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Depression and Increased Risk of Death in Adults with Stroke

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Abstract

OBJECTIVE—Depression is a common condition among individuals with stroke and believed to influence post-stroke mortality. The objective of this study was to evaluate the effect of depression on all-cause mortality among adults with and without a history of stroke.

METHODS—We studied 10,025 participants in the population-based National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study who were alive and interviewed in 1982 and had complete data for the Center for Epidemiologic Studies Depression Scale. Four groups were created based on history of stroke and depression status in 1982: 1) no stroke, no depression (reference group); 2) no stroke, depression present; 3) history of stroke, no depression; and 4) history of stroke present, depression present. Cox proportional hazards regression models were used to calculate multivariate-adjusted hazard ratios (HRs) of death for each group compared with the reference group.

RESULTS—Over 8 years (83,624 person-years of follow-up), 1,925 deaths were documented. Mortality rate per 1,000 person-years of follow-up was highest in the group with both a history of stroke and depression. Compared with the reference group, HRs for all-cause mortality was: no stroke, depression present, 1.23 (95% CI 1.08, 1.40); stroke present, no depression 1.74 (1.06, 2.85); and stroke present, depression present, 1.88 (1.27, 2.79).

CONCLUSIONS—The coexistence of stroke and depression increases the risk of death; however, the combined effect is less than additive.

Keywords

depression; mortality; stroke

INTRODUCTION

Studies suggest that at least 30% of all stroke patients develop depression.^{1–4} Because there are approximately 500,000 new strokes each year in the U.S.⁵, estimates indicate that approximately 150,000 stroke survivors develop depression in the first year post-stroke.¹

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Unfortunately, depression is associated with poor stroke-related outcomes for both patients and their caregivers.^{1,6} Patients with depression experience worse stroke-related outcomes in the form of greater functional disability^{6–9} and higher mortality.^{6, 10–13}

A number of studies suggest that depressive symptoms are key indicators for increased risk of post-stroke mortality.^{10–14} Morris and colleagues found that patients with depression were 3.4 times more likely to die during a 10-year follow-up period than non-depressed patients.¹⁴ They also observed that the relationship between mortality and depression was independent of other common stroke risk factors (e.g. age, sex, social class, and level of social functioning). Similarly, Everson and colleagues examined 169 deaths during a 29 year follow-up period and found that after adjustment for established stroke risk factors, patients reporting the greatest number of depressive symptoms experienced a 50% increased risk of mortality due to stroke.¹¹ Williams et al., also found a higher 3-year mortality risk in patients with depression even though depressed patients were younger and had fewer chronic conditions than the comparison group.¹³

Unfortunately, even though depression after stroke has been associated with greater mortality, it is not entirely clear whether depression is a contributor to post-stroke mortality as an individual stroke risk factor or as an independent factor that negatively influences other stroke risk factors.^{1–11} For example, there is substantial evidence linking depression and stroke mortality, however the contribution of depression to stroke mortality over and above the normal risk of death for individuals without stroke is much less clear. House and colleagues proposed that depressive symptoms may be associated with mortality by behavioral (poor risk factor control and adherence to treatment) or physiological (alterations in autonomic control of cardiac rhythms and increased platelet reactivity).¹⁰ However, the nature of the relationship between depression and stroke mortality is not entirely clear and questions remain regarding prevention and treatment.¹

Few studies have examined whether the risk of death among people with both stroke and depression is greater than the risk of death associated with having stroke or depression alone. To address this issue, we examined mortality in a large nationally representative sample of adults aged 25–75 in years 1971–1975¹⁵ who were re-interviewed in 1982 and followed until 1992.^{16,17} We compared all-cause mortality among four subsets of participants based on their disease status at the 1982 survey to determine whether the risk of death among adults with both stroke and depression was greater than the risk of death from having each condition alone. We examine all-cause mortality using two multivariate models. Our first model includes socio-demographic variables (age, race/ethnicity, poverty, education and marital status) believed to contribute to stroke risk and stroke-related death and our second model includes the same socio-demographic variable in addition to common cardiovascular risk factors (smoking, limited physical activity, limited aspirin use, high BMI and history of cancer, hypertension, heart disease and diabetes) known to increase stroke risk and stroke-related death even in the absence of depression.

