# Effects of Stroke Rehabilitation on Incidence of Poststroke Depression: A Population-Based Cohort Study

*Wen-Hsuan Hou, MD, MSc, PhD; Huey-Wen Liang, MD, PhD; Ching-Lin Hsieh, PhD; Chieh-Yi Hou, MSc; Pei-Chun Wen, DDSc; and Chung-Yi Li, PhD*

**ABSTRACT**

***Objective:*** To investigate the effects of rehabilitation intervention provided within the first 3 months after admission for stroke on the incidence of poststroke depression (diagnosed according to *ICD-9-CM* code 296, 309, or 311, or A-code A212 or A219).

***Method:*** This population-based cohort study examined medical claim data of a random sample of 1 million insured people registered in 2000 in Taiwan. Between 2000 and 2005, there were 7,677 patients admitted as first-time stroke patients. Of these, 1,285 (16.7%) received a rehabilitation regimen within the first 3 months of admission for stroke. The other 83.3% of patients (n = 6,482) belonged to the control group. All study subjects were followed to the end of 2009 to identify any ambulatory treatment for depression as the end point. The incidence density of poststroke depression was calculated assuming a Poisson process. A Cox proportional hazard model was used to estimate the relative risk of poststroke depression in relation to receipt of rehabilitation.

***Results:*** Over a 10-year follow-up, 75 patients (5.8%) with rehabilitation and 566 controls (8.7%) developed poststroke depression, representing incidence densities of 11.3 and 18.5 per 1,000 person-years, respectively. After analyses were controlled for potential confounders, rehabilitation was found to significantly reduce the risk of poststroke depression, with a hazard ratio (HR) of 0.57 (95% CI, 0.45–0.73). The effect was greater for men (HR = 0.52; 95% CI, 0.37–0.71), especially for elderly men (HR = 0.45; 95% CI, 0.28–0.71), than for women (HR = 0.69; 95% CI, 0.47–1.02).

***Conclusions:*** Stroke rehabilitation intervention in the first 3 months after admission for stroke may significantly reduce the risk of poststroke depression. Although this beneficial effect appears to be greater for men than for women, clinicians should also be alert for poststroke depression occurring in women.

*J Clin Psychiatry 2013;74(9):e859–e866*



***Submitted:*** *October 31, 2012; accepted April 17, 2013 (doi:10.4088/JCP.12m08259).*

***Corresponding author:*** *Chung-Yi Li, PhD, Department of Public Health, College of Medicine, National Cheng Kung University, No. 1 University Rd, Tainan 701, Taiwan (cyli99@mail.ncku.edu.tw).*

Depression is common in stroke survivors.[1] Previous studies have reported that the prevalence of poststroke depression ranges from 20% to 80%, depending on the time (ie, more prevalent within 3 months poststroke) and method of depression ascertainment,[2] as well as on the levels of family functioning and social support of the patients.[3] It has been well documented that poststroke depression may deter stroke patients from social participation and limit their activities of daily living, leading to poor rehabilitation outcomes, which may in turn cause poor quality of life and increase the risk of mortality in stroke survivors.[4,5] Thus, in managing the recovery of stroke survivors, it is crucial to prevent or treat depression.

Many studies[6–8] have explored ways to effectively treat poststroke depression. One study[2] investigated whether pharmacologic therapy or psychotherapy can prevent poststroke depression. Despite some evidence supporting the preventive effect of antidepressants for poststroke depression,[2] evidence has been inconsistent with respect to the effectiveness of antidepressant medication use and psychotherapy to improve mood and to prevent poststroke depression.[7,8] Presently, little is known about the effectiveness of stroke rehabilitation in preventing the incidence of depression in stroke survivors.

*Stroke rehabilitation*, defined as any treatment or exercise with the aims of facilitating neurologic recovery, achieving functional recovery, minimizing daily disability, and reintegrating back into family and community,[9] has been proposed as an effective therapeutic approach for poststroke depression in patients with stroke.[10] Previous studies[11] have demonstrated that the severity of impairment in activities of daily living is the strongest single predictor for poststroke depression, suggesting that stroke rehabilitation could prevent poststroke depression by minimizing functional impairments and enhancing participation in activities of daily living.

The purpose of this study was to conduct a population-based cohort study to investigate the association between stroke rehabilitation and the risk of poststroke depression onset among first-time stroke patients. In addition to assessing the overall effectiveness of stroke rehabilitation to prevent poststroke depression onset, we also aimed to explore the age-specific and sex-specific relationships between stroke rehabilitation and risk of depression onset in patients with stroke.

## METHOD

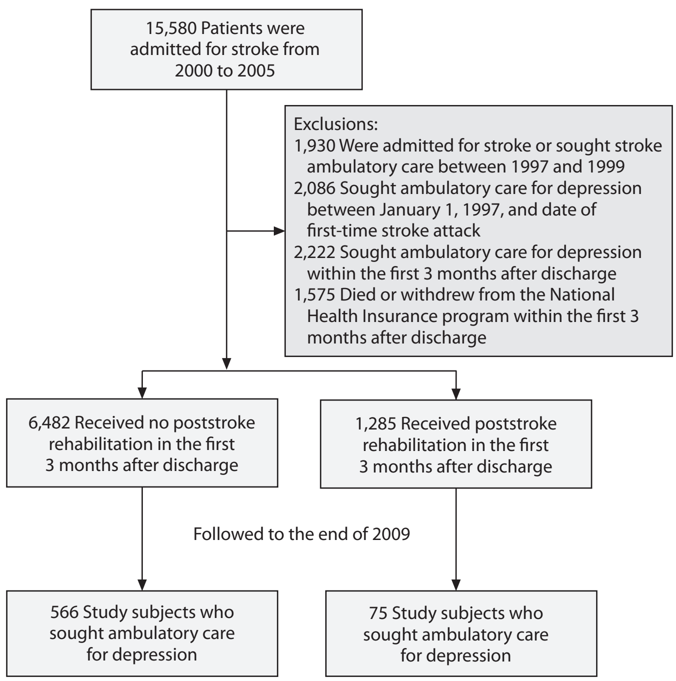
### Source of Data

The data were collected from the claims of 1 million beneficiaries randomly selected from all beneficiaries insured in 2000, with age and sex distributions nearly identical to the entire insured population of Taiwan.[12] The claims were retrieved from the National Health Insurance Research Database (NHIRD) of the Bureau of National Health Insurance (BNHI). The NHIRD provides all inpatient and ambulatory medical claims for around 99% of the Taiwanese people.[13] To ensure the accuracy of the claim files, the BNHI performs quarterly expert reviews on a random sample for every 50 to 100 ambulatory and inpatient claims.[14] Therefore, information

