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Incidence of Depression After Stroke, and Associated Risk Factors and Mortality Outcomes, in a Large Cohort of Danish Patients

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IMPORTANCE More than 30 million people live with a stroke diagnosis worldwide. Depression after stroke is frequent, and greater knowledge of associated risk factors and outcomes is needed to understand the etiology and implications of this disabling complication.

OBJECTIVES To examine whether the incidence of and risk factors for depression differ between patients with stroke and a reference population without stroke and to assess how depression influences mortality.

DESIGN, SETTING, AND PARTICIPANTS Register-based cohort study in Denmark. Participants were all individuals 15 years or older with a first-time hospitalization for stroke between January 1, 2001, and December 31, 2011 (n = 157 243), and a reference population (n = 160 236) matched on age, sex, and municipality. The data were analyzed between January and March 2016.

MAIN OUTCOMES AND MEASURES The incidence of depression and mortality outcomes of depression (defined by hospital discharge diagnoses or antidepressant medication use) were examined using Cox proportional hazards regression analyses.

RESULTS In total, 34 346 patients (25.4%) with stroke and 11 330 (7.8%) in the reference population experienced depression within 2 years after study entry. Compared with the reference population, patients with stroke had a higher incidence of depression during the first 3 months after hospitalization (hazard ratio for stroke vs the reference population, 8.99; 95% CI, 8.61-9.39), which declined during the second year of follow-up (hazard ratio for stroke vs the reference population, 1.93; 95% CI, 1.85-2.08). Significant risk factors for depression for patients with stroke and the reference population included older age, female sex, single cohabitation status, basic educational attainment, diabetes, high level of somatic comorbidity, history of depression, and stroke severity (in patients with stroke). The associations were strongest for the reference population. In both populations, depressed individuals, especially those with new onset, had increased all-cause mortality (hazard ratio for new-onset depression, 1.89 [95% CI, 1.83-1.95] for patients with stroke and 3.75 [95% CI, 3.51-4.00] for the reference population) after adjustment for confounders. Similar patterns were found for natural and unnatural causes of death. In most models, the depression-related relative mortality was approximately twice as high in the reference population vs the stroke population.

CONCLUSIONS AND RELEVANCE Depression is common in patients with stroke during the first year after diagnosis, and those with prior depression or severe stroke are especially at risk. Because a large number of deaths can be attributable to depression after stroke, clinicians should be aware of this risk.

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Editorial
Supplemental content

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In 2013, more than 10 million people had a stroke, and in excess of 30 million people lived with a stroke diagnosis worldwide.[1] Depression is common after stroke, and studies[2-13] have evaluated its frequency, risk factors, and mortality. However, recent systematic reviews[2-4,9,13] of more than 50 cohorts have been hampered by heterogeneity across studies and small sample sizes; consequently, the reported frequency of depression after stroke has varied from 2% to 55% in population-based cohorts,[2-4,13] with pooled estimates between 29% and 31% in recent meta-analyses.[3,4] Only 2 studies[5,6] (with sample sizes <300) examining the risk of depression after stroke included a reference population selected from the community, and they indicated that, although depression is more common after stroke than in control individuals, the differences were not substantial and had largely disappeared after 1 year.

While a history of depression, stroke severity, and disability consistently have been associated with increased risk of depression after stroke, evidence for an association between depression after stroke and sociodemographic factors, lifestyle, or stroke features, such as subtype, is lacking.[4,7-11,13,14] Furthermore, most studies of risk factors have had insufficient sample size to detect small effects, to allow stable multiple regression analyses, or to explore whether stroke subtype or time of depression onset modifies the influence of potential risk factors.

A recent meta-analysis[12] of 13 studies revealed increased mortality in patients with depression after stroke, with a hazard ratio (HR) for mortality of 1.52 (95% CI, 1.01-2.26). The association seemed to be related to length of follow-up, with the HRs largest for follow-up less than 2 years (HR, 4.40; 95% CI, 1.75-11.09) and smallest for follow-up exceeding 5 years (HR, 1.28; 95% CI, 0.99-0.65). None of the studies compared the mortality rate in patients with depression after stroke with a depressed reference population.

Comparing incidence, risk factors, and mortality related to depression among patients with stroke and a reference population would provide better understanding of the mechanisms and consequences of depression after stroke. Therefore, the aims of this population-based cohort study were to test the following hypotheses: (1) depression is more frequent in patients after stroke than in a matched reference population, (2) risk factors for depression after stroke depend on stroke subtype and time of depression onset, and (3) depression after stroke has other risk factors than those associated with depression in a matched reference population. Furthermore, based on our findings in a previous study[15] of patients with acute coronary syndrome, we also hypothesized that depression would be less strongly associated with mortality from all, natural, and unnatural causes in patients with stroke than in the reference population.