RESEARCH DESIGN AND METHODS

The National Health and Nutrition Examination Survey (NHANES) I was a multistage, stratified, national probability sample of the civilian non-institutionalized population of the U.S. aged 1–74 years.¹⁵ The survey was conducted between 1971 and 1975 and included a standardized examination and questionnaires that addressed various health topics. Persons living in poverty areas, women of childbearing age (25–44 years), and elderly persons (≥65 years) were oversampled. The NHANES I sample included 20,729 persons 25–74 years of age, of whom 14,407 (70%) were medically examined.

The NHANES I Epidemiologic Follow-up Study (NHEFS) is a longitudinal study of participants who were between 25 and 74 years old during the 1971–1975 interviews.^{16,17} The first follow-up study was conducted in 1982 and included all persons aged 25–74 years at the NHANES I assessment (n= 14,407). Participants were subsequently interviewed in 1986, 1987, and 1992. The 1982 follow-up interview included data on self-reported medical conditions and an assessment of depression based on the Center for Epidemiologic Studies Depression Scale (CES-D). For this investigation, we analyzed data on participants in the NHEFS cohort who completed the CES-D in 1982 and were followed until the 1992 interview date.

Definition of depression

The CES-D is a self-report scale designed to measure depression in the general population.¹⁸ The scale consists of 20 items rated on a four-point scale with response categories indicating the frequency of occurrence of each item in the previous week. The four-point scale ranges from 0 (rarely or none of the time) to 3 (most or all of the time). Scores for items 4, 8, 12, and 16 are reversed before scores for the 20 items are summed. Total scores range from 0 to 60 with higher scores indicating more depressive symptoms. A cutoff of ≥ 16 has been used extensively for distinguishing depressed from non-depressed patients. The CES-D is a valid and reliable instrument for assessing depression in community samples with high internal consistency, good construct and concurrent validity, and modest test-retest reliability.^{18–20}

Defining the study cohort

Of the 14,407 respondents eligible for inclusion in the 1982 follow-up study, 13,383 were traced, 11,361 were living, and 10,523 were interviewed.¹⁶ We defined our cohort as the 10,025 individuals who were alive and interviewed in 1982 and who had complete data for the CES-D. We excluded 498 individuals who either did not have complete data for the CES-D or were missing data for covariates. We divided the cohort into four groups based on the presence or absence of self-reported stroke and depression (defined as CES-D ≥ 16) in 1982 as follows: 1) individuals without stroke and without depression (reference group); 2) individuals without stroke but with depression (depressed only group); 3) individuals with stroke but without depression (stroke only group), and 4) individuals with both stroke and depression (combined stroke and depression group).

Baseline data collection

Demographic, lifestyle behavior, and comorbidity information were collected as part of the 1982 interview. We included age (in years) as a continuous variable. Race/ethnicity was categorized as white versus black/other. Poverty: A poverty income ratio was calculated. The poverty income ratio is the ratio of a family's income to the US Census Bureau's poverty threshold, which varies with the number and ages of family members and is revised yearly. The poverty income ratio allows comparison across time because it is continually revised to account for inflation. In this study the poverty income ratio was defined as percentage of the U.S. federal poverty level and classified as <125%, 125–399%, and $\geq 400\%$. Education was categorized as <high school graduate, high school graduate, or >high school graduate, and marital status was classified as not married or married. BMI was calculated from self-reported weight and height and categorized as normal weight (18.5–24.9), overweight (25.0–29.9), and obese (≥ 30.0).

Smoking was grouped as never, former, or current smoker, and physical activity based on the individual's engagement in usual recreational activity was categorized as regular, light, or sedentary. Self-reported aspirin use was dichotomized as yes versus no. In addition, respondents were asked to report previously diagnosed medical conditions, including diabetes, hypertension, heart disease, stroke, and cancer. The diagnosis of stroke was based on a "yes" response to the question, "Have you ever been told by a doctor that you have had a stroke?" A

similar approach was used to establish prior diagnosis of the other self reported medical conditions.

