Published in final edited form as:
Stroke. 2011 October ; 42(10): 2770–2775. doi:10.1161/STROKEAHA.111.617043.

Depression and Incident Stroke in Women

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Abstract

Background and Purpose—Depression has been associated with increased risk of coronary heart disease, but prospective data for the association with stroke are limited.

Methods—We followed 80,574 women aged 54 to 79 years in Nurses' Health Study without a prior history of stroke from 2000 to 2006. Depressive symptoms were assessed at multiple time-points by a Mental Health Index (MHI-5) score (1992, 1996 and 2000), and clinical significant depressive symptoms were defined as a score ≤52. Antidepressant medication (ADM) use was asked biennially beginning in 1996, and physician-diagnosed depression was reported biennially beginning in 2000. Depression was defined as currently reporting or having a history of any of these three conditions.

Results—During 6 years of follow-up, 1,033 incident strokes were documented (538 ischemic, 124 hemorrhagic, and 371 unknown strokes). Having a history of depression was associated with a multivariate-adjusted hazard ratio of 1.29 (95% confidence interval, 1.13–1.48) for total stroke. Women who used ADMs were at increased risks of stroke, whether they also had a MHI-5 score ≤52 or diagnosed depression (1.39; 1.15–1.69), or not (1.31; 1.03–1.67). Furthermore, for each cycle, participants who reported current depression had an increased risk of stroke (1.41; 1.18–1.67), whereas individuals who only had a past history of depression were at a non-significantly elevated risk (1.23; 0.97–1.56), compared with women who never reported a diagnosis of depression or ADM use.

Conclusions—Our results suggest that depression is associated with a moderately increased risk of subsequent stroke.

Keywords

depression; stroke; longitudinal study; antidepressant medication; depressive symptoms

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Conflict of Interest
The authors have no conflict of interest to declare.

INTRODUCTION

Stroke is the third leading cause of death in the United States, and nonfatal stroke is a leading cause of permanent disability and economic loss as a result of impairment.[1] Late-life depression may be a marker of sub-clinical cerebrovascular disease,[2] indicating increased stroke risk. Depression may also influence stroke risk via neuroendocrine, immunological and inflammatory effects.[3,4] Several prospective studies investigating the association between depression and incident stroke have been conducted; however, studies using clinically-diagnosed depression as the predictor have yielded mixed results.[5–9] Few studies have been conducted specifically among middle-aged and elderly women,[10] in whom the prevalence of depression is high,[11] and the risk of stroke is substantial.[12]

We previously found that depression was associated with increased risk of sudden death and fatal coronary heart disease (CHD).[13] In the present study, we aimed to examine the association between depression and incident stroke among middle-aged and elderly women of the Nurses' Health Study during 6 years of follow-up. We also examined the association of antidepressant medication (ADM) use with stroke risk, because a recent report suggested an increased risk of subsequent stroke with use of these medications.[14]

SUBJECTS AND METHODS

Study Population

The Nurses' Health Study cohort was established in 1976 when 121,700 female registered nurses aged 30–55 years residing in 11 states responded to a mailed questionnaire regarding their medical history and health practices. Follow-up questionnaires were administered biennially after baseline, to update information on lifestyle practice and occurrence of chronic diseases.[10,15] Follow-up rates through 2006 exceeded 94%. The study protocol was approved by the institutional review boards of Brigham and Women's Hospital and Harvard School of Public Health.

We used the 2000 questionnaire cycle as the baseline since explicit ascertainment of physician-diagnosed depression began in this year (n=94,791). We excluded participants without information on depressive symptoms, depression diagnosis or ADM use (n=12,463), those with prior stroke (n=1,651) and missing values for covariates (n=103) at baseline. Finally, 80,574 participants were included. Compared to women included in the current analysis, excluded participants had similar ages and incidence rates of stroke, but higher BMI and slightly higher prevalence rates of hypertension, diabetes and heart disease (data not shown).