Key Points

Question Do the incidence of and risk factors for depression differ between patients with stroke and a population without stroke and how does depression after stroke influence mortality?

Findings In this register-based cohort study of 157 243 patients with a first-time stroke, the incidence of depression during the first 3 months after stroke was 8 times higher than in a population without stroke, and depression after stroke was associated with prior depression and stroke severity. Absolute mortality rates were higher for all depression states in both populations, but relative mortality was lower in patients with stroke.

Meaning The high mortality associated with depression after stroke indicates that clinicians should be aware of this frequent comorbidity.

Methods

Data Sources

This register-based cohort study was based on linkage of data from the following 7 Danish nationwide registers: the Danish National Patient Registry, Danish Psychiatric Central Register, Danish Stroke Register, Danish Register of Causes of Death, Register of Medicinal Products Statistics, Danish Civil Registration System, and Population's Education Register.[16] The study was approved by the Danish Data Protection Agency. All data were retrieved from administrative registers, and informed consent was not required of participants.

Study Population

All first-time hospitalizations for stroke in individuals 15 years or older occurring in Denmark between January 1, 2001, and December 31, 2011 (n = 157 243) were included in the study. The data were analyzed between January and March 2016. Patients with stroke and transient ischemic attack were identified in the Danish National Patient Registry and the Danish Stroke Register by the following *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) codes: I61 (hemorrhagic stroke), I63 (ischemic stroke), I64 (unspecified stroke), and G45 (transient ischemic attack). The Danish Stroke Register was initiated in 2003 and provides information on selected stroke features for 53 046 patients with stroke.[17] A comparable reference group (n = 160 236) was sampled from the reference population by 1:1 matching on age, sex, and municipality on time of stroke diagnosis using information from the Danish Civil Registration System.

Depression

Depression was defined by a depression diagnosis in the Danish Psychiatric Central Register, Danish National Patient Registry, or Danish Register of Causes of Death (*ICD-10* codes F31.3-F34.1) or by filling of antidepressant prescriptions in the Register of Medicinal Products Statistics by Anatomic Therapeutic Chemical (ATC) Classification System code N06A as described in a previous study.[15] Study entry was defined as the date of stroke admission or matching. To comply with previous studies,[3,11] the study population was followed up for incident depression, categorized as early depression occurring within 3 months after study entry, intermediate depression occurring between 3 months and 1 year after study entry, and late depression occurring between 1 and 2 years after study entry.

Table 1. Number of Cases and Incidence of Early, Intermediate, and Late Depression After Study Entry (2001-2011) in 157 243 Danish Patients With Stroke and 160 236 Individuals in the Reference Population

Variable	Baseline			Follow-up for Depression			
	All Individuals	Current Depression	At Risk for Depression at Study Entry	Early Depression Between 0 and 3 mo	Intermediate Depression Between 3 mo and 1 y	Late Depression Between 1 and 2 y	All Incident Depression Between 0 and 2 y
Patients With Stroke							
Total No.	157 243	21 826	135 417	135 417	99 752	82 911	135 417
No. with depression onset	NA	NA	NA	17 690	11 365	5291	34 346
Person-years[a]	NA	NA	NA	27 610.2	67 501.4	77 739.0	172 850.6
IR (95% CI) of depression onset[b]	NA	NA	NA	601.7 (592.7-611.0)	168.4 (165.3-171.5)	68.1 (66.3-69.9)	198.0 (191.0-195.1)
Reference Population							
Total No.	160 236	14 737	145 499	145 499	142 804	135 307	145 499
No. with depression onset	NA	NA	NA	2449	4302	4579	11 330
Person- years[a]	NA	NA	NA	35 869.0	105 306.6	129 957.8	271 133.4
IR (95% CI) of depression onset[b]	NA	NA	NA	66.4 (63.8-69.1)	40.9 (39.6-42.1)	35.2 (34.2-36.3)	41.5 (40.7-42.3)
Patients With Stroke vs Reference Population							
HR (95% CI)	NA	NA	NA	8.99 (8.61-9.39)	4.06 (3.92-4.21)	1.93 (1.85-2.08)	4.32 (4.23-4.41)
Adjusted HR (95% CI)[c]	NA	NA	NA	8.53 (8.17-8.91)	3.84 (3.70-3.98)	1.82 (1.75-1.89)	4.09 (4.00-4.18)

Abbreviations: HR, hazard ratio; IR, incidence rate; NA, not applicable.

[a] At risk for depression onset.

[b] Per 1000 person-years.

[c] Adjusted for age, sex, education, cohabitation status, somatic comorbidities, and prior depression.

