *Theoretical Statistics*. London: Chapman & Hall; 1974:136–137.
19. Zhu L, Fratiglioni L, Guo Z, Winblad B, Viitanen M. Incidence of stroke in relation to cognitive function and dementia in the Kungsholmen Project. *Neurology*. 2000;54:2103–2107.
20. Barba R, Morin MD, Cemillan C, Delgado C, Domingo J, Del Ser T. Previous and incident dementia as risk factors for mortality in stroke patients. *Stroke*. 2002;33:1993–1998.
21. Frasure-Smith N, Lesperance F, Talajic M. Depression and 18-month prognosis after myocardial infarction. *Circulation*. 1995;91:999–1005.
22. Musselman DL, Tomer A, Manatunga AK, Knight BT, Porter MR, Kasey S, Marzec U, Harker LA, Nemeroff CB. Exaggerated platelet reactivity in major depression. *Am J Psychiatry*. 1996;153:1313–1317.
23. Okamura F, Tashiro A, Utumi A, Imai T, Suchi T, Tamura D, Sato Y, Suzuki S, Hongo M. Insulin resistance in patients with depression and its changes during the clinical course of depression: minimal model analysis. *Metabolism*. 2000;49:1255–1260.
24. Vermeer SE, Hollander M, van Dijk EJ, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and white matter lesions increase stroke risk in the general population: the Rotterdam Scan Study. *Stroke*. 2003;34:1126–1129.
25. Skoog I, Palmertz B, Andreasson LA. The prevalence of white-matter lesions on computed tomography of the brain in demented and nondemented 85-year-olds. *J Geriatr Psychiatry Neurol*. 1994;7:169–175.
26. Serebruany VL, Glassman AH, Malinin AI, Nemeroff CB, Musselman DL, van Zyl LT, Finkel MS, Krishnan KR, Gaffney M, Harrison W, Califf RM, O'Connor CM. Platelet/endothelial biomarkers in depressed patients treated with the selective serotonin reuptake inhibitor sertraline after acute coronary events: the Sertraline AntiDepressant Heart Attack Randomized Trial (SADHART) Platelet Substudy. *Circulation*. 2003;108:939–944.
27. Glassman AH, O'Connor CM, Califf RM, Swedberg K, Schwartz P, Bigger JT Jr, Krishnan KR, van Zyl LT, Swenson JR, Finkel MS, Landau C, Shapiro PA, Pepine CJ, Mardekian J, Harrison WM, Barton D, McIvor M. Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA*. 2002;288:701–709.

Depression as a Risk Factor for the Incidence of First-Ever Stroke in 85-Year-Olds

Martin Liebetrau, Bertil Steen and Ingmar Skoog

Stroke. 2008;39:1960-1965; originally published online May 1, 2008;
doi: 10.1161/STROKEAHA.107.490797
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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