Depression Measurement

Depressive symptoms were assessed in 1992, 1996 and 2000 with the five-item Mental Health Index (MHI-5), a subscale of the Short-Form 36 Health Status Survey. The participants were asked how much of the time over the past month (all, most, good bit, some, little, or none) they 1) felt nervous, 2) felt so down that nothing could cheer them up, 3) felt calm and peaceful, 4) felt down and blue, or 5) felt happy. Scores are re-scaled from 0 to 100, with lower scores indicating more severe depressive symptoms.[16] The MHI-5 has been shown to have high sensitivity and specificity for major depression,[17] and it was considered as a dichotomous variable for the presence (MHI-5≤52) or absence (MHI-5 >52) of significant depressive symptoms for each time it was queried.[18]

Participants were first asked to report regular use of ADM in 1996, while types of ADMs were first ascertained on the 2000 questionnaire, when participants were specifically asked about their regular use during the past 2 years of selective serotonin reuptake inhibitors

(SSRIs, including fluoxetine, sertraline, paroxetine, citalopram), or other antidepressants, of which the tricyclic antidepressants (TCAs) amitriptyline, imipramine, and nortriptyline were provided as examples. In 2000, the nurses were first asked whether they ever had a lifetime physician diagnosis of depression (1996 or before, 1997–1998, 1999, on or after 2000); the information on ADM and physician-diagnosed depression was updated biennially thereafter.

Assessment of Stroke

During 6 years of follow-up, 1,237 women in the study population self-reported a stroke. In addition, 221 fatal strokes were ascertained by next of kin, postal authorities, or the National Death Index. Medical records, autopsy reports, or death certificates were sought for all reported strokes, and 886 were received and reviewed by a study physician, of which 648 were confirmed. Of the 572 reported strokes for which a medical record or death certificate was unavailable, 385 cases were confirmed by the participants or next of kin, and these were designated probable stroke. Therefore, our current analysis included 1033 confirmed (n=648) and probable (n=385) stroke cases.

Strokes were confirmed using the National Survey of Stroke criteria,[19] requiring neurological deficit of rapid or sudden onset lasting ≥24 hours or until death. Physicians blinded to risk factor status reviewed the medical records. Cerebrovascular pathology due to infection, trauma, or malignancy was excluded, as were “silent” strokes discovered only by radiologic imaging We categorized types of stroke as ischemic (embolic or thrombotic), hemorrhagic (subarachnoid or intracerebral), and unknown, based on imaging and clinical data.[19] Computed tomography or magnetic resonance imaging reports were available for 95% of those with medical records. A validation study in this cohort demonstrated high reliability and validity of the stroke classification.[20] In a sensitivity analysis, the exclusion of probable strokes did not alter the results; therefore, we included both confirmed and probable strokes in this analysis.

Covariates

In the biennial follow-up questionnaires, we inquired and updated demographic and lifestyle behavior information, including body weight, cigarette smoking, alcohol consumption, physical activity, menopausal status, hormone therapy use, current aspirin and multivitamin uses, marital status, ethnicity, and parental history of myocardial infarction (MI). Dietary information was assessed using a semi-quantitative food frequency questionnaire, and a Dietary Approaches to Stop Hypertension (DASH) diet score was used to characterize their usual diet pattern. In addition, respondents were asked to report previously diagnosed medical conditions, e.g., diabetes, hypertension, elevated cholesterol, heart disease (including MI, angina, and coronary artery revascularization) and cancer.

Statistical Analysis

As described above, the three measures of depression status were queried at different time-points; however, all were available in 2000. Because it can be difficult to determine when a particular episode of depression started or ended, our primary analysis defined depression as currently reporting or having a history of any of the three conditions: physician-diagnosed depression, regular use of ADMs, or MHI-5 ≤52.[15] Depressed participants were further divided into three groups: MHI-5 ≤52 or physician-diagnosed depression without ADM use; MHI-5 ≤52 or physician-diagnosed depression with ADM use; MHI-5 >52 and no physician-diagnosed depression, but with ADM use. This classification was based on prior knowledge that ADM might increase stroke risk via mechanisms different from depression itself. Dummy variables were created for each category to compare with the reference group of no depression. In a separate analysis, we classified women into never, past, and current depression according to their clinical depression status at each two-year questionnaire

period. Since the MHI-5 score was not updated during 2000–2006, clinical depression (having a physician-diagnosed depression, regular ADM use, or both) was used in this specific analysis. In each analysis, the associations of depression with types of stroke (ischemic or hemorrhagic stroke) were also examined.

