Prospective Study of Anxiety and Incident Stroke

Maya J. Lambiase, PhD; Laura D. Kubzansky, PhD; Rebecca C. Thurston, PhD

Background and Purpose—Higher levels of anxiety are associated with increased risk for coronary heart disease. However, few studies have investigated whether anxiety is associated with stroke risk. The purpose of this study was to examine the association between anxiety symptoms and incident stroke in a nationally representative longitudinal study of the US population.

Methods—Participants (n=6019) in the First National Health and Nutrition Examination Survey were assessed at baseline and followed for 16.29±4.75 years. Multivariate Cox proportional hazards regression models were used to estimate hazard ratios and 95% confidence intervals of incident stroke associated with a 1 SD increase in anxiety symptoms. Models were adjusted for standard cardiovascular risk factors and additionally for depression.

Results—A total of 419 incident stroke cases were identified from hospital/nursing home discharge reports and death certificates. Reporting more anxiety symptoms at baseline was associated with increased risk of incident stroke after adjusting for standard biological and behavioral cardiovascular risk factors (hazard ratio, 1.14; 95% confidence interval, 1.03–1.25). Findings persisted when additionally controlling for depression. Exploratory analyses considering the role of potential confounding versus pathway variables suggested that behavioral factors may be a key pathway linking anxiety to stroke risk.

Conclusions—Higher anxiety symptom levels were associated prospectively with increased risk for incident stroke independent of other risk factors, including depression. Anxiety is a modifiable experience that is highly prevalent among the general population. Its assessment and treatment may contribute to developing more effective preventive and intervention strategies for improving overall cardiovascular health. (Stroke. 2014;45:438-443.)

Key Words: anxiety ■ behavior ■ cerebrovascular disorders ■ prospective studies ■ stroke

Stroke is among the leading causes of death and long-term disability in the United States. Few studies have examined whether psychosocial factors are associated with an increased risk for stroke. Of the studies that have considered psychosocial factors and stroke, most have focused on depression or psychological stress/distress; few have considered anxiety. Understanding the association between anxiety and stroke is important given that anxiety symptoms are common and anxiety disorders are one of the most prevalent psychiatric disorders among the general population. In addition, anxiety is associated with established stroke risk factors, such as cigarette smoking, alcohol abuse, and physical inactivity.

To date, only 1 study has explicitly considered anxiety in relation to incident stroke. This study considered generalized anxiety disorder and failed to find an association with stroke risk, although the low number of individuals meeting the diagnostic criteria for generalized anxiety disorder may have limited these analyses. Another study considered the association between anxiety and stroke primarily in relation to the effects of depression and reported that only depression was prospectively associated with incident stroke. However, this study did not do a comprehensive analysis of the unique contributions of anxiety to stroke risk. Thus, a more systematic consideration of whether anxiety is associated with incident stroke is needed to elucidate any relation between anxiety and stroke independently from depression.

The primary aim of the present study was to examine the association between anxiety symptoms and risk of incident stroke using data from the First National Health and Nutrition Examination Survey and Follow-up Studies, a nationally representative longitudinal study of the US population. We considered anxiety symptoms, given prior work suggesting dose–response relations between anxiety and coronary heart disease at subclinical levels of anxiety. We hypothesized that individuals reporting higher anxiety symptoms would have increased risk for incident stroke, independent of other known demographic, biological, and behavioral risk factors for stroke, including depression. In exploratory fashion, we examined potential confounders and pathways (ie, health behaviors) through which anxiety may influence stroke risk, as well as whether associations between anxiety and stroke varied by sex or race.
Materials and Methods
Sample and Study Design
The present study used data from the First National Health and Nutrition Examination Survey (NHANES I) and Follow-up Studies (NHEFS). NHANES I (1971–1975) collected data on a representative sample of the US civilian population, aged 1 to 74 years. The study included oversampling of women of childbearing age, persons living in poverty areas, and elderly persons. The baseline assessment, conducted on the full cohort, included an in-person structured interview, physical examination, and blood draw. In addition, a representative subsample of noninstitutionalized adults aged 25 to 74 years (n=6913) underwent a more comprehensive medical examination, provided supplemental medical history information, and completed selected psychological measures.

Follow-up studies were conducted in 1982, 1987, and 1992 on the entire surviving NHANES I cohort aged 25 to 74 years at baseline and in 1986 on participants aged 55 to 74 years at baseline. Follow-up assessments included an interview with the respondent or proxy (for decedents), tracking of participants via the National Death Registry and acquisition of death certificates, and obtainment of overnight hospital/nursing home stay records. Details of the NHEFS study design and sampling methods are published elsewhere.15–17

The analyses presented here included members of the detailed subsample (n=6913) who were traced at ≥1 follow-ups. Participants were excluded from analysis if they reported a history of stroke (n=118) or coronary heart disease (n=347) at baseline. In addition, participants with missing or unknown values for ≥1 study variables (n=429) were also excluded. The final sample included 6019 participants (men=2746; women=3273).