Clinical Points

- Poststroke depression increased morbidity and mortality in stroke survivors.
- This study provides evidence that best supports the protective effect of stroke rehabilitation intervention on depression incidence.
- The stroke rehabilitation intervention appears to be effective in patients of all age and sex stratifications, with a stronger protective effect noted in male patients.

**Figure 1. Flowchart of Selection and Follow-Up of Study Subjects**




obtained from the NHIRD is considered to be complete and accurate.[15] We used several NHIRD datasets in this study, including ambulatory care visit claims, inpatient expenditures by admissions, and the registry for beneficiaries. Access to the research data was approved by the Review Committee of the National Health Research Institutes.

## Study Subjects and End Points

The inpatient expenditures by admissions claims showed that, between 2000 and 2005, a total of 15,580 patients were admitted for a principal or secondary diagnosis of stroke (*ICD-9-CM* codes: 430–434, 436–437). After the exclusion of 1,930 patients who were admitted or had sought ambulatory service for stroke in 1997–1999, the remaining 13,650 patients were considered as the incident cases of stroke for the years 2000–2005. We further excluded 2,086 patients who had ambulatory care visits for depression (*ICD-9-CM* code: 296, 309, 311, or A-code: A212, A219) between January 1, 1997, and the date of admission for first-time stroke attack (ie, the index date). There were 2,222 patients who sought ambulatory care for depression within the first 3 months of stroke attack, and there were 1,575 patients who died in hospital or withdrew (including death) from the National Health Insurance (NHI) program within the first 3 months after stroke attack. These patients were also excluded, leaving 7,767 patients in the study. Patients who were not followed for a full 3 months after discharge were excluded because the stroke rehabilitation program is considered most effective within the first 3 months after the stroke attack.[16] The annual numbers of stroke incident cases from 2000 to 2005 were 1,401; 1,338; 1,348; 1,165; 1,305; and 1,210, respectively.

We linked the cohort of stroke patients to the ambulatory care visit claims and searched for their rehabilitation visits within the 3-month period following the stroke attack, finding a total of 8,288 rehabilitation visits by 1,285 stroke patients (16.7% of total sample). Information on receipt of stroke rehabilitation was based on the treatment code of NHI claims. Fundamentally, the rehabilitation orders include facilitation of hemiplegic limbs, muscle strengthening, moving, activities of daily living, ambulation, and balance training to achieve functional improvement.[17] It was found that 83.3% (6,482) of the patients received no poststroke rehabilitation. The patients of both groups (ie, rehabilitation and nonrehabilitation) were linked to the ambulatory care visit claims and inpatient expenditures by admissions claims in the years 2000–2009 to identify possible treatment for depression. A flowchart showing the study criteria, the exclusion criteria, and the follow-up procedure is presented in Figure 1.

## Statistical Analysis

The index date for each stroke patient was the date of discharge after his or her first stroke attack. The 10-year follow-up period began as early as January 1, 2000, and ended on December 31, 2009. The age of each patient was calculated as the difference in time between the index date and the date of birth. The insurance premium for each beneficiary with the NHI was proportional to his or her wages. A higher premium is indicative of higher wages. For those who were not actively employed or were self-employed, the insurance premium was zero. We grouped the patients' residential areas into 3 urbanization levels (ie, urban area, satellite city, and rural area) according to the National Statistics of Regional Standard Classification.[18] The information on insurance premiums and residential areas was obtained from the registry for beneficiaries.

The age-specific and sex-specific hazard rates were determined with person-years as the denominator under the Poisson assumption. To assess the independent effects of stroke rehabilitation on the risk of depression, we conducted a Cox proportional hazard regression analysis with age, sex, insurance premium, urbanization level, and selected comorbidities adjusted simultaneously in the model. We adjusted the urbanization level for the presence of an urban-rural difference in accessibility to medical care in Taiwan.[19]

The comorbidities considered in our analysis included a number of major illnesses, including cancer (*ICD-9-CM* code: 140–208), arthritis or rheumatism (*ICD-9-CM* code: 714.0, 729.0), chronic obstructive pulmonary disease (*ICD-9-CM* code: 490–496), peripheral arterial disease (*ICD-9-CM* code: 440–449), and diabetes mellitus (*ICD-9-CM* code: 250), which were found to pose a significantly increased risk of depressive symptoms.[20] The above comorbidities were identified from the study subject's ambulatory care visit claims or inpatient expenditures by admissions claims in the 1-year period prior to the stroke attack. Type of stroke (ie, ischemic or hemorrhagic stroke) and length of hospital stay associated with the index stroke admission were also considered as covariates. The follow-up ended on the date of diagnosis of depression in either inpatient or outpatient care or on the date of censoring, which was either the date of withdrawal (including death) from the NHI program or the date of end of follow-up, ie, December 31, 2009. All statistical analyses were performed using SAS, version 9.3 (SAS Institute; Cary, North Carolina) and Stata/SE 12.0 for Windows (StataCorp; College Station, Texas). A *P* value < .05 was considered statistically significant.