Outcome measures

The main outcome measure was all-cause mortality across the four groups in the cohort. Follow-up data were collected in four waves: 1982–1984, 1986, 1987, and 1992. For each wave, patient or proxy interviews were conducted and health care facility records as well as death certificates were obtained. Death for each cohort member was ascertained through a search of the National Death Index or through tracing of vital status via a proxy interview. The underlying causes of death on the death certificates were classified according to ICD-9. End points for this study were deaths from all causes. The reliability of the National Death Index for epidemiological studies has been previously validated.^{21,22} Length of follow-up for each individual was calculated from the date of the baseline interview (1982–1984) to either the date of death or the date of last follow-up.

Statistical analysis

Statistical analysis was performed with SAS V9.3²³ and SUDAAN V8.0²⁴ using the approach recommended by the National Center for Health Statistics for analyzing the NHEFS.²⁵ Means or proportions of baseline risk factors were calculated for the reference group (individuals without stroke and without depression) and the other three groups (individuals with depression alone, individuals with stroke alone, and individuals with both stroke and depression). All-cause mortality rates per 1,000 person-years of follow-up were calculated for the four groups. Life expectancy and survival times for the four groups were estimated by the Kaplan-Meier product-limit method.

Cox proportional hazards regression models were used to calculate multivariate-adjusted HRs of death for each group compared with the reference group. Simulation data have shown that the Cox model is preferred to the cumulative logistic or person-time logistic regression models for analyzing data from the NHEFS because it takes into account differential follow-up time and does not require the survival time to be exponentially distributed.²⁵ Two multivariate models were developed: a minimal model (model 1) that included confounding sociodemographic variables and a full model (model 2) that included variables in model 1 and additional variables that were likely to be mediators of the relation between stroke/depression and mortality. Model 1 included age in 1982, sex, race/ethnicity, poverty: income ratio, education, and marital status. In addition to the variables in model 1, model 2 included smoking, physical activity, BMI, aspirin use, and comorbid medical conditions at baseline (cancer, hypertension, heart disease, and stroke). In these models, age at death (or age at last contact for censored subjects) was used as the dependent variable. The assumption of proportionality of hazard was assessed for the four stroke/depression classification groups and each study covariate; all multivariate models satisfied this assumption.

RESULTS

In this nationally representative sample of 10,025 adults followed for an average duration of 8 years (83,624 person-years of follow-up), 1,925 (19%) of the study subjects died. Stroke accounted for 74 deaths (4%). Table 1 shows the baseline characteristics of the study participants. In general, the group of individuals with both stroke and depression were more likely to be female, White, married, have less than a high school education, live sedentary lifestyles, and to be overweight/obese. They were also more likely to have history of cancer, hypertension, heart disease, and diabetes at baseline compared with the other three groups.

Table 2 presents mortality rates and multivariate-adjusted HRs of death from all-cause according to stroke and depression diagnoses at the 1982 interview. Mortality rates per 1,000 person years of follow-up from all causes were highest in individuals with both stroke and depression (105.1) and lowest in individuals without stroke and without depression (20.3). Multivariate adjusted HRs of deaths from all causes was significantly higher for people with stroke but highest for those with both stroke and depression. For model 1, compared with the reference group (individuals without stroke and without depression), the adjusted HR of death was 2.83 fold higher for those with both stroke and depression. After further multivariate adjustment (model 2), the HR of death was 1.88 fold higher for people with both stroke and depression.

Table 3 presents multivariate-adjusted HRs of death from all cause mortality according to all relevant covariate factors (sociodemographic and clinical co-morbidities). In the final model, other factors associated with increased risk of death included male gender, smoking, being overweight, light/sedentary physical activity levels, and having comorbidities (cancer, hypertension, diabetes, heart disease). In contrast, having >high school education and being married were associated with decreased risk of death. Figure 1 shows the Kaplan-Meier curve of survival times during the period of follow-up for the four groups.

