The Association Between Stroke, Depression, and 5-Year Mortality Among Very Old People

Carl Hornsten, MD; Hugo Lövheim, MD, PhD; Yngve Gustafson, MD, PhD

Background and Purpose—Depression after stroke has been associated with increased mortality, but little is known about this association among very old people.

Methods—A population-based study among people ≥85 years of age was conducted in northern Sweden and Finland, comprising cross-sectional assessments and subsequent survival data. The 452 individuals who had completed the Geriatric Depression Scale-15 assessment were selected. Depression was defined as a score of ≥5 on the geriatric depression scale.

Results—Of those with a history of stroke, 38 of 88 (43.2%) people were depressed, and 11 of the 38 (28.9%) were treated with antidepressants, compared with 91 of 364 (25.0%) depressed (P=0.001) and 17 of 91 (18.7%) treated with antidepressants among those without stroke. Having a history of stroke and ongoing depression was associated with increased 5-year mortality compared with having only stroke (hazard ratio, 1.90; confidence interval, 1.15–3.13), having only depression (hazard ratio, 1.59; confidence interval, 1.03–2.45), and compared with having neither stroke nor depression (hazard ratio, 2.50; confidence interval, 1.69–3.69). Having only stroke without depression did not increase mortality compared with having neither stroke nor depression.

Conclusions—A history of stroke was associated with increased mortality among very old people but only among those who were also depressed. Depression seemed to be underdiagnosed and undertreated. (Stroke. 2013;44:2587-2589.)

Key Words: cerebrovascular disorders • depression • epidemiology • mortality • stroke • very old

Very old people have a high prevalence of stroke and depression. Past studies have indicated that depression after stroke increases mortality,1-3 but very old people are underrepresented in the literature. In addition, stroke-free comparison groups have rarely been used. Only 1 study4 has investigated the association between depression and mortality among people with stroke compared with stroke-free comparison groups, and it did not include any participants who were very old.

The aim of this article was to investigate the association between depression and mortality among people who had stroke compared with people without stroke using a population-based sample of people ≥85 years age.

Materials and Methods

Study Setting
This article is based on a population-based study among very old people in northern Sweden and Finland, which took place between 2005 and 2007. Half of the 85-year-old, all 90-year-old, and all ≥25-year-old population were invited to participate. The study was approved by regional ethical review boards.

Sample Selection
Of 962 individuals eligible for participation, the 452 people who had completed the Geriatric Depression Scale-15 during a home visit were selected.

Data Collection
Cross-sectional data were collected through structured interviews and assessments with the participants in their homes, interviews with staff and relatives, and investigation of medical charts. Participants or their close relatives gave informed consent. Cross-sectional data and 5-year survival data were combined to form cohort data.

Assessment Scales
The Geriatric Depression Scale 15-item version consists of 15 questions that screen for depressive symptoms. Five points or more is considered to indicate depression.

The Mini-Mental State Examination is a test for cognitive impairment. The scores range from 0 to 30, where a higher score indicates better cognitive function.

The Barthel Activities of Daily Living Index is an assessment of functional dependence. The scale ranges from 0 to 20, where a score of 20 indicates independence in personal activities of daily living.

Medical Diagnoses and Definitions
Depression was considered to be present with a Geriatric Depression Scale-15 score of ≥5. Stroke was considered to be present if the medical charts included a stroke diagnosis or if the individual, a caregiver, or a relative reported the diagnosis and it was found to be credible on the basis of supporting information in medical charts or from other assessments.
Statistical Analysis
R 2.15.2 was used. Pearson χ² test was used to compare proportions. Welch t test was used to compare means. Survival was analyzed using Kaplan–Meier curves and Cox proportional hazards regression. The variable age seemed to break the proportional hazards assumption, so it was entered as a time-dependent variable. A P value of <0.05 was considered statistically significant (see online-only Data Supplement for additional methodological details).