## RESULTS

The stroke patients who received rehabilitation were more likely to be male (63.3%) and, on average, 2.3 years younger than those without rehabilitation. Both groups were comparable with respect to insurance premium and residential urbanization level. The patients with stroke rehabilitation tended to suffer fewer major illnesses prior to the stroke attack (Table 1). Over a 10-year follow-up, 75 patients (5.8%) with rehabilitation and 566 controls (8.7%) developed poststroke depression. After we controlled for potential confounders (eg, age, sex, insurance premium, residential area, type of stroke, length of hospital stay, and major illness–related depression), stroke rehabilitation significantly and substantially reduced the risk of depression, with a hazard ratio (HR) of 0.57 (95% CI, 0.45–0.73). The HRs remained unchanged when frequency of rehabilitation was taken into account. The multivariate analysis also showed that older stroke patients tended to be at significantly greater risk of depression after stroke rehabilitation (HR = 1.43; 95% CI, 1.03–1.99) than younger patients. Additionally, stroke patients with a length of hospital stay of 22–28 days and those with a length of hospital stay of > 28 days had significantly higher HRs, 1.64 (95% CI, 1.17–2.28) and 1.56 (95% CI, 1.19–2.04), respectively (Table 2), than did those with a length of hospital stay of 1–7 days. Figure 2 compares the cumulative failure (event) rates of depression for the group receiving rehabilitation and the group without intervention. The patients receiving stroke rehabilitation had a significantly lower event rate over the study period (*P* value for log-rank test = .0001).

The sex-specific and age-specific analyses showed that men who received stroke rehabilitation had a lower incidence density of poststroke depression than their nonrehabilitation counterparts (10.5 vs 19.2 per 1,000 person-years), representing a covariate-adjusted HR of 0.52 (95% CI, 0.37–0.71). A reduced HR was observed in elderly patients (aged ≥ 65 years) (HR = 0.45; 95% CI, 0.28–0.71) from the age-stratified analysis. On the other hand, the beneficial effect of stroke rehabilitation on poststroke depression was less clear for female patients. Stroke rehabilitation was also associated with a reduced though statistically insignificant HR of 0.69 (95% CI, 0.47–1.02) in female patients, and the corresponding HR estimates for younger and elderly women were also insignificantly reduced at 0.64 (95% CI, 0.33–1.23) and 0.70 (95% CI, 0.43–1.13), respectively (Table 3).

**Table 1. Demographic Characteristics and Comorbidities of Study Subjects (N = 7,677)**

| Variable | No Rehabilitation | Rehabilitation | $P^a$ |
|---|---|---|---|
| Total | 6,482 (100.0) | 1,285 (100.0) | |
| Age at first-time stroke, y | | | < .001 |
| < 45, n (%) | 454 (7.0) | 111 (8.6) | |
| 45–64, n (%) | 1,950 (30.1) | 457 (35.6) | |
| ≥ 65, n (%) | 4,078 (62.9) | 717 (55.8) | |
| Mean (SD) | 67.1 (14.2) | 64.8 (13.7) | |
| Sex, n (%) | | | .036 |
| Female | 2,584 (39.9) | 472 (36.7) | |
| Male | 3,898 (60.1) | 813 (63.3) | |
| Insurance premium, NTD,[b] n (%) | | | .092 |
| Dependence | 1,735 (26.8) | 340 (26.4) | |
| < Median NTD[c] | 1,537 (23.7) | 272 (21.3) | |
| > Median NTD[c] | 3,210 (49.5) | 673 (52.3) | |
| Residential area, n (%) | | | .467 |
| Urban area | 2,222 (34.3) | 454 (35.3) | |
| Satellite city | 1,805 (27.9) | 337 (26.2) | |
| Rural area | 2,455 (37.8) | 494 (38.5) | |
| Type of stroke, n (%) | | | < .001 |
| Ischemic | 5,367 (82.8) | 963 (74.9) | |
| Hemorrhagic | 1,115 (17.2) | 322 (25.1) | |
| Length of hospital stay, d | | | < .001 |
| 0–7, n (%) | 3,494 (53.8) | 403 (31.3) | |
| 8–14, n (%) | 1,429 (22.1) | 381 (29.7) | |
| 15–21, n (%) | 567 (8.8) | 180 (14.0) | |
| 22–28, n (%) | 325 (5.0) | 116 (9.0) | |
| > 28, n (%) | 667 (10.3) | 205 (16.0) | |
| Mean (SD) | 12.6 (27.9) | 15.4 (14.8) | .001 |
| Cancer, n (%) | | | .003 |
| No | 5,384 (83.1) | 1,111 (86.5) | |
| Yes | 1,098 (16.9) | 174 (13.5) | |
| Arthritis or rheumatism, n (%) | | | .392 |
| No | 6,336 (97.8) | 1,251 (97.4) | |
| Yes | 146 (2.2) | 34 (2.6) | |
| Chronic obstructive pulmonary disease, n (%) | | | .051 |
| No | 4,333 (66.9) | 895 (69.7) | |
| Yes | 2,149 (33.1) | 390 (30.3) | |
| Peripheral arterial disease, n (%) | | | .103 |
| No | 5,880 (90.7) | 1,184 (92.1) | |
| Yes | 602 (9.3) | 101 (7.9) | |
| Diabetes, n (%) | | | .072 |
| No | 4,035 (62.25) | 834 (64.90) | |
| Yes | 2,447 (37.75) | 451 (35.10) | |

[a]Based on $\chi^2$ test. [b]1 US$ = 30 NTD. [c]Median = 18,300 NTD.
Abbreviations: NTD = New Taiwan Dollars, SD = standard deviation.