CONCLUSIONS

This is the first study to our knowledge to determine whether the risk of death among adults with stroke and depression is greater or less than the sum of the risk of death from having each condition alone. After adjusting for relevant socio-demographic factors and clinical comorbidities, individuals with both stroke and depression had a 1.88 fold risk of death from all causes compared to those without a history of stroke or depression (reference group). Additionally, depressed individuals without stroke had a 1.23 risk of death from all causes, while those with stroke but without depression had a 1.74 risk of death when compared to the reference group. However, the hazard ratio for the combined stroke and depression group was less than the sum of the hazard ratios for the depression only and the stroke only groups suggesting that the combined effect was less than additive.

Our findings are consistent with other studies of all-cause stroke mortality after stroke that show an increased risk of death among stroke survivors who exhibit depressive symptoms.^{10–12} However, by comparing individuals with and without a history of stroke, we are able to further consider whether depression alone has either an additive or synergistic effect on risk of death.^{26,27} Our findings indicate that when controlling for all relevant clinical factors associated with stroke, the risk of death among the combined stroke and depression group is 88% higher than those in the reference group (no stroke and no depression). Further, the risk of death is 74% higher in the stroke only group compared to the reference group. Similarly, the risk of death is 23% higher in those in the depression only group compared to the reference group. While these findings indicate a substantially greater risk of death for those individuals with both stroke and depression, the magnitude of the increase does not appear substantial enough to conclude that having both depression and stroke has an additive or synergistic effect on all-cause mortality.

In this study, risk of death related to depression alone ranged from 1.2 – 1.4. These findings are lower than previous reports of risk of death related to depression.^{28–30} In a meta-analysis of 25 studies including ~107,000 patients, Cuijpers and colleagues found that the HR for all cause mortality in depressed patients was 1.81 (95% CI = 1.58, 2.07).²⁸ Interestingly, the death rate reported by Cuijpers et al. (2002) was also significantly higher than our findings in a previous study of all-cause mortality among individuals with and without depression and diabetes using this same cohort.³¹ We attribute some of the differences in risk of death to the

small sample of individuals in this study with stroke who died; both depressed and non-depressed (N =74). We also attribute some of the differences to significant variation in study design, diagnostic criteria, and the follow-periods among studies included in the meta-analysis by Cuijpers and colleagues.

We also note that the odds of death in the highest risk group (stroke and depression) in our study was significantly lower than previously published odds of death among patients with both stroke and depression.^{10,14} Because the odds of death that we report are lower, we must give some consideration to explanations of these differences. Time of depression onset in relationship to the time of stroke onset may be one such factor. To our knowledge, no previous studies have examined the relationship between the two. However, there is evidence that suggests that depression in the acute phase of stroke has a greater effect on mortality than depression in patients in the more chronic phase of recovery.^{10, 14} For example, Morris and colleagues found that patients with minor or major depression in the acute phase of recovery (2 weeks after stroke) were 3.4 times more likely to have died than patients that were not depressed.¹⁴ Since the time post-onset of stroke was not identified at the time of the interview, it is possible that our participants may have been many years post stroke with depression of unknown duration. Even though they reported depression at the time of the interview, the duration of the depression was not reported. Therefore, we did not examine the relationship between time of onset of depression and time of stroke. As such, we must consider that depression occurring years later or during the more chronic phase of recovery may not influence mortality as depression during the more acute phase thereby resulting in lower odds of death among our participants than has been reported in previous studies.

Even though our findings generally agree with previous studies reporting increased mortality in individuals with stroke and depression,^{10–13} we do not have enough data to establish the mechanisms by which depression increases mortality. What is clear from this study is that the effect of depression on risk of death is independent of common socio-demographic and clinical factors. Our findings suggest that comorbidity, smoking, physical activity, BMI and aspirin use explain some, but not all of the effects of depression on mortality in people with stroke. For example, in our minimal model that included only socio-demographic variables, the hazards of death was 2.83 for the combined stroke and depression group. In contrast, when we controlled for comorbidity, smoking, physical activity, BMI and aspirin use, the hazards of death decreased to 1.88, suggesting that depression may exert some of its effect via these variables. Even so, future studies need to identify the mediators and moderators of the effect of depression on mortality in adults with stroke.