Results
In the total sample, 88 of 452 (19.5%) people had a history of stroke, and 129 (28.5%) were depressed. Thirty-eight of 88 (43.2%) people with a history of stroke were depressed compared with 91 of 364 (25.0%) people without stroke (P=0.001). Among those depressed, 11 of 38 (28.9%) people with a history of stroke were treated with antidepressants compared with 17 of 91 (18.7%) people without stroke. In addition, 19 of 88 (21.6%) people with a history of stroke were treated with antidepressants compared with 45 of 364 (12.4%) people without stroke (P=0.040). Among those treated with antidepressants, 11 of 19 (57.9%) people with a history of stroke were still depressed, compared with 17 of 45 (37.8%) people without stroke.

After 5 years, 62 of 88 (70.5%) people with a history of stroke had died compared with 198 of 364 (54.4%) people without stroke (P=0.009). In univariate regression models, having a history of stroke (hazard ratio [HR], 1.53; confidence interval [CI], 1.15–2.03) and being depressed (HR, 1.72; CI, 1.33–2.22) were associated with increased 5-year mortality. The sample was divided into factorial groups on the basis of stroke and depression status for further analysis. Kaplan–Meier survival curves for the 4 groups are presented in the Figure.

Having a history of stroke and ongoing depression was associated with increased 5-year mortality compared with having only stroke (HR, 1.90; CI, 1.15–3.13), having only depression (HR, 1.59; CI, 1.03–2.45), and having neither stroke nor depression (HR, 2.50; CI, 1.69–3.69). Having only a history of stroke without depression was not associated with increased 5-year mortality compared with having neither stroke nor depression (HR, 1.31; CI, 0.89–1.94). The group differences remained after adjusting for age and sex but were weakened after adjusting for Mini-Mental State Examination or Barthel Activities of Daily Living Index (Tables I and II in the online-only Data Supplement).

Discussion
A history of stroke increased mortality among very old people with ongoing depression, but not among those without depression, indicating that the increased mortality from stroke was strongly associated with depression. In a similar study among younger individuals, the increased mortality from stroke did not seem to be associated with depression. The finding that ongoing depression was associated with increased mortality among very old people who had had a stroke is in line with previous results from stroke cohorts, including 1 study with a very old mean age, although negative results have also been reported.

The increased mortality among very old people with a history of stroke was associated with depression, functional dependence, and cognitive impairment. When functional dependence or cognitive impairment was controlled for, the association between depression and mortality was weakened, indicating a clustering of factors associated with mortality. It is possible that among people with stroke, depression leads to cognitive impairment and functional dependence, in turn causing mortality, or that cognitive impairment and functional dependence lead to depression, in turn causing mortality.

It is notable that in the present study, only 28.9% of people with a history of stroke and ongoing depression were treated with antidepressants, indicating undertreatment. From another perspective, 57.9% of those with a history of stroke who were treated with antidepressants were still depressed, indicating only a modest response to treatment among the participants in this study. Although antidepressants could improve survival, it has to be considered that depression may only be a risk marker for mortality, in which case medication may not help.

Strengths and Limitations
The use of an assessment scale cut-off value to define depression might have led to an overestimation of the prevalence of depression. Furthermore, diagnosed depression in the medical charts and use of antidepressant medication were not used to evaluate depression, which means that successfully treated depressive patients would not have been considered depressed. However, one benefit of this approach is increased transparency and reproducibility.

Because cross-sectional data were used for the baseline assessments, the temporal onset of stroke in relation to depression was not taken into account. Many participants had a stroke several years ago, which means that the results might represent the long-term effects of stroke rather than the immediate effects.
The number of dropouts was not negligible, although a high dropout rate can be expected when investigating very old people. Although it is likely that the dropouts had more functional impairments compared with the participants, the present study still included many individuals with cognitive and physical impairments.