## DISCUSSION

This 10-year follow-up, population-based cohort study examined whether early stroke rehabilitation could lower the risk of poststroke depression onset in first-attack stroke patients. The magnitude of overall risk reduction was estimated at about 43%, higher for men (48%) than for

**Table 2. Hazard Ratio (HR) of Depression in Relation to Poststroke Rehabilitation and Selected Covariates**

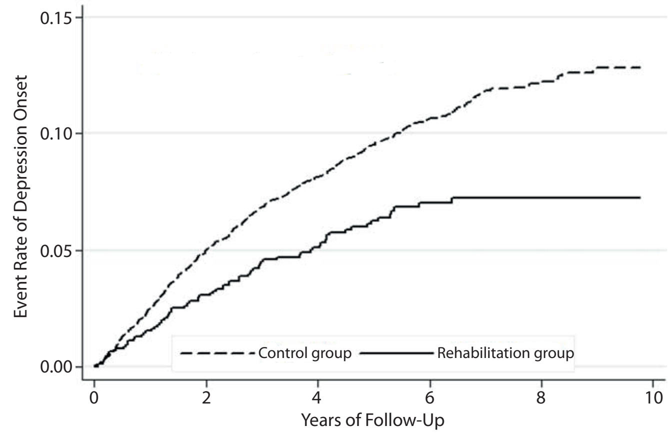
| Selected Characteristic | No. of Person-Years[a] | No. of Events | Incidence Density[b] (per 1,000 patient-years) | Unadjusted[c] HR | Unadjusted[c] 95% CI | Adjusted[c] HR | Adjusted[c] 95% CI |
|---|---|---|---|---|---|---|---|
| Overall | 37,163 | 641 | 17.2 | | | | |
| Rehabilitation | | | | | | | |
| No | 30,554 | 566 | 18.5 | 1.00 | | 1.00 | |
| Yes | 6,609 | 75 | 11.3 | **0.62** | **0.48–0.78** | **0.57** | **0.45–0.73** |
| 1–3 visits | 3,083 | 34 | 11.0 | **0.60** | **0.42–0.85** | **0.56** | **0.39–0.79** |
| > 3 visits | 3,525 | 41 | 11.6 | **0.63** | **0.46–0.87** | **0.58** | **0.42–0.81** |
| Age at stroke onset, y | | | | | | | |
| < 45 | 3,042 | 41 | 13.5 | 1.00 | | 1.00 | |
| 45–64 | 13,210 | 213 | 16.1 | 1.31 | 0.93–1.82 | 1.33 | 0.95–1.87 |
| > 64 | 20,550 | 387 | 18.8 | 1.45 | 1.05–2.01 | **1.43** | **1.03–1.99** |
| Sex | | | | | | | |
| Male | 22,351 | 393 | 17.6 | 1.00 | | 1.00 | |
| Female | 14,813 | 248 | 16.7 | 0.96 | 0.82–1.12 | 0.93 | 0.79–1.09 |
| Insurance premium, NTD[d] | | | | | | | |
| Dependence | 9,165 | 167 | 18.2 | 1.00 | | 1.00 | |
| < Median NTD[e] | 8,318 | 155 | 18.6 | 1.03 | 0.83–1.29 | 1.02 | 0.82–1.28 |
| > Median NTD[e] | 19,680 | 319 | 16.2 | 0.93 | 0.77–1.12 | 0.94 | 0.77–1.15 |
| Residential area | | | | | | | |
| Urban area | 13,898 | 219 | 15.8 | 1.00 | | 1.00 | |
| Satellite city | 10,358 | 177 | 17.1 | 1.01 | 0.82–1.23 | 1.01 | 0.83–1.23 |
| Rural area | 12,906 | 245 | 19.0 | 1.03 | 0.86–1.24 | 1.08 | 0.89–1.31 |
| Type of stroke | | | | | | | |
| Ischemic | 29,983 | 535 | 17.8 | 1.00 | | 1.00 | |
| Hemorrhagic | 7,179 | 106 | 14.8 | 0.84 | 0.65–1.03 | **0.80** | **0.64–0.99** |
| Length of hospital stay, d | | | | | | | |
| 1–7 | 20,045 | 317 | 15.8 | 1.00 | | 1.00 | |
| 8–14 | 8,720 | 152 | 17.4 | 1.09 | 0.90–1.32 | 1.17 | 0.96–1.42 |
| 15–21 | 3,257 | 60 | 18.4 | 1.13 | 0.86–1.49 | 1.30 | 0.98–1.72 |
| 22–28 | 1,800 | 41 | 22.8 | **1.39** | **1.01–1.92** | **1.64** | **1.17–2.28** |
| > 28 | 3,342 | 71 | 21.2 | **1.30** | **1.01–1.68** | **1.56** | **1.19–2.04** |
| History of major illness | | | | | | | |
| Cancer | | | | | | | |
| No | 31,640 | 542 | 17.1 | 1.00 | | 1.00 | |
| Yes | 5,524 | 99 | 17.9 | 1.04 | 0.84–1.29 | 1.01 | 0.82–1.26 |
| Arthritis or rheumatism | | | | | | | |
| No | 36,356 | 621 | 17.1 | 1.00 | | 1.00 | |
| Yes | 807 | 20 | 24.8 | 1.44 | 0.92–2.25 | 1.44 | 0.92–2.25 |
| Chronic obstructive pulmonary disease | | | | | | | |
| No | 26,406 | 452 | 17.1 | 1.00 | | 1.00 | |
| Yes | 10,758 | 189 | 17.6 | 1.00 | 0.84–1.18 | 0.93 | 0.78–1.11 |
| Peripheral arterial disease | | | | | | | |
| No | 34,010 | 591 | 17.4 | 1.00 | | 1.00 | |
| Yes | 3,154 | 50 | 15.9 | 0.91 | 0.68–1.21 | 0.93 | 0.78–1.11 |
| Diabetes | | | | | | | |
| No | 22,769 | 411 | 18.1 | 1.00 | | 1.00 | |
| Yes | 14,394 | 230 | 16.0 | 0.95 | 0.80–1.11 | 0.94 | 0.79–1.10 |

[a]The inconsistency between total no. of person-years and summation of person-years across subgroups in some variables was due to missing date of censoring for some study participants. [b]Based on Poisson assumption. [c]Bold typeface indicates statistical significance; HR value of 1.00 refers to reference group. [d]1 US$ = 30 NTD. [e]Median = 18,300 NTD.
Abbreviations: CI = confidence interval, NTD = New Taiwan Dollars.

women (31%). For male patients, the study found a more noticeable beneficial effect in elderly patients (55%) than in younger ones (40%). The corresponding estimates for female patients were 36% and 30%, respectively.