Individuals contributed person-time from the return of the 2000 baseline questionnaire until the date of stroke, death, June 30th 2006, or the date of return of their last questionnaires, whichever came first. Time-dependent Cox proportional hazards models were used, and depression and most of the covariates were updated every 2 years except ethnicity and parental history of myocardial infarction. We controlled for age (continuous), marital status (currently having spouse or not), parental history of myocardial infarction (yes/no), ethnicity (whites/non-whites), menopausal status (premenopausal or postmenopausal) and postmenopausal hormone use (never, past or current use), current aspirin use (yes/no), current multivitamin use (yes/no), body mass index (<23.0, 23.0–24.9, 25.0–29.9, 30.0–34.9, ≥35.0 kg/m^2), smoking status (never, past, or current smoking of 1–14, 15–24, or ≥25 cigarettes/d), alcohol intake (0, 0.1–4.9, 5.0–14.9, ≥15 g/d), physical activity (<3, 3–8.9, 9–17.9, 18–26.9, ≥27 metabolic equivalent-hours/week), and quintile of Dietary Approaches to Stop Hypertension dietary score. Histories of hypertension, hypercholesterolemia, diabetes, cancer and heart diseases (yes/no) were further included in the final model. Data were analyzed with the Statistical Analysis Systems software package, version 9.1 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

The mean age of the participants was 66 years (range: 54–79) in 2000. The reported prevalence of depression was 22.3% in 2000. Compared to participants without a history of depression, depressed women were younger, more likely to be single, had a higher BMI and smoke cigarettes, and less likely to be physically active (Table 1). The prevalence of major comorbidities was also higher in depressed women.

During 6 years of follow-up, 1,033 incident strokes were documented (538 ischemic, 124 hemorrhagic, and 371 unknown types of strokes). In age-adjusted analyses, depression was associated to an increased risk of total stroke with a hazard ratio (HR) of 1.49 (95% CI, 1.30–1.70; Table 2). The HR was attenuated but remained significant after controlling for various covariates including major comorbidities (1.29; 1.13–1.48). Results were not significant for either hemorrhagic or ischemic stroke separately, possibly due to lower power. No significant interactions between depression, age and major comorbidities with total stroke risk were found (Supplemental Table 1).

Increased risk of stroke was seen among women who used ADM, with (1.39; 1.15–1.69) or without (1.31; 1.03–1.67) a MHI-5 score ≤52 or diagnosed depression, compared with non-depressed women (Table 2). Furthermore, compared with women without a history of clinical depression (having a physician-diagnosed depression, regular ADM use, or both), women with a past history of clinical depression had a non-significantly elevated risk (1.23; 0.97–1.56), while those currently reporting clinical depression for the particular two-year questionnaire period had a significantly increased risk (1.41; 1.18–1.67; Table 3). Finally, women who used ADMs were at increased risks of stroke (1.30; 1.08–1.55; Supplemental Table 2). The risk was significant for SSRIs (1.39; 1.13–1.72), the largest use category, but not for other ADMs (1.14; 0.82–1.58).

DISCUSSION

The findings from this well-characterized cohort of more than 80,000 US women with a 6-year follow-up add to the growing evidence that depression is associated with stroke risk. Additionally, our data suggest that women currently reporting clinical depression have an increased stroke risk. Finally, ADM use (particularly SSRIs) was associated with an increased stroke risk.