Collecting baseline data during home visits may have not only improved the participation rate but also resulted in less detailed assessments (e.g., the absence of blood tests or radiological parameters). The limitations of the baseline data collection and the moderate sample size may have limited the investigation of possible confounding factors, especially vascular risk factors.

Each age group contributed roughly a third of the included individuals, which makes the age distribution skewed to include more people of higher age compared with a random sample of individuals ≥85 years of age. To account for this, the multivariate regression models were adjusted for age.

Conclusions
The present study highlights that the combination of stroke and depression leads to high mortality among very old people. Treatment of depression with antidepressants seems to be underused among very old people, but could potentially improve their survival. Research into treatment of depression after stroke, specifically among very old people, is indicated.

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Disclosures
None.

References
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Cover title: Stroke, depression, and mortality in very old age

Tables and figures:

- Supplementary table I. Clinical characteristics for the sample.
- Supplementary table II. Cox regression models of group differences in five-year mortality.

Key words: cerebrovascular disorders, stroke, depression, mortality, epidemiology, very old

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Supplemental methods

Study setting

The population-based Gerontological Regional Database (GERDA) study was started in 2000 to investigate factors that affect the general health and well-being of very old people in one urban municipality and five rural municipalities in the Swedish county of Västerbotten. Between 2005 and 2007, a second data collection was performed in these municipalities and the study was extended to include data from two municipalities in the Finnish county of Pohjanmaa as well.

In the chosen municipalities, half of the 85-year-olds, all 90-year-olds, and all of those aged 95 years and older were invited to participate. Every other person on a list of 85-year-olds was contacted. There were no exclusion criteria apart from age. The study was approved by the Regional Ethical Review Board in Umeå (§99-326, §05-063M) and the Ethics Committee of Vaasa Central Hospital (§05-87).

Sample selection

Cross-sectional data from the 2005-2007 data collection from Sweden and Finland, and survival data ranging five years forward for each participant were combined to form cohort data. Of the 962 individuals eligible for participation, 76 died before they could be contacted, 170 declined to participate, 97 declined a home visit, and 7 were not included for other reasons; this left 612 people who were visited in their homes. Those not visited in their homes did not differ with regard to sex or age. Out of the 612 people who were visited in their homes, 124 individuals were not assessed with the Geriatric Depression Scale-15 (GDS-15), and 36 individuals answered 13 or fewer questions from the assessment. Those visited in their homes with missing or incomplete GDS-15 assessments were slightly older (1.073 years, p=0.015) and had substantially lower scores on the Mini-Mental State Examination (-10.520 points, p<0.001) and the Barthel Activities of Daily Living Index (-7.674 points, p<0.001) compared to those with complete assessments. The 452 people who had been assessed with the GDS-15 during a home visit with 14 or 15 of the full 15 questions answered were selected for this paper.

Data collection

Cross-sectional data about the participants was collected through structured interviews and assessments with the participants in their homes, interviews with staff and/or relatives, and investigation of medical charts from hospitals and general practitioners. The data collectors were physicians, medical students, physiotherapists, and nurses. A member of the staff of data collectors contacted every individual to acquire informed consent to full or partial participation. If cognitive impairment was suspected, informed consent was sought from a relative.

Time of death data was acquired from the Swedish National Tax Board or digital medical records in Sweden, and from the Population Register Center in Finland.

Assessment scales

The Geriatric Depression Scale 15-item version (GDS-15)1 consists of 15 questions that screen for depressive symptoms. Five points or more is considered to indicate depression1. The GDS-15 is considered a valid screening tool for depression among older individuals2 and it has been found to be one of the best depression rating scales for geriatric stroke patients
with regard to sensitivity and predictive value\textsuperscript{3}. The GDS-15 has been found to be useful to assess depressive symptoms for people with cognitive impairment as well (MMSE\textgeq10)\textsuperscript{4}.