Current depression was a depression diagnosis within the last 100 days before study entry. Previous depression was a depression diagnosis from 100 days up to 5 years before study entry. In analyses with mortality as outcome, we separated incident depression into recurrent (those with a previous depression diagnosis) and new onset (those without a previous depression diagnosis). We also examined whether type of diagnosis definition (*ICD-10* codes or ATC code) influenced incidence and mortality outcomes and performed a sensitivity analysis that excluded individuals diagnosed as having depression based on a single filling of an antidepressant prescription.

Mortality

Information on all-cause mortality and death from natural and unnatural (suicides, homicides, and accidents) causes was recorded. These data were obtained from the Danish Civil Registration System and the Danish Register of Causes of Death.

Potential Risk Factors

Based on previous reviews on risk factors for depression,[7-9] we included information on age, sex, and marital status obtained from the Danish Civil Registration System and data on highest achieved school education from the Population's Education Register. Education was grouped into basic (grades 7-9 of obligatory schooling) and higher (high school, vocational diploma, or higher) education. Information on year of hospital admission was retrieved from the Danish National Patient Registry. Furthermore, type 1 and type 2 diabetes and other somatic comorbidities (coronary heart disease, chronic obstructive pulmonary disease, obesity, migraine, dementia, cancer, kidney, and connective tissue or inflammatory diseases) were identified 5 years before study entry by *ICD-10* codes and ATC code as previously described.[15] From the Danish Stroke Register, we included information on smoking, alcohol consumption, and stroke severity. Stroke severity was measured by the validated Scandinavian Neurological Stroke Scale, which rates physical disabilities,[18] and based on findings from previous prediction investigations,[19] we categorized patients into the following 4 stroke groups: severe (0-19 points), moderate (20-39 points), mild (40-49 points), and very mild (50-59 points).

Statistical Analysis

Cox proportional hazards regression models were applied to analyze (1) the incidence of depression after study entry, (2) associations between potential risk factors and depression, and (3) associations between depression and mortality. Individuals were observed from baseline and followed up until depression diagnosis, emigration, death, stroke (6766 from the reference group), or end of follow-up (3 months, 1 year, or 2 years after study entry), whichever came first. Individuals with current depression were excluded from analyses of incidence and risk factors because they were not at risk of developing depression. In the mortality analyses, individuals who died within 7 days after study entry (9818 cases and 1 from the reference group) were excluded, and depression was entered as a time-dependent variable by splitting the data set on time of depression onset, with the influence of early and intermediate depression onset on subsequent mortality also examined. Follow-up was initiated 7 days, 3 months, and 1 year after study entry. Confounders were identified using the directed acyclic graphs in eFigure 1 and eFigure 2 in the Supplement. Log-minus-log curves tested the proportional

Table 2. Adjusted HRs and 95% CIs for the Association Between Patient Characteristics and Depression Within 2 Years After Study Entry in 135 417 Danish Patients With Stroke and 145 499 Individuals in the Reference Population[a]

