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Depression and Incident Stroke in Women

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

Methods—We followed-up 80 574 women aged 54 to 79 years in Nurses' Health Study without a history of stroke from 2000 to 2006. Depressive symptoms were assessed at multiple time points by a Mental Health Index score (1992, 1996, and 2000), and clinical significant depressive symptoms were defined as a score ≤52. Antidepressant medication 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 3 conditions.

Results—During 6 years of follow-up, 1033 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 (HR) of 1.29 (95% confidence interval [CI], 1.13–1.48) for total stroke. Women who used antidepressant medications were at increased risk for stroke, whether they also had a Mental Health Index score ≤52 or diagnosed depression (HR, 1.39; 95% CI, 1.15–1.69) or not (HR, 1.31; 95% CI, 1.03–1.67). Furthermore, for each cycle, participants who reported current depression had an increased risk of stroke (HR, 1.41; 95% CI, 1.18–1.67), whereas individuals who only had a history of depression were at nonsignificantly elevated risk (HR, 1.23; 95% CI, 0.97–1.56) compared with women who never reported a diagnosis of depression or antidepressant medication use.

Conclusions—Our results suggest that depression is associated with a moderately increased risk of subsequent stroke. **(*Stroke*. 2011;42:00-00.)**

Key Words: antidepressant medication ■ depression ■ depressive symptoms ■ longitudinal study ■ stroke

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 subclinical cerebrovascular disease,[2] indicating increased stroke risk. Depression may also influence stroke risk via neuroendocrine, immunologic, 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 an increased risk of sudden death and fatal coronary heart disease.[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 to 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.[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.

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We used the 2000 questionnaire cycle as the baseline because 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) and those with previous stroke (n=1651) 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 body mass index 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 5-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 rescaled 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 score ≤52) or absence (MHI-5 score >52) of significant depressive symptoms for each time it was queried.[18]

Participants were first asked to report regular use of ADM in 1996, whereas types of ADM 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, including fluoxetine, sertraline, paroxetine, citalopram, or other antidepressants, of which the tricyclic antidepressants 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, 1237 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 attributable to infection, trauma, or malignancy was excluded, as were 'silent strokes discovered only by radiological imaging. We categorized types of stroke as ischemic (embolic or thrombotic), hemorrhagic (subarachnoid or intracerebral), and unknown, based on imaging and clinical data.[19] CT or MRI 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. Dietary information was assessed using a semiquantitative food frequency questionnaire, and a Dietary Approaches to Stop Hypertension diet score was used to characterize their usual diet pattern. In addition, respondents were asked to report previously diagnosed medical conditions, eg, diabetes, hypertension, elevated cholesterol, heart disease (including myocardial infarction, angina, and coronary artery revascularization), and cancer.

Table 1. Baseline Age-Adjusted Characteristics of the Study Population According to Baseline Depression Status*

	Baseline Depression Status	
Characteristics	Yes	No
N (%)	17 956 (22.3)	62 618 (77.7)
Age, y	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, hr/wk	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, white (%)	98.1	97.4
Parental history of myocardial infarction (%)	20.1	18.4
Alcohol consumption, g/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
Postmenopausal, and never user	16.9	24.2
Postmenopausal, and past user	30.4	26.4
Postmenopausal, 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 3 conditions at baseline: Mental Health Index-5 score ≤52, physician-diagnosed depression, and antidepressant medication use.

Statistical Analysis

As described, the 3 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 3 conditions: physician-diagnosed depression, regular use of ADM, or MHI-5 score ≤52.[15] Participants with depression were further divided into 3 groups: MHI-5 score ≤52 or physician-diagnosed depression without ADM use; MHI-5 score ≤52 or physician-diagnosed depression with ADM use; and MHI-5 score >52 and no physician-diagnosed depression but with ADM use. This classification was

Table 2. Hazard Ratios and 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 Score ≤52 or Diagnosed Depression, No Medication	MHI-5 Score ≤52 or Diagnosed Depression, With Medication	MHI-5 Score >52 and No Diagnosed Depression, With Medication
Total stroke					
Cases/person-years	727/346 820	306/111 643	103/41 265	129/45 712	74/24 667
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	90/347 416	34/111 883	14/41 345	13/45 813	7/24 725
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	395/347 111	143/111 780	46/41 312	63/45 771	34/24 698
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	242/347 296	129/111 814	43/41 321	53/45 784	33/24 709
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)

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, and Dietary Approaches to Stop Hypertension dietary score.