Relatively few prospective studies have examined depression as a risk factor for stroke, even though depression has been consistently identified as a significant risk factor for cardiovascular disease.[3] Our prior publication in the same cohort found that depressive symptoms (measured by MHI-5) were associated with increased risk of fatal CHD, and ADM use was associated with significantly increased risk of sudden cardiac death.[13] Our current results suggest that depression is also a significant risk factor for stroke. The present study is consistent with two previous cohort studies.[5,21] Larson et al.[5] found a 2.7-fold increased risk of incident stroke associated with baseline depression status (determined by the Diagnostic Interview Schedule) among 1,703 adults during a 13-year follow-up. Similarly, Liebetrau et al.[21] found a positive association in 401 participants aged 85 years old during a 3-year follow-up. However, both studies were limited by small numbers of stroke outcomes. In contrast, Surtees et al.[9] observed no association between baseline major depression and stroke risk in 20,627 European participants aged 41–80 years during 8.5 years of follow-up. Nevertheless, a 2007 meta-analysis pooled results from both case-control and cohort studies and estimated that depressed mood was associated with an RR of 1.43 (95% CI, 1.17–1.75) for stroke.[22] Recently, O'Donnell and the INTERSTROKE investigators[23] found that self-reported depressive symptoms (for 2 or more weeks in the last year) were associated with a 35% increased odds of stroke in over 3000 cases and 3000 matched controls from 22 countries.

ADM use has recently attracted much attention due to its reported potential associations with increased risks of CHD[13] and stroke.[14,24] ADM use has been associated with weight gain,[25] increased inflammation,[26] abnormal bleeding,[27] and hypertension;[28] thus, it may increase risk of stroke. In our study, participants who used ADMs had an increased risk, with a 39% increased risk for total stroke with SSRIs, which is highly similar to the results from the Women's Health Initiative (1.45; 1.08–1.97).[14] A large case-control study also found a 20–40% increased risk of stroke associated with ADMs.[24] However, null associations also have been reported.[29–30] ADM use may be a marker of depression severity, rather than a causal mechanism. The results were not changed when we adjusted for depressive symptoms score in our cohort (data not shown); however, residual confounding may exist. Additionally, ADMs are also used for other conditions (e.g., anxiety disorders, insomnia, and neuropathic pain), and the indication for use was not available in our study. Additional studies of large sample sizes and with information on dose and duration are needed to investigate the effects of ADMs on cardiovascular outcomes including stroke.

Depression may be associated with an increased risk of stroke through a variety of mechanisms. Depression has known neuroendocrine (sympathetic nervous system activation, dysregulation of the hypothalamic-pituitary-adrenocortical axis, platelet aggregation dysfunction, etc.)[3] and immunological/inflammatory effects,[4] which could influence stroke risk. Late-life depression may represent a manifestation of sub-clinical vascular disease.[2] Depression may be associated with poor health behaviors (*i.e.*, smoking, physical inactivity, poor diet, lack of medication compliance),[31] obesity[32] and other major comorbidities,[33] which might increase stroke risk. However, whatever the mechanism, recognizing that depressed women may be at a higher risk of stroke merits additional research into preventive strategies in this group.

The present study has key strengths. Biennially repeated assessments of risk factors and disease outcomes were utilized, and time-dependent Cox models were utilized. Furthermore, three different sources of information (MHI-5, ADM use, and physician-diagnosed depression) were used to determine depression status. This study also has several limitations. First, the sample was a relatively homogeneous population of predominantly white registered nurse, which may limit generalizability to other populations. Potential selection bias is possible because we had to exclude a large proportion of women without detailed information on depression measures and participants with early onset stroke. In addition, information on physician-diagnosed depression and ADM use was self-reported, and the depressive symptoms questionnaire was not updated during the follow-up; therefore, the prevalence of depression might be underestimated. Nevertheless, the lifetime prevalence of depression at baseline in our study (22.3%) is consistent with that expected for women of this age group.[7,34] Moreover, we could not distinguish between chronic and recurrent courses of depression due to limited information. Lastly, we cannot infer causation, or fully exclude the possibility that the results could be explained by other unmeasured or unknown potentially related factors (e.g., anxiety, dispositional optimism and/or hostility).