	Patients With Stroke		Reference Population		Interaction Parameter	
Variable	Cases, No. (%)[b]	HR (95% CI)	Cases, No. (%)[b]	HR (95% CI)	HR (95% CI)	*P* Value
Sex						
Male	17 060 (23.9)	1 [Reference]	4627 (6.1)	1 [Reference]	1 [Reference]	
Female	17 286 (27.0)	1.21 (1.18-1.23)	6658 (9.6)	1.63 (1.57-1.69)	0.75 (0.72-0.78)	<.001
Age, y						
<65	11 110 (24.9)	1 [Reference]	2699 (5.5)	1 [Reference]	1 [Reference]	
≥65	23 236 (25.6)	1.20 (1.17-1.23)	8586 (8.9)	1.69 (1.62-1.77)	0.73 (0.69-0.76)	<.001
Cohabitation Status Plus Age, Sex, and Education						
Living with a partner	16 733 (25.1)	1 [Reference]	5205 (6.6)	1 [Reference]	1 [Reference]	
Single	17 609 (25.6)	1.03 (1.01-1.06)	6078 (9.2)	1.14 (1.10-1.19)	0.79 (0.75-0.82)	<.001
Education Plus Age and Sex						
Higher	14 399 (24.9)	1 [Reference]	4298 (6.3)	1 [Reference]	1 [Reference]	
Basic	14 664 (26.8)	1.09 (1.07-1.12)	4435 (8.2)	1.17 (1.12-1.22)	0.87 (0.83-0.92)	<.001
Unknown	5283 (23.0)	1.03 (0.99-1.06)	2552 (11.2)	1.53 (1.45-1.61)	0.61 (0.58-0.65)	
Previous Depression Plus Age, Sex, Education, Cohabitation Status, and Diabetes						
No	27 357 (22.8)	1 [Reference]	7254 (5.4)	1 [Reference]	1 [Reference]	
Yes	6989 (44.8)	2.36 (2.30-2.43)	4031 (32.9)	7.04 (6.77-7.32)	0.35 (0.33-0.37)	<.001
Diabetes Plus Age, Sex, and Education						
No	30 363 (25.3)	1 [Reference]	10 261 (7.6)	1 [Reference]	1 [Reference]	
Yes	3983 (26.1)	1.09 (1.05-1.13)	1024 (9.9)	1.31 (1.22-1.39)	0.84 (0.78-0.90)	<.001
Other Somatic Comorbidities Plus Age, Sex, Education, and Cohabitation Status						
0	6155 (22.4)	1 [Reference]	1796 (4.0)	1 [Reference]	1 [Reference]	
1-2	20 172 (25.8)	1.22 (1.18-1.25)	6645 (8.3)	1.89 (1.79-1.99)	0.61 (0.58-0.65)	<.001
≥3	8019 (27.1)	1.41 (1.37-1.46)	2844 (13.9)	3.23 (3.04-3.43)	0.42 (0.39-0.45)	
Study Entry						
2001-2003	10 673 (26.0)	1 [Reference]	3429 (7.9)	1 [Reference]	1 [Reference]	
2004-2006	9700 (25.4)	1.02 (1.00-1.05)	3262 (7.9)	1.00 (0.96-1.05)	1.02 (0.97-1.08)	
2007-2009	8794 (25.3)	1.01 (0.98-1.04)	2916 (7.7)	0.97 (0.93-1.02)	1.04 (0.98-1.10)	.05
2010-2011	5179 (24.1)	0.96 (0.93-0.99)	1678 (7.2)	0.89 (0.84-0.94)	1.07(1.00-1.15)	

Abbreviations: HR, hazard ratio.

[a] Adjusted for the variables noted under each risk factor.

[b] The denominators are the numbers for each variable for patients with stroke and the reference population, respectively, for the depression outcome.

hazards assumption and showed no signs of violation. Interactions were tested by including interaction terms and using likelihood ratio tests. A significance level of 5% was used, and analyses were performed with statistical software programs (Stata, version14; StataCorp LP and SAS, version 9.4; SAS Institute Inc).

Results

Incidence of Depression

At study entry, 21 826 patients (13.9%) with stroke and 14 737 (9.2%) in the reference population had a current depression diagnosis and were not included in the analyses (**Table 1**). Of the remaining 135 417 patients with stroke, 34 346 (25.4%) had a depression diagnosis within 2 years after stroke (incidence rate [IR], 198.0; 95% CI, 191.0-195.1 per 1000 person-years), and more than half of the cases (n = 17 690) appeared within the first 3 months (IR, 601.7; 95% CI, 529.7-611.0). In the reference population (n = 145 499), 11 330 (7.8%) had a depression diagnosis within 2 years after study entry (IR, 41.5; 95 % CI, 40.7-42.3), and less than one-fourth of cases (n = 2449) appeared within the first 3 months (IR, 66.4; 95% CI, 63.8-69.1). In the Cox proportional hazards regression analyses, the HRs comparing the IRs in patients with stroke and the reference population were 8.99 (95% CI, 8.61-9.39) after 3 months and 1.93 (95% CI, 1.85-2.08) in the second year of follow-up. Adjustment for confounders only attenuated the HRs slightly. The results were similar in analyses restricted to the 5231 patients with stroke and 807 in the reference population defined as being depressed by an *ICD-10* code but excluding depression based on a single filling of an antidepressant prescription.

Risk Factors for Depression

eTable 1 in the Supplement summarizes the distribution of potential sociodemographic and clinical risk factors for early, intermediate, and late depression in patients with stroke and the reference population. The HRs for the associations are listed in **Table 2** and in eTable 2 in the Supplement. Older age, female

Table 3. Adjusted HRs and 95% CIs for the Association Between Patient Characteristics and Depression Within 2 Years After Study Entry in 53 046 Danish Patients With Stroke[a]