A previous study[21] has documented that various types of pharmacotherapy (eg, antidepressants, psychostimulants, microcirculation improvers), psychotherapy, electroconvulsive therapy, or repetitive transcranial magnetic stimulation could be effective for treating poststroke depression. More recently, the therapeutic effects of exercise training and rehabilitation programs for poststroke depression have been reported.[6,22,23] One systematic review[23] concluded that physical exercise reduces depressive mood status; that community-based rehabilitation programs enhance health-related quality of life, a broad multidimensional concept that usually includes self-reported measures of physical and mental health; and that leisure rehabilitation may improve health-related quality of life and/or participation. Unfortunately, there were numerous inconsistencies in the protocols, types, durations, frequencies, and intensities of the rehabilitation programs.[23] To the best of our knowledge, our study is the first to examine the effect of stroke rehabilitation within 3 months postadmission in preventing the occurrence of poststroke depression.

**Figure 2. Comparison of Kaplan-Meier Failure Estimates of Depression Onset Between the 2 Study Groups[a]**




| No. at risk (no. of failure events): | | | | | | |
|---|---|---|---|---|---|---|
| Control group | 6,482 (288) | 5,009 (157) | 4,057 (87) | 2,226 (30) | 909 (4) | 0 |
| Rehabilitation group | 1,285 (37) | 1,104 (22) | 905 (15) | 493 (1) | 184 (0) | 0 |

[a]*P* for log-rank test = .0001.

**Table 3. Overall, Age-Specific, and Sex-Specific Incidence Densities and Relative Hazards of Depression in Stroke Patients With and Without Rehabilitation Intervention**

| | No Rehabilitation | | | Rehabilitation | | | | |
|---|---|---|---|---|---|---|---|---|
| Variable | No. of Subjects | No. of Events | Incidence Density (per 1,000 patient-years) | No. of Subjects | No. of Events | Incidence Density[a] (per 1,000 patient-years) | HR (95% CI) in Association With Rehabilitation[b] | AHR[c] (95% CI) in Association With Rehabilitation[b] |
| Men | | | | | | | | |
| < 65 years of age | 1,575 | 141 | 16.3 | 398 | 24 | 10.6 | 0.65 (0.42–1.01) | **0.60 (0.38–0.93)** |
| ≥ 65 years of age | 2,323 | 208 | 21.8 | 415 | 20 | 10.4 | **0.48 (0.31–0.77)** | **0.45 (0.28–0.71)** |
| Total | 3,898 | 349 | 19.2 | 813 | 44 | 10.5 | **0.55 (0.41–0.76)** | **0.52 (0.37–0.71)** |
| Women | | | | | | | | |
| < 65 years of age | 829 | 78 | 16.5 | 170 | 11 | 11.3 | 0.67 (0.36–1.27) | 0.64 (0.33–1.23) |
| ≥ 65 years of age | 1,755 | 139 | 18.2 | 302 | 20 | 13.7 | 0.76 (0.47–1.21) | 0.70 (0.43–1.13) |
| Total | 2,584 | 217 | 17.5 | 472 | 31 | 12.7 | 0.73 (0.50–1.06) | 0.69 (0.47–1.02) |
| Overall | 6,482 | 566 | 18.5 | 1,285 | 75 | 11.3 | **0.62 (0.48–0.78)** | **0.57 (0.45–0.73)** |

[a]Based on Poisson assumption.
[b]Bold typeface indicates statistical significance.
[c]Based on Cox proportional hazards regression with adjustment for age, sex, insurance premium, residential area, type of stroke, length of hospital stay, and selected major illnesses related to depression including cancer, arthritis or rheumatism, chronic obstructive pulmonary disease, peripheral arterial disease, and diabetes.
Abbreviations: AHR = adjusted hazard ratio, CI = confidence interval, HR = hazard ratio.

Several mechanisms have been proposed to explain the positive link between physical exercise, an integral part of rehabilitation programs, and well-being, a subjectively perceived quality of one's life including both emotional reactions and cognitive judgments. Physiologic explanations include an increase in the concentrations of circulating β-endorphins and monoamines and an increase in body temperature and fitness level.[24] Psychological benefits were achieved after a short period of time and even after aerobic or tai chi training, suggesting that increases in fitness level may improve psychological well-being. Biological changes, together with the relief of somatic symptoms, may also lead to better physical function and health-related quality of life.[24,25] As for the social aspect, rehabilitation could directly improve physical function and reduce the likelihood of disability, which may adversely affect mood. Therefore, rehabilitation may delay or prevent the onset of depression by improving physical function and imparting independence.[26] A previous study[27] has also reported that both aerobic and anaerobic exercise may be used to treat depression. Others[28,29] have addressed a dose-gradient effect (eg, high intensity vs lower intensity) of physical activities on outcomes of depression. Furthermore, frequent and regular, but not too frequent, daily exercise has been found to be associated with low depression scores.[30]

Our study results supported previous findings that a higher prevalence of poststroke depression is associated with older age,[31] longer hospital stays,[32] poorer physical function,[33,34] and increased stroke severity.[35] Our data showed that patients with ischemic stroke are more prone to poststroke depression, mainly due to the fact that ischemic insults can directly and heavily damage cortical and subcortical circuits.[36] Contrary to a systematic review[32] indicating that poststroke depression appears to be slightly more common in women than in men, our data showed the reverse to be true, but the difference was not statistically significant.