CONCLUSIONS

These data provide additional evidence that depression is associated with a moderately increased risk of incident stroke. The association between current depression status, antidepressant medication use and risk of stroke deserves further scrutiny. Further research is necessary to determine whether the risk associated with depression can be reduced by other therapies or preventive strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are indebted to the participants in the Nurses' Health Study for their continuing outstanding support and colleagues working in the Study for their valuable help.

Funding/Support

The project was supported by NIH grants HL34594, CA87969, and HL088521. Dr. Sun was supported by a career development award K99HL098459 from the National Heart, Lung, and Blood Institute. Dr. Ascherio received a grant from the National Alliance for Research on Schizophrenia & Depression (Project ID: 5048070-01). The funding sources were not involved in the data collection, data analysis, manuscript writing and publication.

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Table 1

Baseline age-adjusted characteristics of the study population according to baseline depression status.*

Characteristics	Baseline depression status	
	Yes	No
No. (%)	17956 (22.3)	62618 (77.7)
Age, years	65.0	66.3
Body mass index, kg/m^2	27.4	26.6
Mental Health Index-5 score	68.7	83.7
Physical activity level, metabolic equivalent-hours/week	14.1	18.0
Dietary Approaches to Stop Hypertension diet score	23.6	24.0
Marital status, having spouse (%)	67.2	74.2
Current aspirin use (%)	44.6	45.6
Current multivitamin use (%)	68.6	67.1
Race, Whites (%)	98.1	97.4
Parental history of myocardial infarction (%)	20.1	18.4
Alcohol consumption, grams/d	4.6	5.2
Smoking status (%)		
Never	39.4	46.0
Past	49.9	45.4
Current	10.7	8.6
Menopausal status and hormone use (%)		
Premenopausal	2.0	2.0
Post, and never user	16.9	24.2
Post, and past user	30.4	26.4
Post, and current user	46.0	41.8
Unknown	4.7	5.6
History of diabetes (%)	12.3	8.3
History of hypertension (%)	55.4	47.7
History of hypercholesterolemia (%)	67.3	59.5
History of cancer (%)	18.2	15.4
History of heart disease (%)	16.4	10.2

* Data were expressed as mean or percentage. Depression was defined as currently reporting or having a history of any of the three conditions at baseline: Mental Health Index-5 score ≤52, physician-diagnosed depression, antidepressant medication use.

Table 2

Hazard ratio (95% confidence intervals) of incident stroke according to depression status: Nurses' Health Study (2000–2006).*