Variable	Cases, No. (%)[b]	HR (95% CI)
Stroke Plus Age and Sex		
Ischemic stroke	14 289 (28.0)	1 [Reference]
Hemorrhagic stroke	2978 (23.3)	1.16 (1.12-1.21)
Transient ischemic attack	944 (12.3)	0.36 (0.34-0.39)
Unknown	16 135 (25.3)	0.94 (0.92-0.97)
Smoking Plus Age, Sex, and Education		
No	4262 (27.1)	1 [Reference]
Previous	2936 (27.3)	1.04 (0.99-1.09)
Current	5147 (30.5)	1.17 (1.12-1.22)
Unknown	2600 (27.0)	1.30 (1.23-1.36)
Alcohol Consumption Plus Age, Sex, and Education		
Within recommendation[c]	11 627 (28.4)	1 [Reference]
Above recommendation	1056 (28.1)	1.06 (0.99-1.13)
Unknown	2262 (27.1)	1.22 (1.17-1.28)
Scandinavian Neurological Stroke Scale Score Plus Age, Sex, and Education		
Very mild, 50-59 points	5348 (22.6)	1 [Reference]
Mild, 40-49 points	3232 (31.7)	1.58 (1.51-1.65)
Moderate, 20-39 points	3069 (29.8)	2.48 (2.37-2.60)
Severe, 0-19 points	2019 (29.8)	2.92 (2.77-3.08)
Unknown[d]	1277 (27.4)	1.49 (1.40-1.58)

Abbreviation: HR, hazard ratio.

[a] Adjusted for the variables noted under each risk factor.

[b] The denominators are the numbers for each variable among 53 046 patients with stroke from the Danish Stroke Register.

[c] With a recommended level of alcohol consumption of no more than 7 drinks per week for women and no more than 14 drinks per week for men.

[d] Unknown stroke subtype includes a mix of hemorrhagic and ischemic strokes.

sex, single cohabitation status, basic educational attainment, diabetes, history of depression, and more than 2 somatic comorbidities were all associated with higher rates of depression in both populations (Table 2). However, interaction analyses indicated that all associations were stronger in the reference population than in patients with stroke, especially for a history of depression and the number of somatic comorbidities. The patterns of association were almost the same for early, intermediate, and late depression onset except for year of diagnosis, for which the HR increased for early depression, while a slight decrease was observed for intermediate and late depression (eTable 2 in the Supplement). In patients with stroke, we also examined the influence of stroke subtype, lifestyle, and stroke severity (**Table 3**). The risk of depression was 3 times lower in patients with transient ischemic attack compared with those with a stroke diagnosis. Stroke severity and current smoking were also associated with increased risk of depression after stroke, whereas alcohol consumption above the recommendations (>7 drinks per week for women and >14 drinks per week for men) was not. There was a stepwise increase in the risk of depression after stroke for increased stroke severity, with $P < .001$ for trend. The results were similar when analyses were repeated for depression defined only by *ICD-10* codes or stratified by ischemic and hemorrhagic strokes.

Timing of Depression and Mortality

During follow-up (range, 7 days to 2 years), 33 210 patients (22.5%) with stroke and 11 365 individuals (7.1%) in the reference population died (a total of 9818 cases who died within the first 7 days were excluded). In both populations, mortality was increased in individuals with previous, recurrent, current, and new-onset depression (**Table 4**). The estimates were similar for younger and older patients. While absolute mortality was higher in patients with stroke than in the reference population, relative mortality was significantly lower in patients with stroke than in the reference population for all incident depression states. The analyses were repeated for natural and unnatural causes of deaths, with similar findings for natural deaths. Because the number of deaths from unnatural causes was small (n = 1118), the HRs were consequently imprecisely estimated. The patterns of association were almost the same for mortality within 3 months, 3 months to 1 year, and 1 to 2 years (eTable 3 and eTable 4 in the Supplement). In patients with stroke, the mortality rate for patients with new-onset depression within the first 3 months was similar to the mortality rate for patients with later depression onset. For the reference population, the mortality rate was highest for early new-onset depression (**Table 5**).

Discussion

In this study that included 157 243 patients with first-time stroke and a matched population-based reference group, the incidence of depression after stroke was 8 times higher in the first 3 months and then approximated the level for the reference population after 1 and 2 years. A range of risk factors was associated with higher rates of depression in both populations, with strongest relative associations in the reference population. We found increased mortality from all, natural, and unnatural causes in previous, recurrent, current, and new-onset depression compared with no depression in both populations. Absolute mortality rates were higher in all subgroups of patients with stroke, but relative mortality associated with depression was significantly lower.