Although the age-specific and sex-specific differences in poststroke depression incidence or prevalence have been frequently documented, there is limited information on age-specific and sex-specific differences for stroke patients in response to prevention or treatment of poststroke depression.[32] Our study showed that elderly men benefited the most from stroke rehabilitation in preventing poststroke depression onset. Similar findings were also noted in a community-based study[37] that reported that men and elderly (aged > 75 years) patients had fewer poor outcomes during treatment and rehabilitation in stroke units. Explanations for the age difference in the response to the preventive effect of rehabilitation could be that younger patients were relatively few in number and that their rates of developing adverse outcomes were somewhat lower than those of elderly patients.[37] Additionally, some evidence supports the notion that the beneficial effect of rehabilitation on reduced poststroke depression is intermediated by the increasing physical independence and decreasing emotional distress or the social isolation of stroke patients. A previous study[38] found that male gender and older age were associated with an increased risk of loss related to activities of daily living. In addition, Neri et al,[39] who surveyed 176 elderly people who had cared for a spouse and/or parents in the past 5 years, found that being male is a risk factor for social isolation indicated by discontinuity of activities and social roles. It is likely that elderly men with stroke are more vulnerable than other stroke patients to an increased risk of activities-of-daily-living disability and limited social participation. This possibility may explain why the elderly male stroke patients benefited the most from rehabilitation, which may effectively have increased their physical independence and lifted barriers to social participation.

This study had the following strengths. First, it was a population-based study including a highly representative sample of stroke patients admitted to hospitals in Taiwan in the year 2000. Therefore, the data allow little room for selection bias. Second, the advantage of using insurance claim datasets in clinical research is that doing so provides easy access to longitudinal records for a large sample of demographically diverse patients.[40,41] The size of the dataset made it possible to conduct stratified analyses according to certain variables of interest, such as age and sex. Third, this stroke cohort was collected from the NHI database, and all the research information was retrieved from the NHI claims, which entails little likelihood of nonresponse or loss to follow-up of the cohort members. Fourth, we managed to adjust, in multivariate regression models, for a number of sociodemographic variables, several major comorbidities, and stroke severity indicators (ie, stroke type and length of hospital stay) that are considered to be potential confounders. This approach may have helped elucidate the independent effect of stroke rehabilitation on the risk of depression onset.

Several limitations of our study should be noted. First, exclusive reliance on claim data may have resulted in a potential disease misclassification bias. The incidence of depression estimated from claim data could be biased because some people who suffer from depression seek no ambulatory care. Similarly, some people might erroneously receive a depression diagnosis simply because of their increased interaction with the health care system due to their stroke condition, ie, surveillance bias. To address this concern, we calculated the number of outpatient visits within the period between the index date (ie, date of admission for stroke) and date of depression diagnosis or date of end of follow-up for each study participant. The mean (standard deviation [SD]) number of ambulatory care visits for the rehabilitation and nonrehabilitation groups was 18.48 (29.64) per person-year (range, 1–120) and 19.42 (31.97) per person-year (range, 0–92), respectively. We further included the number of ambulatory care visits in the multivariate Cox regression model to assess whether number of visits posed an influence on the relative risk estimates of depression in relation to rehabilitation. The reanalytic results are shown below. It is expected to find that a greater number of ambulatory care visits is positively and significantly associated with an increased risk of depression (adjusted HR = 1.09; 95% CI, 1.08–1.09). However, adjustment for number of ambulatory care visits does not alter the strength of association between rehabilitation and risk of depression.

Second, because the validity of depression diagnosis is essential to the study results, we performed a sensitivity analysis that limited the depressive subjects diagnosed by psychiatrists. We noted that 65 (86.7%) of 75 depressive subjects from the rehabilitation group were diagnosed by psychiatrists, while only 68.4% (387 of 566) of the depressive subjects from the nonrehabilitation group fit the same criteria. The reanalytic results indicated that the protective effect of rehabilitation was somewhat attenuated but was still statistically significant (HR = 0.72; 95% CI, 0.55–0.95). The rehabilitation intensity–specific HRs were also attenuated at 0.76 (95% CI, 0.54–1.07) (1–3 visits) and 0.69 (95% CI, 0.46–1.01) (> 3 visits), which became insignificant partly because of reduced sample size of patients with depression.

Third, we were unable to take into account a comprehensive list of potential confounders in the analysis, which might also have resulted in residual confounding in our study. The unadjusted potential confounders may include certain socioeconomic factors (including family support and financial condition) and healthy lifestyles (such as physical and leisure-time activities), since accessibility,[42] financial condition,[43] support of family or friends,[44] socioeconomic status,[45] and geographic region[46] cause variations in the utilization of rehabilitation services and poststroke depression prevalence. Stroke severity is among the potential confounders strongly related to risk of depression onset. Because information on stroke severity is not available from the NHI claims, we managed to adjust for it by using length of hospital stay associated with first-time admission for stroke as a proxy. We also noted strong associations of length of hospital stay with drug and surgery fees. To address this concern, we adjusted for the urbanization level of each patient's residential area.

Fourth, our study might suffer from potential confounding by indication, meaning that stroke patients who received rehabilitation were involved with certain indications related to patients and hospitals. To address this potential problem, we calculated, for each study patient, the propensity score based on the variables available from the NHI claims, including a patient's age, sex, insurance premium, residential area, type of stroke, and comorbidity, as well as hospital accreditation level. The mean (SD) propensity scores calculated for the rehabilitation and nonrehabilitation groups were 0.077 (0.027; range, 0.043–0.204) and 0.084 (0.031; range, 0.040–0.224), respectively. We further included the propensity score in the multivariate Cox regression model to adjust for such potential confounding by indication. The estimated HR associated with rehabilitation was slightly reduced, at 0.62 (95% CI, 0.49–0.80), but remained significant statistically.

Fifth, our data showed that 965 control patients (14.8%) did receive rehabilitation later than 3 months after stroke attack (ie, late rehabilitation), suggesting a potential for exposure contamination. We conducted a sensitivity analysis by excluding the patients with late rehabilitation from the control group, and the reanalysis yielded essentially the same results.

Sixth, we excluded those who died early or withdrew from NHI within 3 months poststroke from the analyses. Those who died early may have had more severe comorbidities or more severe neurologic complications. Since this study did not include those who died early after stroke, the beneficial effect of stroke rehabilitation for these patients could not be evaluated.