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

MHI indicates Mental Health Index.

*Depression was defined as currently reporting or having a history of any of the 3 conditions at baseline: Mental Health Index-5 score ≤52, physician-diagnosed depression, and antidepressant medication use.

based on previous 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 with no depression. In a separate analysis, we classified women into never, past, and current depression according to their clinical depression status at each 2-year questionnaire period. Because the MHI-5 score was not updated during 2000 to 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 30, 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/nonwhites), menopausal status (premenopausal or postmenopausal), 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 per week), and quintile of Dietary Approaches to Stop Hypertension dietary score. Histories of hypertension, hypercholesterolemia, diabetes, cancer, and heart disease (yes/no) were further included in the final model. Data were analyzed with the Statistical Analysis Systems software package version 9.1 (SAS Institute).

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 body mass index, smoked cigarettes, and were 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, 1033 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 (HR, 1.29; 95% CI, 1.13–1.48). Results were not significant for either

Table 3. Hazard Ratio and 95% Confidence Intervals of Incident Stroke According to Current Clinical Depression Status: Nurses' Health Study (2000–2006)*

	Current Clinical Depression Status		
Outcome	Never	Past	Current
Total stroke			
Cases/person-years	796/376 719	77/28 998	160/52 746
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	98/377 371	9/29 058	17/52 870
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	428/377 043	31/29 031	79/52 817
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	270/377 231	37/29 043	64/52 836
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)

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, and Dietary Approaches to Stop Hypertension dietary score.

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

*Clinical depression was defined as having physician-diagnosed depression and/or antidepressant medication use.

hemorrhagic or ischemic stroke separately, possibly because of lower power. No significant interactions between depression, age, and major comorbidities with total stroke risk were found (Supplemental Table I, http://stroke.ahajournals.org).

Increased risk of stroke was seen among women who used ADM, with (HR, 1.39; 95% CI, 1.15–1.69) or without (HR, 1.31; 95% CI, 1.03–1.67) a MHI-5 score ≤52 or diagnosed depression, compared with nondepressed women (Table 2). Furthermore, compared with women without a history of clinical depression (having physician-diagnosed depression, regular ADM use, or both), women with a history of clinical depression had a nonsignificantly elevated risk (HR, 1.23; 95% CI, 0.97–1.56), whereas those currently reporting clinical depression for the particular 2-year questionnaire period had a significantly increased risk (HR, 1.41; 95% CI, 1.18–1.67; Table 3). Finally, women who used ADM were at increased risks for stroke (HR, 1.30; 95% CI, 1.08–1.55; Supplemental Table II). The risk was significant for selective serotonin reuptake inhibitors (HR, 1.39; 95% CI, 1.13–1.72), the largest use category, but not for other ADM (HR, 1.14; 95% CI, 0.82–1.58).

Discussion

The findings from this well-characterized cohort of >80 000 U.S. 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 are at increased risk for stroke. Finally, ADM use (particularly selective serotonin reuptake inhibitors) 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 previous publication in the same cohort found that depressive symptoms (measured by MHI-5) were associated with an increased risk of fatal coronary heart disease, and ADM use was associated with a 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 2 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 1703 adults during a 13-year follow-up. Similarly, Liebetrau et al[21] found a positive association in 401 participants aged 85 years 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 to 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 relative risk 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 weeks in the past year) were associated with a 35% increased odds of stroke in >3000 cases and 3000 matched controls from 22 countries.

ADM use has recently attracted much attention because of its reported potential associations with increased risks of coronary heart disease[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 ADM were at increased risk, with a 39% increased risk for total stroke with selective serotonin reuptake inhibitors, which is highly similar to the results from the Women's Health Initiative (HR, 1.45; 95% CI, 1.08–1.97).[14] A large case-control study also found a 20% to 40% increased risk of stroke associated with ADM.[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, ADM are also used for other conditions (eg, 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 ADM 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, and others)[3] and immunologic/inflammatory effects,[4] which could influence stroke risk. Late-life depression may represent a manifestation of subclinical vascular disease.[2] Depression may be associated with poor health behaviors (ie, 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 higher risk for 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, 3 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 nurses, 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 because of limited information. Last, we cannot infer causation or fully exclude the possibility that the results could be explained by other unmeasured or unknown potentially related factors (eg, 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.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Supplemental Table 1. Multivariate hazard ratio (95% confidence intervals) of stroke risk according to depression status in different subgroups in the Nurses' Health Study (2000-2006).*