Incidence of Depression

In our study, the percentage of patients with stroke with incident depression after 2 years was comparable to that reported in previous population-based studies (22%) or studies with more than 1 year of follow-up (25%).[4] The risk of depression in patients with stroke was 4 times higher than in the reference population, was highest after 3 months, and leveled off but remained significantly higher after 1 year. To date, only 2 smaller, population-based studies have included a reference population, which found the frequency of depression in patients with stroke to be approximately twice that in a reference population, with no significant difference after 6 months[5] or 1 year,[6] potentially owing to lack of statistical power. A few studies[4,20,21] have compared the risk of depression in patients with stroke with the risk in patients with other somatic diseases and found the largest risk in

Table 4. Adjusted Hazard Ratios and 95% CIs for the Association Between Depression State Before and Within 2 Years After Study Entry and Mortality at 0 to 2 Years for 147 425 Danish Patients With Stroke and 160 234 Individuals in the Reference Population[a]

	Patients With Stroke			Reference Population			
Variable	Cases	Model 1	Model 2	Cases	Model 1	Model 2	Interaction Parameter Model 2
All-Cause Mortality							
No depression	18 006	1 [Reference]	1 [Reference]	6811	1 [Reference]	1 [Reference]	1 [Reference]
Previous depression	4120	1.47 (1.42-1.52)	1.27 (1.23-1.32)	830	1.54 (1.43-1.66)	1.27 (1.18-1.37)	1.40 (1.29-1.52)
Recurrent depression	1265	1.61 (1.52-1.71)	1.42 (1.34-1.51)	400	2.30 (2.08-2.54)	1.84 (1.66-2.03)	0.50 (0.45-0.56)
Current depression	4239	1.75 (1.70-1.81)	1.48 (1.43-1.53)	2216	2.79 (2.66-2.93)	2.04 (1.94-2.15)	0.56 (0.52-0.59)
New-onset depression	5580	1.91 (1.85-1.97)	1.89 (1.83-1.95)	1108	4.52 (4.24-4.82)	3.75 (3.51-4.00)	0.28 (0.26-0.30)[b]
Death From Natural Causes							
No depression	17 643	1 [Reference]	1 [Reference]	6607	1 [Reference]	1 [Reference]	1 [Reference]
Previous depression	4019	1.47 (1.42-1.52)	1.26 (1.22-1.31)	806	1.54 (1.43-1.66)	1.27 (1.18-1.37)	1.39 (1.28-1.51)
Recurrent depression	1229	1.60 (1.51-1.70)	1.41 (1.33-1.50)	387	2.29 (2.07-2.54)	1.82 (1.65-2.02)	0.50 (0.45-0.56)
Current depression	4100	1.73 (1.67-1.79)	1.46 (1.41-1.51)	2139	2.77 (2.64-2.91)	2.02 (1.92-2.13)	0.55 (0.52-0.58)
New-onset depression	5459	1.90 (1.85-1.96)	1.89 (1.83-1.95)	1068	4.49 (4.20-4.79)	3.71 (3.59-3.96)	0.28 (0.26-0.31)[b]
Death From Unnatural Causes[c]							
No depression	363	1 [Reference]	1 [Reference]	204	1 [Reference]	1 [Reference]	1 [Reference]
Previous depression	101	1.89 (1.51-2.37)	1.78 (1.42-2.24)	24	1.48 (0.97-2.25)	1.32 (0.86-2.03)	1.79 (1.10-2.87)
Recurrent depression	36	2.18 (1.54-3.08)	2.15 (1.51-3.04)	13	2.54 (1.45-4.45)	2.25 (1.28-3.96)	0.65 (0.34-1.26)
Current depression	139	2.91 (2.38-3.55)	2.83 (2.30-3.48)	77	3.33 (2.56-4.33)	2.72 (2.07-3.58)	0.77 (0.56-1.08)
New-onset depression	121	1.98 (1.60-2.45)	1.99 (1.61-2.47)	40	5.59 (3.97-7.88)	4.91 (3.48-6.93)	0.25 (0.17-0.38)[b]

[a] Model 1 is adjusted for age. Model 2 is adjusted for age, sex, education, cohabitation status, somatic comorbidities, diabetes, and year of study entry.

[b] $P < .001$.

[c] Adjusted hazard ratios for suicide in 124 patients with stroke are 3.75 (95% CI, 2.05-6.86) for previous depression, 9.49 (95% CI, 5.17-13.45) for recurrent depression, 8.15 (95% CI, 4.97-13.36) for current depression, and 3.58 (95% CI 2.10-6.09) for new-onset depression. Adjusted hazard ratios for suicide in 75 individuals in the reference population are 2.26 (95% CI, 1.00-5.11) for previous depression, 3.28 (95% CI, 1.00-10.74) for recurrent depression, 4.17 (95% CI, 2.26-7.70) for current depression, and 7.85 (95% CI, 3.86-15.96) for new-onset depression.

patients with stroke. In another Danish study,[21] patients with stroke had 3 times higher filling of antidepressant prescriptions than patients with osteoarthritis within the first 3 months after diagnosis.