The major clinical implications of these findings are that practitioners need to pay more attention to depression as a risk factor in people with stroke.²⁷ Current secondary prevention efforts are targeted at CVD risk factor reduction. However, recent studies have shown that pharmacologic interventions targeting depression after stroke are significantly beneficial and results in lower mortality.^{32, 33} Jorge and colleagues found that 67.9% of patients who received 12 week treatments of antidepressants during the first 6 months after stroke were alive at follow-up compared to 35.7% of placebo treated patients.³² Similarly, Ried, Tueth and Jia found that 80% of veterans treated for depression after stroke survived for one year or longer.³³ Therefore, we must also consider that our observed lower mortality rates among our highest risk group (stroke and depression) relative to previous studies may have resulted from administration of antidepressants. Additionally, some of the patients with a history of stroke but not depressed at the time of the examination in 1982 may have experienced depression prior to or after the examination. This is an additional factor that may have influenced mortality rates but could not be accounted for in this study.

We also note that few interventions incorporate stress reduction and/or recognition and treatment of depression in the armamentarium of strategies to improve outcomes in people with stroke. Clinicians who treat people with stroke should routinely screen for depression and offer evidence-based treatment for those individuals who screen positive, given the growing evidence that depression increases mortality in stroke patients. Future studies are needed to determine the effectiveness of treatment of depression on stroke outcomes as well as to delineate the behavioral and physiologic relationship between depression and mortality in adults with stroke.^{10,11,13}

This study has a number of limitations. First, the data in this study is based on self-report. However, a number of studies have shown that self-report data on chronic disease and risk factors are reliable.^{34,35} Second, even though the CES-D is a widely accepted, valid and reliable tool for the identification of depression in community samples^{18–20}, the diagnosis of depression was not based on the “gold standard” of a clinical interview. Third, because we used administrative data, we were unable to examine the possible behavioral and biopsychosocial aspects of depression. Further, the use of administrative data has the potential to result in an under diagnosis of depression.¹³ Fourth, we did not have data related to stroke severity, time post-stroke, depression severity, the presence and duration of depression prior to stroke onset or duration of depression after stroke onset to determine their effects on stroke mortality. Previous studies note that the number of depressive symptoms is associated with increasing risk of mortality.^{11,12,14}

In spite of these limitations, the findings of this study remain important and show that after adjusting for relevant socio-demographic factors and clinical comorbidities, individuals with both stroke and depression had an increased risk of death. However, the hazard ratio for the combined stroke and depression group was less than the sum of the hazard ratios for the depression only and the stroke only groups suggesting that the combined effect was less than additive.

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Figure 1.
Estimated probability of survival (all-cause mortality) according to stroke and depression diagnosis in 1982.

Table 1
Baseline Characteristics in 1982 according to Presence or Absence of Stroke and Depression

	No STROKE, Not Depressed	No STROKE, Depressed	STROKE, Not Depressed	STROKE, Depressed
N	7,426	2,475	59	65
Mean age in 1982, years	56	57.4	69.2	68.9
Sex(%)				
Men	40.1	28.0	52.5	43.1
Women	59.9	72.0	47.5	56.9
Race/Ethnicity(%)				
White	87.2	82.0	84.7	84.6
Black/Other	12.8	18.0	15.3	15.4
Poverty-Income Ratio(%)				
<125%	17.5	26.8	31.8	43.1
125–399%	61.0	59.6	54.5	43.1
400+%	21.5	13.6	13.6	13.7
Education(%)				
<High school graduate	37.9	51.6	64.3	74.6
High school graduate	30.4	26.2	7.1	8.5
>High school graduate	31.7	22.1	28.6	16.9
Marital Status(%)				
Single	4.8	5.5	3.4	4.6
Widowed/divorced	24.2	34.0	32.2	41.5
Married	71.0	60.5	64.4	53.8
Physical Activity(%)				
Regular	16.9	13.1	1.7	3.1
Light	51.8	40.4	32.2	18.5
Sedentary	31.3	46.5	66.1	78.5
Body Mass Index(%)				
<18.5 (underweight)	2.1	3.3	1.7	1.6
18.5–24.9 (normal weight)	44.1	42.5	42.4	35.9
25.0–29.9 (overweight)	36.1	33.7	42.4	42.2
30.0+ (obese)	17.6	20.5	13.6	20.3