Anxiety Symptoms
Anxiety symptoms were measured using the anxious/tense subscale of the General Well-Being Schedule (GWB-A), a measure of psychological functioning administered at baseline to all members of the detailed subsample by trained interviewers. The GWB-A asks participants to rate the severity of their symptoms during the past month on the following items: (1) Have you been anxious, worried, or upset? (0=extremely to 5=not at all); (2) Have you been under or felt you were under any strain, stress, or pressure? (0=almost more than I could stand to 5=not at all); (3) Have you been bothered by nervousness or your nerves? (0=extremely to 5=not at all); and (4) How relaxed or tense have you been? (0=very tense to 10=very relaxed). GWB-A scores were reverse scored so higher values reflect higher anxious symptoms. Because the last item used a different response scale, we considered whether it unduly influenced the overall score; as there was no evidence of undue influence, we summed across items for a total scale score. Continuous GWB-A scores were used in main analyses but were also tertiled to assess possible discontinuity in effects. The GWB and its subscales have been demonstrated to be valid and reliable.14 The GWB-A showed strong internal consistency in the present investigation (α=0.85).

Incident Stroke
Stroke events were identified through hospital/nursing home discharge reports and death certificates. At each follow-up, participants reported overnight hospital/nursing home stays since the last study contact. Discharge reports were obtained for all overnight stays during the study period. Participants were also tracked via the National Death Index and death certificates were obtained for decedents. A stroke event was defined as an International Classification of Diseases, Ninth Revision (ICD-9) codes 431 to 434.9, 436, and 437 to 437.1 listed on a hospital/nursing home discharge report or as a cause of death on the death certificate. Hospital admission date or the date of death was used as the event date. For participants with >1 event, the earliest event was used.

Covariates
Age and race/ethnicity (white, nonwhite) were obtained from the updated/corrected values included in the 1982 interview. All other covariates were obtained from the baseline NHANES I examination. Sex, education (less than high school, high school, some college, and college degree), marital status (married, not married), blood pressure (BP) medication use during past 6 months, doctor-diagnosed history of diabetes mellitus, recreational physical activity (low, moderate, and high), alcohol use (none, ≤2 drinks per week, and >2 drinks per week), and cigarette smoking (current, never/former) were obtained via self-report. Seated BP height (m), and weight (kg) were measured and body mass index was calculated (kg/m²). Total serum cholesterol was obtained from the blood draw. We also considered reported use of medication for lack of pep (eg, psychotropic medication) as a covariate, but because it was not associated with stroke and did not affect any results, it was not included in the final analyses.

Depressive symptoms at baseline were considered in several ways. Depressive symptoms were assessed with the depressed mood subscale of the GWB (GWB-D) administered to the entire analytic sample (α=0.63) and with the Center for Epidemiological Studies of Depression scale (CESD) administered to a subsample (n=2644; α=0.95). Anxiety was highly correlated with the GWB-D (r=0.73) and less correlated with the CESD (r=0.55). To address concerns about multicollinearity between GWB-D and GWB-A scores, a residualized depression variable was derived from the linear regression model fitting GWB-D to GWB-A scores, which reflects the portion of depression that is not associated with anxiety. To comprehensively address the issue of depression and remaining multicollinearity between GWB subscales, we also considered CESD scores as the CESD was more distinct from our measure of anxiety. We conducted multiple imputation to impute missing CESD values. We considered CESD scores as a continuous variable and also as a dichotomy according to the cut point for clinical depression (CESD score ≥16 versus <16).

Analytic Plan
Differences in baseline characteristics and stroke events across terciles of anxiety symptoms were examined via ANOVA and logistic regression. Multivariate Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of incident stroke associated with a 1 SD increase in anxiety symptoms. Time from baseline interview to stroke event date, nonstroke death date, or last date known alive was used as the follow-up time.

We first examined the association between anxiety symptoms and incident stroke adjusting for demographic factors (model 1: age, sex, race/ethnicity, education, and marital status). Subsequently, cardiovascular (model 2: model 1+systolic BP, diastolic BP, BP medication, diabetes mellitus, and body mass index) and behavioral (model 3: model 2+alcohol use, physical activity, and smoking) risk factors were added as covariates. Models were additionally adjusted for depressive symptoms. Interactions between sex and race with anxiety were examined via cross-product terms in fully adjusted models. Finally, to explore the impact of potential confounders (ie, demographic, cardiovascular) and possible pathways (ie, behaviors), changes in the anxiety HR from the age/sex-adjusted model were calculated separately for blocks of these variables via the formula 1−log(HRage/sexadjusted)/log(HRage/sexadjusted). Analyses were conducted using SAS, version 9.3 software. All tests were 2-sided with an α level of 0.05.