The Mini-Mental State Examination (MMSE)\textsuperscript{5} is a test for cognitive impairment. The scores range from 0 to 30, where a higher score indicates better cognitive function.

The Barthel Activities of Daily Living (Barthel ADL, B-ADL) Index\textsuperscript{6} is an assessment of functional dependence. The scale ranges from 0 to 20, where a score of 20 indicates independence in personal ADL.

**Medical diagnoses and definitions**

Depression was considered to be present with a GDS-15 score of five or more.

Stroke was considered to be present if the medical charts included a stroke diagnosis, or if the individual, a caregiver, or a relative reported the diagnosis and it was found to be credible based on supporting information in the medical charts or from other assessments. Both ischemic and hemorrhagic strokes were included. Every diagnosis was evaluated according to the same criteria by a specialist in geriatric medicine (YG) for all patients both in Sweden and in Finland.

Survival times were calculated as the difference in days between the time of inclusion into the study and the time of death, with right censoring after five years.

**Statistical analysis**

The statistical analyses were performed with R version 2.15.2 and its survival package. Pearson’s Chi-square test was used to compare proportions between groups. Welch’s t-test was used to compare means between groups. Cumulative survival was compared between groups using Kaplan-Meier curves for plotting, and Cox proportional hazards regression for descriptives and statistical testing. The assumption of proportional hazards was tested with regression analyses of scaled Schoenfeld residuals against ranked time. Percentages, means, and hazard ratio (HR) were used to describe group differences. A p value of \textless 0.05 was considered statistically significant.

Differences between groups five-year mortality were tested with Cox proportional hazards models. Every group was compared to every other group. The univariate models were complemented with multivariate models, where the variables sex, age, MMSE score, and Barthel ADL Index score were entered as covariates. Covariate selection was based on clinical relevance, but only a small number of covariates could be included due to the small number of events in some groups. The MMSE score and Barthel ADL Index score were entered in separate models due to a strong correlation between the variables. The variable age appeared to break the assumption of proportional hazards, so it was time-transformed with a penalized spline function, and then entered as a time-dependent variable in the final models.
Supplemental tables

Supplementary table I. Clinical characteristics for the sample.

<table>
<thead>
<tr>
<th></th>
<th>Total n=452</th>
<th>No stroke GDS&lt;5 n=273</th>
<th>No stroke GDS≥5 n=91</th>
<th>Stroke GDS&lt;5 n=50</th>
<th>Stroke GDS≥5 n=38</th>
<th>χ²/t test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>311 (68.8)</td>
<td>188 (68.9)</td>
<td>65 (71.4)</td>
<td>29 (58.0)</td>
<td>29 (76.3)</td>
<td>0.260</td>
</tr>
<tr>
<td>Swedish</td>
<td>324 (71.7)</td>
<td>189 (69.2)</td>
<td>65 (71.4)</td>
<td>38 (76.0)</td>
<td>32 (84.2)</td>
<td>0.240</td>
</tr>
<tr>
<td>Institutionalized</td>
<td>135 (29.9)</td>
<td>65 (23.8)</td>
<td>30 (33.0)</td>
<td>18 (36.0)</td>
<td>22 (57.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dementia</td>
<td>130 (28.8)</td>
<td>68 (24.9)</td>
<td>30 (33.0)</td>
<td>16 (32.0)</td>
<td>16 (42.1)</td>
<td>0.097</td>
</tr>
<tr>
<td>Heart disease</td>
<td>295 (65.3)</td>
<td>165 (60.4)</td>
<td>64 (70.3)</td>
<td>36 (72.0)</td>
<td>30 (78.9)</td>
<td>0.047</td>
</tr>
<tr>
<td>Diabetes</td>
<td>68 (15.0)</td>
<td>42 (15.4)</td>
<td>8 (8.8)</td>
<td>10 (20.0)</td>
<td>8 (21.1)</td>
<td>0.184</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>64 (14.2)</td>
<td>28 (10.3)</td>
<td>17 (18.7)</td>
<td>8 (16.0)</td>
<td>11 (28.9)</td>
<td>0.008</td>
</tr>
<tr>
<td>Age</td>
<td>89.9±4.4</td>
<td>89.7±4.4</td>
<td>90.9±4.6</td>
<td>89.0±4.1</td>
<td>90.7±4.4</td>
<td>0.042</td>
</tr>
<tr>
<td>GDS</td>
<td>3.6±2.6</td>
<td>2.2±1.2</td>
<td>6.8±2.0</td>
<td>2.5±1.2</td>
<td>7.1±2.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MMSE</td>
<td>22.3±5.3</td>
<td>23.1±5.3</td>
<td>20.9±4.7</td>
<td>22.2±5.0</td>
<td>19.8±6.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Barthel ADL</td>
<td>17.5±4.1</td>
<td>18.2±3.6</td>
<td>16.7±4.3</td>
<td>17.4±4.3</td>
<td>14.4±5.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP</td>
<td>147.7±23.0</td>
<td>146.9±21.9</td>
<td>149.7±27.6</td>
<td>148.3±20.8</td>
<td>147.5±22.0</td>
<td>0.851</td>
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<tr>
<td>BMI</td>
<td>25.5±4.2</td>
<td>25.4±4.0</td>
<td>26.1±4.4</td>
<td>25.4±4.2</td>
<td>25.3±5.3</td>
<td>0.635</td>
</tr>
</tbody>
</table>