Risk Factors for Depression

More than 20 studies, including 18 000 patients, have examined different risk factors for depression after stroke, and in accord with the present study, most studies[4,7-9] have shown that a history of depression and stroke severity are associated with depression after stroke. Female sex was associated with depression after stroke in 8 of 18 studies and older age in only 3 of 16 studies. Similarly, no consistent associations have been found in the few studies on the influence of low education (1 of 3 studies), single cohabitation status (2 of 5 studies), smoking (0 of 2 studies), or concomitant physical illness (0 of 3 studies) on depression after stroke. In support of the studies showing an association, we found that older age, female sex, single cohabitation status, basic educational attainment, and high level of somatic comorbidity were associated with depression in patients with stroke, as well as in the reference population. During the study period from 2001 through 2011, we saw an increase in diagnosis of depression within 3 months of stroke. This trend seems comparable to the results from a recent study[22] of time trends in depression diagnosis after acute coronary syndrome in Denmark between 2001 and 2009 and might be explained by increased focus on depression in these groups of patients. No other studies, to our knowledge, seem to have compared risk factors for depression after stroke with depression risk factors in a reference population. However, our study showed that risk estimates for the above variables were weaker than those seen in the reference population, which might suggest a difference in etiology or reflect the general increased risk of depression in patients with stroke.

Depression and Mortality

Our study revealed increased all-cause mortality in individuals with previous, recurrent, current, and new-onset depression, which is supported by a meta-analysis[12] examining the influence of depression after stroke on subsequent mortality. However, previous studies that included prospective survival analyses have been small (with sample sizes <800) and have not distinguished between depression states or adjusted for potential confounders. In a recent study (n = 1354),[23] depression was only associated with increased mortality in patients with stroke younger than 65 years. To our knowledge, no previous studies have examined the association for specific

Table 5. Adjusted Hazard Ratios and 95% CIs for the Association Between Depression State After Study Entry and Mortality for 136 787 Danish Patients With Stroke and 159 940 Individuals in the Reference Population[a]

	Patients With Stroke			Reference Population		
Variable	Cases	Model 1	Model 2	Cases	Model 1	Model 2
All-Cause Mortality						
Depression state at 3 mo and mortality between 3 mo and 1 y after study entry						
No depression	4884	1 [Reference]	1 [Reference]	2013	1 [Reference]	1 [Reference]
Previous depression	860	1.19 (1.11-1.28)	1.03 (0.96-1.11)	346	1.70 (1.52-1.90)	1.35 (1.20-1.52)
Recurrent depression	1608	1.66 (1.57-1.75)	1.48 (1.39-1.56)	574	2.35 (2.14-2.57)	1.69 (1.54-1.87)
New-onset depression	1313	1.76 (1.65-1.87)	1.75 (1.64-1.86)	59	3.97 (3.06-5.14)	3.08 (2.38-4.00)
Depression state at 1 y and mortality between 1 and 2 y after study entry						
No depression	3732	1 [Reference]	1 [Reference]	3868	1 [Reference]	1 [Reference]
Previous depression	491	1.16 (1.06-1.28)	0.99 (0.90-1.09)	459	1.54 (1.40-1.69)	1.29 (1.17-1.42)
Recurrent depression	1680	1.76 (1.66-1.86)	1.61 (1.52-1.71)	1336	2.43 (2.28-2.59)	1.84 (1.72-1.96)
New-onset depression	1678	1.71 (1.62-1.81)	1.71 (1.62-1.81)	330	2.81 (2.51-3.14)	2.30 (2.05-2.57)
Death From Natural Causes						
Depression state at 3 mo and mortality between 3 mo and 1 y after study entry						
No depression	4797	1 [Reference]	1 [Reference]	1963	1 [Reference]	1 [Reference]
Previous depression	845	1.19 (1.11-1.28)	1.03 (0.95-1.11)	337	1.70 (1.52-1.91)	1.35 (1.20-1.51)
Recurrent depression	1568	1.65 (1.55-1.74)	1.46 (1.38-1.55)	555	2.33 (2.12-2.56)	1.68 (1.52-1.85)
New-onset depression	1297	1.77 (1.66-1.88)	1.76 (1.65-1.87)	56	3.86 (2.96-5.04)	3.00 (2.30-3.90)
Depression state at 1 y and mortality between 1 and 2 y after study entry						
No depression	3643	1 [Reference]	1 [Reference]	3754	1 [Reference]	1 [Reference]
Previous depression	476	1.15 (1.05-1.27)	0.99 (0.90-1.09)	454	1.57 (1.42-1.73)	1.31 (1.19-1.44)
Recurrent depression	1624	1.74 (1.64-1.84)	1.59 (1.50-1.69)	1292	2.42 (2.27-2.58)	1.83 (1.71-1.95)
New-onset depression	1635	1.71 (1.61-1.81)	1.71 (1.61-1.81)	319	2.79 (2.49-3.13)	2.28 (2.03-2.56)
Death From Unnatural Causes						
Depression state at 3 mo and mortality between 3 mo and 1 y after study entry						
No depression	87	1 [Reference]	1 [Reference]	50	1 [Reference]	1 [Reference]
Previous depression	15	1.16 (0.67-2.01)	1.08 (0.62-1.87)	9	1.78 (0.88-3.62)	1.54 (0.75-3.15)
Recurrent depression	40	2.37 (1.63-3.44)	2.32 (1.58-3.42)	19	3.10 (1.83-5.25)	2.44 (1.41-4.22)
New-onset depression	16	1.24 (0.73-2.11)	1.23 (0.72-2.10)	3	8.06 (2.51-25.84)	6.68 (2.08-21.49)
Depression state at 1 y and mortality between 1 and 2 y after study entry						
No depression	89	1 [Reference]	1 [Reference]	114	1 [Reference]	1 [Reference]
Previous depression	15	1.48 (0.86-2.56)	1.32 (0.76-2.30)	5	0.57 (0.23-1.39)	0.51 (0.21-1.24)
Recurrent depression	56	2.48 (1.77-3.46)	2.43 (1.72-3.42)	44	2.77 (1.96-3.93)	2.27 (1.58-3.27)
New-onset depression	43	1.86 (1.29-2.67)	1.87 (1.30-2.69)	11	3.24 (1.74-6.02)	2.78 (1.49-5.19)