OUTCOME	NO DEPRESSION	DEPRESSION	Depression categories defined by different methods		
			MHI-5 ≤52 or diagnosed depression, no medication	MHI-5 ≤52 or diagnosed depression, with medication	MHI-5 >52 and no diagnosed depression, but with medication
Total Stroke					
Cases/Person-years	727/346820	306/111643	103/41265	129/45712	74/24667
Age-adjusted model	1.00	1.49 (1.30–1.70)	1.32 (1.07–1.62)	1.64 (1.35–1.97)	1.52 (1.20–1.93)
Multivariate model 1	1.00	1.37 (1.20–1.57)	1.24 (1.01–1.53)	1.48 (1.22–1.79)	1.40 (1.10–1.78)
Multivariate model 2	1.00	1.29 (1.13–1.48)	1.18 (0.96–1.45)	1.39 (1.15–1.69)	1.31 (1.03–1.67)
Hemorrhagic Stroke					
Cases/Person-years	90/347416	34/111883	14/41345	13/45813	7/24725
Age-adjusted model	1.00	1.31 (0.88–1.95)	1.43 (0.82–2.52)	1.29 (0.72–2.32)	1.15 (0.53–2.47)
Multivariate model 1	1.00	1.22 (0.82–1.82)	1.32 (0.75–2.33)	1.21 (0.67–2.18)	1.07 (0.49–2.32)
Multivariate model 2	1.00	1.20 (0.80–1.79)	1.31 (0.74–2.30)	1.18 (0.65–2.14)	1.04 (0.48–2.27)
Ischemic Stroke					
Cases/Person-years	395/347111	143/111780	46/41312	63/45771	34/24698
Age-adjusted model	1.00	1.28 (1.06–1.55)	1.08 (0.80–1.47)	1.48 (1.13–1.93)	1.29 (0.91–1.83)
Multivariate model 1	1.00	1.18 (0.97–1.43)	1.03 (0.76–1.40)	1.32 (1.01–1.73)	1.18 (0.83–1.67)
Multivariate model 2	1.00	1.11 (0.91–1.35)	0.98 (0.72–1.33)	1.24 (0.95–1.63)	1.09 (0.77–1.56)
Stroke of Unknown Type					
Cases/Person-years	242/347296	129/111814	43/41321	53/45784	33/24709
Age-adjusted model	1.00	1.90 (1.53–2.35)	1.68 (1.21–2.32)	2.03 (1.50–2.73)	2.03 (1.41–2.93)
Multivariate model 1	1.00	1.74 (1.40–2.17)	1.55 (1.12–2.15)	1.85 (1.36–2.50)	1.89 (1.31–2.73)
Multivariate model 2	1.00	1.63 (1.31–2.03)	1.46 (1.05–2.02)	1.72 (1.26–2.33)	1.75 (1.21–2.53)

Abbreviations: MHI, Mental Health Index.

*Depression defined as in Table 1.

Multivariate model 1: adjusted for age, marital status, parental history of myocardial infarction, ethnicity, physical activity level, body mass index, alcohol consumption, smoking status, menopausal status, postmenopausal hormone therapy, current aspirin use, current multivitamin use, Dietary Approaches to Stop Hypertension dietary score.

Multivariate model 2: multivariate model 1 plus history of hypertension, hypercholesterolemia, diabetes, cancer and heart diseases.

Table 3

Hazard ratio (95% confidence intervals) of incident stroke according to current clinical depression status: Nurses' Health Study (2000–2006).*

Outcome	Current clinical depression status		
	Never	Past	Current
Total Stroke			
Cases/Person-years	796/376719	77/28998	160/52746
Age-adjusted model	1.00	1.40 (1.11–1.77)	1.63 (1.38–1.94)
Multivariate model 1	1.00	1.31 (1.03–1.65)	1.50 (1.26–1.78)
Multivariate model 2	1.00	1.23 (0.97–1.56)	1.41 (1.18–1.67)
Hemorrhagic Stroke			
Cases/Person-years	98/377371	9/29058	17/52870
Age-adjusted model	1.00	1.32 (0.66–2.61)	1.39 (0.83–2.33)
Multivariate model 1	1.00	1.25 (0.63–2.48)	1.31 (0.77–2.20)
Multivariate model 2	1.00	1.22 (0.61–2.44)	1.28 (0.76–2.17)
Ischemic Stroke			
Cases/Person-years	428/377043	31/29031	79/52817
Age-adjusted model	1.00	1.05 (0.73–1.52)	1.51 (1.18–1.91)
Multivariate model 1	1.00	0.98 (0.68–1.41)	1.36 (1.06–1.73)
Multivariate model 2	1.00	0.92 (0.64–1.33)	1.28 (1.00–1.63)
Stroke of Unknown Type			
Cases/Person-years	270/377231	37/29043	64/52836
Age-adjusted model	1.00	1.98 (1.40–2.80)	1.93 (1.47–2.53)
Multivariate model 1	1.00	1.85 (1.31–2.62)	1.78 (1.35–2.35)
Multivariate model 2	1.00	1.72 (1.21–2.43)	1.66 (1.26–2.19)

*Clinical depression was defined as having physician-diagnosed depression, and/or antidepressant medication use. Multivariate models 1 and 2 are the same as shown in Table 2.