Seventh, this cohort study was involved with a long-term follow-up. It is likely that the stroke patients who died earlier may have had a smaller chance of developing depression. To address this potential source of bias, we treated "mortality" as a competing-risks event and performed survival analysis with a competing-risks regression model. We noted that 176 of 1,285 patients (13.7%) from the rehabilitation group did not encounter any depression diagnosis and died during the follow-up period. The corresponding figures for the nonrehabilitation group were 1,015 of 6,482 (15.7%). The reanalytic results that took into account mortality as a competing-risks event were essentially the same as those reported from the original analysis.

Last, because we retrieved all patients who had visited rehabilitation within the 3-month period following the stroke attack from the NHI claim data, there was great diversity in the stroke rehabilitation techniques, protocols, durations, frequencies, and periods between different therapists, clinics, or hospitals, which led to heterogeneous effects of stroke rehabilitation. Therefore, further studies to quantify and qualify the dose-response effects and causal relationships of stroke rehabilitation to prevent poststroke depression are needed.

In conclusion, this large cohort study demonstrated a beneficial effect of rehabilitation on the risk of depression onset in patients with stroke. Findings from this study may have important clinical implications because comprehensive evidence has shown that patients with stroke may be at higher risk of depression, a debilitating illness that can lead to early death.[41] We recommend that clinicians inform stroke patients and their families or caregivers of the effectiveness of timely rehabilitation programs and that health policy makers consider setting clinical guidelines that make rehabilitation mandatory. Another limitation is that, although the NHI coverage may successfully remove financial barriers of access to treatment for patients who suffer from stroke, future studies should be conducted to further identify the nonfinancial factors that prevent stroke patients from receiving rehabilitation. Meanwhile, clinicians should also devote additional attention to the mental health of stroke patients who are unable to receive rehabilitation.

***Author affiliations:*** Department of Physical Medicine and Rehabilitation, Taipei Medical University-Shuang Ho Hospital, New Taipei City, School of Gerontology Health Management, College of Nursing, Taipei Medical University, and Department of Physical Medicine and Rehabilitation, Taipei Medical University Hospital, Taipei (Dr W.-H. Hou); Department of Physical Medicine and Rehabilitation, National Taiwan University Hospital, and National Taiwan University College of Medicine, Taipei (Dr Liang); School of Occupational Therapy, College of Medicine, National Taiwan University, and Department of Physical Medicine and Rehabilitation, National Taiwan University Hospital, Taipei (Dr Hsieh); Department of Physical Medicine and Rehabilitation, E-Da Hospital, Yan-Chau District, Kaohsiung (Mr C.-Y. Hou); Department of Dentistry, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Chia-Yi City (Dr Wen); Department and Graduate Institute of Public Health, College of Medicine, National Cheng Kung University, Tainan (Drs Wen and Li); and Department of Public Health, College of Public Health, China Medical University, Taichung (Dr Li), Taiwan.
***Author contributions:*** Drs Wen and Li contributed equally to this article.
***Potential conflicts of interest:*** None reported.
***Funding/support:*** This study was supported by research grants from the National Scientific Council, Taiwan (grant 101-2314-B-006-076-MY3), Taipei Medical University, Taipei, Taiwan (grants TMU101-AE1-B21 and 102CM-TMU-07), and the E-Da Hospital, Kaohsiung, Taiwan (grant EDAHT-101010).
***Additional information:*** Information on the National Health Insurance Research Database can be found at http://nhird.nhri.org.tw/en/index.htm. The data are managed and supervised by the Bureau of National Health Insurance. The data can be accessed only by local researchers, and utilization of the data is allowed only at specific computer sites designated by the Bureau of National Health Insurance.

## REFERENCES

1. Taylor-Piliae RE, Hepworth JT, Coull BM. Predictors of depressive symptoms among community-dwelling stroke survivors [published online ahead of print June 15, 2012]. *J Cardiovasc Nurs*. 2012.
2. Whyte EM, Mulsant BH, Rovner BW, et al. Preventing depression after stroke. *Int Rev Psychiatry*. 2006;18(5):471–481.
3. Lenzi GL, Altieri M, Maestrini I. Post-stroke depression. *Rev Neurol (Paris)*. 2008;164(10):837–840.
4. Tharwani HM, Yerramsetty P, Mannelli P, et al. Recent advances in poststroke depression. *Curr Psychiatry Rep*. 2007;9(3):225–231.
5. House A, Knapp P, Bamford J, et al. Mortality at 12 and 24 months after stroke may be associated with depressive symptoms at 1 month. *Stroke*. 2001;32(3):696–701.
6. Turner-Stokes L, Hassan N. Depression after stroke: a review of the evidence base to inform the development of an integrated care pathway, part 2: treatment alternatives. *Clin Rehabil*. 2002;16(3):248–260.
7. Anderson CS, Hackett ML, House AO. Interventions for preventing depression after stroke. *Cochrane Database Syst Rev*. 2004;(2):CD003689.
8. Hackett ML, Anderson CS, House A, et al. Interventions for preventing depression after stroke. *Cochrane Database Syst Rev*. 2008;(3):CD003689.
9. Stein J, Branstater ME. Stroke rehabilitation. In: Frontera WR, Gans BM, Walsh NE, et al, eds. *Delisa's Physical Medicine & Rehabilitation*. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2010:551.
10. Arseniou S, Arvaniti A, Samakouri M. Post-stroke depression: recognition and treatment interventions [Greek, Modern]. *Psychiatrike*. 2011;22(3): 240–248.