[a] Model 1 is adjusted for age. Model 2 is adjusted for age, sex, education, cohabitation status, somatic comorbidities, diabetes, and year of study entry.

causes of death or compared the estimates for patients with stroke with the mortality risk for depression in a reference population.

The increase in the incidence of depression within the first months after stroke diagnosis, as well as the weaker associations with acknowledged risk factors for depression and subsequent mortality, suggests that depression after stroke differs from depression arising without known prior somatic illness. There are a number of theories (lesion location, vascular depression, neurotransmitter, inflammation, neuroplasticity, and hypothalamic-pituitary-adrenal axis activation hypotheses) for the neurobiological pathogenesis of depression after stroke, with limited and conflicting evidence.[13,24] The results from the present study do not support any particular theory. Another explanation is that the rise is owing to increased awareness of depression after stroke due to screening initiatives and prophylactic treatment with antidepressants. The discussions of preventing depression after stroke and improving outcomes overall by initiating prophylactic antidepressant treatment soon after stroke diagnosis[13] might have increased prescription of antidepressants among neurologists.[25] However, a 2013 meta-analysis[26] did not provide sufficient evidence for treatment effects, and in observational studies selective serotonin reuptake inhibitor treatment after stroke has been associated with higher mortality[23,27] independent of depression diagnosis.[23] This finding has recently been highlighted[28] and might have contributed to a more conservative treatment strategy.

Our study has both strengths and limitations. We observed a nationwide cohort virtually without any loss to follow-up, making nonresponse bias an unlikely explanation

for our findings. Also, information on stroke and depression was retrieved from registers with high validity for stroke registration.[29,30] However, our definition of depression was based on psychiatric diagnoses and antidepressant prescriptions, and most cases were defined by filling of antidepressant prescriptions. Such drugs may be prescribed for various diseases, and single prescriptions have been found more frequently in individuals with no recorded depression diagnosis.[31] Consequently, we performed a sensitivity analysis based on more than 1 filling of an antidepressant prescription to limit this potential misclassification. These analyses produced results similar to those presented. Furthermore, when we repeated analyses with the inclusion of only cases with a hospital diagnosis of depression, the results were similar. Finally, the Danish Stroke Register did not include information on lesion location or biochemical features; consequently, we could only provide indirect support for possible etiologic mechanisms. Future studies should examine how potential biomarkers relate to the co-occurrence of stroke and depression.

Conclusions

Depression is common in patients with stroke the first year after occurrence, with patients with prior depression or severe stroke being at highest risk. Incident depression after stroke is an independent risk factor for mortality from natural and unnatural causes. However, the association between depression and risk factors and mortality from both natural and unnatural causes was weaker in patients with stroke than in a matched reference population, which suggests different etiologic mechanisms. Assuming causality, the high rates of depression in patients with stroke indicate that a large number of deaths occurring during rehabilitation may be attributable to this condition, which suggests that clinicians should remain vigilant concerning this risk, especially in patients with a history of depression and a high number of somatic comorbidities. We suggest that future clinical studies should focus on how treatment and rehabilitation influence the risk of depression in patients with stroke.

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