	No STROKE, Not Depressed		STROKE, Not Depressed		STROKE, Depressed	
Smoking(%)						
Never smoked	45.0	46.4	49.2	40.0		
Former smoker	27.7	23.8	37.3	33.8		
Current smoker	27.3	29.8	13.6	26.2		
Cancer (%)	3.6	5.3	3.4	9.2		
Hypertension (%)	42.1	50.6	76.3	78.5		
Heart disease (%)	14.3	23.6	44.1	56.9		
Diabetes (%)	5.9	9.7	23.7	33.8		
Aspirin use (%)	21.8	30.6	40.7	39.1		

Table 2

HR of death from all causes according to Presence or Absence of Stroke and Depression in 1982

	No STROKE, Not Depressed		No STROKE, Depressed		STROKE, Not Depressed		STROKE, Depressed	
N	7,426		2,475		59		65	
Person-years of follow-up	63,121		20,048		389		390	
All-cause mortality								
Death (n)	1,280		571		33		41	
Mortality rate (per 1,000)	20.3		28.5		84.7		105.1	
Hazard ratio (95% CI)								
Multivariate model 1	1.00 (reference)		1.41 (1.23, 1.61)		2.12 (1.32, 3.39)		2.83 (1.94, 4.13)	
Multivariate model 2	1.00 (reference)		1.23 (1.08, 1.40)		1.74 (1.06, 2.85)		1.88 (1.27, 2.79)	

Table 3

Multivariate Adjusted Hazard Ratio (HR) of Death from All Causes

	MODEL1	MODEL2
	HR (95% CI)	HR (95% CI)
Age in 1982 (years)	0.84 (0.83, 0.85)	0.83 (0.82, 0.84)
Sex		
Men	2.19 (1.97, 2.44)	2.11 (1.86, 2.39)
Women	1.00 (reference)	1.00 (reference)
Race/Ethnicity		
White	1.06 (0.89, 1.26)	0.99 (0.82, 1.19)
Black/Other	1.00 (reference)	1.00 (reference)
Poverty-Income Ratio		
<125%	1.00 (reference)	1.00 (reference)
125–399%	0.88 (0.77, 0.99)	0.93 (0.80, 1.07)
400+%	0.85 (0.70, 1.04)	0.88 (0.71, 1.08)
Education		
<High school graduate	1.00 (reference)	1.00 (reference)
High school graduate	0.89 (0.78, 1.01)	0.88 (0.76, 1.00)
>High school graduate	0.80 (0.69, 0.92)	0.82 (0.70, 0.97)
Marital Status		
Single/widowed/divorced	1.00 (reference)	1.00 (reference)
Married	0.71 (0.63, 0.81)	0.74 (0.65, 0.84)
No Stroke, Not Depressed	1.00 (reference)	1.00 (reference)
No Stroke, Depressed	1.41 (1.23, 1.61)	1.23 (1.08, 1.40)
Stroke, Not Depressed	2.12 (1.32, 3.39)	1.74 (1.06, 2.85)
Stroke, Depressed	2.83 (1.94, 4.13)	1.88 (1.27, 2.79)
Smoking		
Never smoked		1.00 (reference)
Former smoker		1.22 (1.09, 1.37)
Current smoker		1.81 (1.57, 2.09)
History of Cancer		
No		1.00 (reference)
Yes		1.71 (1.41, 2.09)
History of Hypertension		
No		1.00 (reference)
Yes		1.14 (1.02, 1.27)
History of Heart Disease		
No		1.00 (reference)
Yes		1.65 (1.47, 1.85)
History of Diabetes		
No		1.00 (reference)
Yes		1.97 (1.72, 2.24)
Physical Activity		

	MODEL1	MODEL2
	HR (95% CI)	HR (95% CI)
Regular		1.00 (reference)
Light		1.28 (1.07, 1.54)
Sedentary		1.58 (1.33, 1.88)
Body Mass Index		
<=24.9 (under/normal weight)		1.00 (reference)
25.0–29.9 (overweight)		0.85 (0.76, 0.96)
30.0+ (obese)		0.94 (0.81, 1.10)
Aspirin use		
No		1.00 (reference)
Yes		0.94 (0.82, 1.09)