Stratified factors	No. of stroke	No depression	Depression	P for interaction
Age Group, years				
<70	286	1.00	1.51 (1.17-1.93)	0.23
≥70	747	1.00	1.21 (1.02-1.42)	
History of Hypertension				
No	273	1.00	1.28 (0.96-1.69)	0.90
Yes	760	1.00	1.29 (1.10-1.51)	
History of Hypercholesterolemia				
No	274	1.00	1.36 (1.03-1.79)	0.93
Yes	759	1.00	1.27 (1.08-1.48)	
History of diabetes				
No	841	1.00	1.28 (1.09-1.49)	0.60
Yes	192	1.00	1.32 (0.98-1.79)	
History of heart diseases				
No	785	1.00	1.37 (1.17-1.61)	0.26
Yes	248	1.00	1.08 (0.83-1.42)	
History of cancer				
No	822	1.00	1.29 (1.10-1.50)	0.87

Yes	211	1.00	1.31 (0.97-1.76)	

*Adjusted for age (continuous), 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, history of hypertension, hypercholesterolemia, diabetes, cancer and heart diseases; but not for stratified factor itself.

Supplemental Table 2. Hazard ratio (95% confidence intervals) of incident stroke according to the types of antidepressant medication use: Nurses' Health Study (2000-2006).

Outcome	No ADM use	ADM use	Further categorized according to types of ADMs		
			SSRIs	Other ADMs (mainly TCAs)	SSRIs plus other ADMs
Total Stroke					
Cases/Person-years	893/409753	140/49303	97/31661	38/14972	5/2669
Age-adjusted model	1.00	1.50 (1.25-1.79)	1.60 (1.29-1.97)	1.33 (0.96-1.83)	1.22 (0.51-2.94)
Multivariate model 1	1.00	1.37 (1.14-1.64)	1.47 (1.19-1.81)	1.21 (0.87-1.68)	1.07 (0.44-2.58)
Multivariate model 2	1.00	1.30 (1.08-1.55)	1.39 (1.13-1.72)	1.14 (0.82-1.58)	0.99 (0.41-2.39)
Hemorrhagic Stroke					
Cases/Person-years	109/410479	15/49412	10/31736	5/15003	0/2674
Age-adjusted model	1.00	1.28 (0.75-2.21)	1.33 (0.70-2.55)	1.36 (0.56-3.35)	-
Multivariate model 1	1.00	1.21 (0.70-2.09)	1.27 (0.66-2.45)	1.26 (0.51-3.10)	-
Multivariate model 2	1.00	1.19 (0.69-2.06)	1.25 (0.65-2.41)	1.24 (0.50-3.05)	-
Ischemic Stroke					
Cases/Person-years	468/410117	70/49366	45/31707	21/14990	4/2669
Age-adjusted model	1.00	1.43 (1.12-1.84)	1.42 (1.05-1.93)	1.41 (0.91-2.18)	1.84 (0.69-4.93)
Multivariate model 1	1.00	1.29 (1.00-1.67)	1.29 (0.95-1.75)	1.26 (0.81-1.96)	1.62 (0.60-4.33)
Multivariate model 2	1.00	1.23 (0.95-1.58)	1.23 (0.90-1.67)	1.19 (0.76-1.84)	1.50 (0.56-4.03)
Stroke of Unknown Type					
Cases/Person-years	316/410320	55/49382	42/31710	12/14999	1/2673

Age-adjusted model	1.00	1.66 (1.25-2.22)	1.95 (1.41-2.69)	1.19 (0.67-2.12)	-
Multivariate model 1	1.00	1.53 (1.14-2.04)	1.79 (1.29-2.47)	1.10 (0.62-1.97)	-
Multivariate model 2	1.00	1.43 (1.07-1.92)	1.68 (1.21-2.33)	1.03 (0.58-1.83)	-

Abbreviations: ADM, antidepressant medication; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

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.