11. Robinson RG, Spalletta G. Poststroke depression: a review. *Can J Psychiatry*. 2010;55(6):341–349.
12. Lai SW, Liao KF, Liao CC, et al. Polypharmacy correlates with increased risk for hip fracture in the elderly: a population-based study. *Medicine (Baltimore)*. 2010;89(5):295–299.
13. Lu JF, Hsiao WC. Does universal health insurance make health care unaffordable? lessons from Taiwan. *Health Aff (Millwood)*. 2003;22(3):77–88.
14. Cheng TM. Taiwan's new national health insurance program: genesis and experience so far. *Health Aff (Millwood).* 2003;22(3):61–76.
15. Sun Y, Chang YH, Chen HF, et al. Risk of Parkinson disease onset in patients with diabetes: a 9-year population-based cohort study with age and sex stratifications. *Diabetes Care*. 2012;35(5):1047–1049.
16. Ottenbacher KJ, Jannell S. The results of clinical trials in stroke rehabilitation research. *Arch Neurol*. 1993;50(1):37–44.
17. Chou YC, Liao CC, Su LT, et al. Stroke rehabilitation is associated with a reduction in dementia risk: a population-based retrospective cohort study. *J Rehabil Med*. 2012;44(4):319–324.
18. Chen HF, Chen P, Su YH, et al. Age- and sex-specific risks of colorectal cancers in diabetic patients. *Tohoku J Exp Med*. 2012;226(4):259–265.
19. Tan HF, Tseng HF, Chang CK, et al. Accessibility assessment of the Health Care Improvement Program in rural Taiwan. *J Rural Health*. 2005;21(4):372–377.
20. Polsky D, Doshi JA, Marcus S, et al. Long-term risk for depressive symptoms after a medical diagnosis. *Arch Intern Med*. 2005;165(11):1260–1266.
21. Narushima K, Robinson RG. Stroke-related depression. *Curr Atheroscler Rep*. 2002;4(4):296–303.
22. Lai SM, Studenski S, Richards L, et al. Therapeutic exercise and depressive symptoms after stroke. *J Am Geriatr Soc*. 2006;54(2):240–247.
23. Graven C, Brock K, Hill K, et al. Are rehabilitation and/or care co-ordination interventions delivered in the community effective in reducing depression, facilitating participation and improving quality of life after stroke? *Disabil Rehabil*. 2011;33(17–18):1501–1520.
24. Martinsen EW. Physical activity and depression: clinical experience. *Acta Psychiatr Scand suppl*. 1994;89(s377):23–27.
25. Singh NA, Clements KM, Fiatarone MA. A randomized controlled trial of progressive resistance training in depressed elders. *J Gerontol A Biol Sci Med Sci*. 1997;52(1):M27–M35.
26. Lawlor DA, Hopker SW. The effectiveness of exercise as an intervention in the management of depression: systematic review and meta-regression analysis of randomised controlled trials. *BMJ*. 2001;322(7289):763–767.
27. Martinsen EW, Hoffart A, Solberg Ø. Comparing aerobic with nonaerobic forms of exercise in the treatment of clinical depression: a randomized trial. *Compr Psychiatry*. 1989;30(4):324–331.
28. Dunn AL, Trivedi MH, Kampert JB, et al. Exercise treatment for depression: efficacy and dose response. *Am J Prev Med*. 2005;28(1):1–8.
29. Singh NA, Stavrinos TM, Scarbek Y, et al. A randomized controlled trial of high versus low intensity weight training versus general practitioner care for clinical depression in older adults. *J Gerontol A Biol Sci Med Sci*. 2005;60(6):768–776.
30. Hassmén P, Koivula N, Uutela A. Physical exercise and psychological well-being: a population study in Finland. *Prev Med*. 2000;30(1):17–25.
31. Fure B, Wyller TB, Engedal K, et al. Emotional symptoms in acute ischemic stroke. *Int J Geriatr Psychiatry*. 2006;21(4):382–387.
32. Poynter B, Shuman M, Diaz-Granados N, et al. Sex differences in the prevalence of post-stroke depression: a systematic review. *Psychosomatics*. 2009;50(6):563–569.
33. Carota A, Berney A, Aybek S, et al. A prospective study of predictors of poststroke depression. *Neurology*. 2005;64(3):428–433.
34. Lai SM, Duncan PW, Keighley J, et al. Depressive symptoms and independence in BADL and IADL. *J Rehabil Res Dev*. 2002;39(5):589–596.
35. Berg A, Palomäki H, Lehtihalmes M, et al. Poststroke depression: an 18-month follow-up. *Stroke*. 2003;34(1):138–143.
36. Vataja R, Pohjasvaara T, Mäntylä R, et al. Depression-executive dysfunction syndrome in stroke patients. *Am J Geriatr Psychiatry*. 2005;13(2):99–107.
37. Jorgensen HS, Kammersgaard LP, Houth J, et al. Who benefits from treatment and rehabilitation in a stroke unit? a community-based study. *Stroke*. 2000;31(2):434–439.
38. Wu SC, Leu SY, Li CY. Incidence of and predictors for chronic disability in activities of daily living among older people in Taiwan. *J Am Geriatr Soc*. 1999;47(9):1082–1086.
39. Neri AL, Yassuda MS, Fortes-Burgos AC, et al. Relationships between gender, age, family conditions, physical and mental health, and social isolation of elderly caregivers. *Int Psychogeriatr*. 2012;24(3):472–483.
40. Jollis JG, Ancukiewicz M, DeLong ER, et al. Discordance of databases designed for claims payment versus clinical information systems: implications for outcomes research. *Ann Intern Med*. 1993;119(8):844–850.
41. Remick RA. Diagnosis and management of depression in primary care: a clinical update and review. *CMAJ*. 2002;167(11):1253–1260.
42. Buntin MB. Access to postacute rehabilitation. *Arch Phys Med Rehabil*. 2007;88(11):1488–1493.
43. Horner RD, Swanson JW, Bosworth HB, et al; VA Acute Stroke (VAST) Study Team. Effects of race and poverty on the process and outcome of inpatient rehabilitation services among stroke patients. *Stroke*. 2003;34(4):1027–1031.
44. Smeeton NC, Corbin DO, Hennis AJ, et al. A comparison of acute and long-term management of stroke patients in Barbados and South London. *Cerebrovasc Dis*. 2009;27(4):328–335.
45. Arrich J, Müllner M, Lalouschek W, et al. Influence of socioeconomic status and gender on stroke treatment and diagnostics. *Stroke*. 2008;39(7):2066–2072.
46. Lee HC, Chang KC, Huang YC, et al. Inpatient rehabilitation utilization for acute stroke under a universal health insurance system. *Am J Manag Care*. 2010;16(3):e67–e74.