GDS, Geriatric Depression Scale-15. MMSE, Mini-Mental State Examination. Barthel ADL, Barthel Activities of Daily Living Index. SBP, systolic blood pressure. BMI, body mass index. Numbers within parenthesis are percentages of column totals. Numbers after plus-minus signs are standard deviations. χ²/t test, statistical testing of group differences with Pearson’s Chi-square tests for proportions and generalized Welch’s t tests for means.
Supplementary table II. Cox regression models of group differences in five-year mortality.

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th>Basic model</th>
<th>Model w. MMSE</th>
<th>Model w. B-ADL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>CI</td>
<td>HR</td>
<td>CI</td>
</tr>
<tr>
<td>Group 2 v. 1</td>
<td>1.57*</td>
<td>1.16-2.13</td>
<td>1.46‡</td>
<td>1.07-1.98</td>
</tr>
<tr>
<td>Group 3 v. 1</td>
<td>1.31</td>
<td>0.89-1.94</td>
<td>1.31</td>
<td>0.88-1.94</td>
</tr>
<tr>
<td>Group 4 v. 1</td>
<td>2.50‡</td>
<td>1.69-3.69</td>
<td>2.56‡</td>
<td>1.72-3.81</td>
</tr>
<tr>
<td>Group 2 v. 2</td>
<td>0.84</td>
<td>0.54-1.29</td>
<td>0.90</td>
<td>0.58-1.39</td>
</tr>
<tr>
<td>Group 3 v. 2</td>
<td>1.59‡</td>
<td>1.03-2.45</td>
<td>1.75‡</td>
<td>1.13-2.71</td>
</tr>
<tr>
<td>Group 4 v. 3</td>
<td>1.90‡</td>
<td>1.15-3.13</td>
<td>1.95‡</td>
<td>1.17-3.25</td>
</tr>
</tbody>
</table>

Group 1, No stroke and GDS<5.
Group 2, No stroke and GDS≥5.
Group 3, Stroke and GDS<5.
Group 4, Stroke and GDS≥5.

HR, hazard ratio. CI, confidence interval. MMSE, Mini-Mental State Examination. B-ADL, Barthel Activities of Daily Living Index. GDS, Geriatric Depression Scale-15. The basic model was adjusted for age and sex. The two additional models were adjusted for age, sex, and MMSE or B-ADL respectively.* p<0.01. † p<0.001. ‡ p<0.05.
Supplemental references