Results
A total of 419 incident stroke cases (men=221, women=198) were identified during a mean follow-up period of 16.2±4.7 years. Baseline characteristics are presented in Table 1. Higher anxiety symptoms levels were associated with higher risk of stroke. Findings suggested a dose–response relation, with every 1 SD increase in anxiety associated with a 17% increase in stroke risk when adjusting for demographic factors (Table 2). Associations of anxiety with stroke remained significant in models adjusting for cardiovascular and behavioral risk factors. In addition, controlling for depression either via...
residualized GWB-D (HR, 1.20; 95% CI, 1.06–1.34), continuous CESD (HR, 1.14; 95% CI, 1.04–1.27), or dichotomous CESD (HR, 1.13; 95% CI, 1.02–1.24) scores did not change results. Similar results were observed for anxiety considered in tertiles controlling for age and sex (high versus low anxiety: HR, 1.43; 95% CI, 1.14–1.80; Figure) and when adjusting for other cardiovascular risk factors (high versus low, model 3: HR, 1.33; 95% CI, 1.05–1.69) and residualized GWB-D scores (high versus low: HR, 1.38; 95% CI, 1.03–1.83). Controlling for CESD scores did not change these results (data not shown). Neither interactions between sex and anxiety nor between race and anxiety were significant (Ps>0.37). The percent reduction in the HR corresponding to the anxiety–stroke association accounted for by blocks of demographic, cardiovascular, and behavioral risk factors was 8.3%, 10.3%, and 18.3%, respectively, indicating that the behavioral factors had the most pronounced role in relations between anxiety and stroke. Of these behaviors, smoking and physical activity were the most influential (data not shown). However, we note that relations between anxiety and stroke remained after adjusting for these risk factors, indicating that these factors did not fully explain associations between anxiety and stroke.

We conducted several additional analyses. First, to consider whether individuals with higher anxiety may have poorer baseline health, which could account for the observed relationship between anxiety symptoms and incident stroke, we repeated all analyses excluding the first 3 years of follow-up, and results were unchanged. Second, we examined the interaction between race and anxiety limiting the sample to white and black participants (given the few individuals of other racial/ethnic groups in the sample) and did not observe a significant interaction (P=0.27).

Discussion

In the present study, higher anxiety symptoms were associated with increased risk for stroke in a representative sample of the

Table 1. Participant Characteristics by Tertiles of Anxiety Symptoms

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Low (n=2296)</th>
<th>Medium (n=1770)</th>
<th>High (n=1953)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y‡</td>
<td>50.44 (14.26)</td>
<td>46.66 (13.82)</td>
<td>46.08 (13.30)</td>
</tr>
<tr>
<td>Sex, n (%)‡</td>
<td>1070 (46.60)</td>
<td>968 (54.68)</td>
<td>1235 (63.24)</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1226 (53.40)</td>
<td>802 (45.32)</td>
<td>718 (36.76)</td>
</tr>
<tr>
<td>Race/ethnicity, n (%)*</td>
<td>310 (13.50)</td>
<td>198 (11.18)</td>
<td>280 (14.34)</td>
</tr>
<tr>
<td>Nonwhite</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1986 (86.50)</td>
<td>1572 (88.82)</td>
<td>1673 (85.66)</td>
</tr>
<tr>
<td>Education, n (%)</td>
<td>Less than high school</td>
<td>937 (40.82)</td>
<td>640 (36.16)</td>
</tr>
<tr>
<td>High school</td>
<td>797 (34.72)</td>
<td>636 (35.94)</td>
<td>671 (34.36)</td>
</tr>
<tr>
<td>Some college</td>
<td>433 (18.86)</td>
<td>374 (21.12)</td>
<td>380 (19.46)</td>
</tr>
<tr>
<td>College degree</td>
<td>129 (5.62)</td>
<td>120 (6.78)</td>
<td>128 (6.56)</td>
</tr>
<tr>
<td>Married, n (%)</td>
<td>476 (20.74)</td>
<td>365 (20.62)</td>
<td>450 (23.04)</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1820 (79.26)</td>
<td>1405 (79.38)</td>
<td>1503 (76.96)</td>
</tr>
<tr>
<td>Systolic BP, mean (SD), mmHg‡</td>
<td>135.68 (22.74)</td>
<td>132.36 (21.58)</td>
<td>130.7 (22.32)</td>
</tr>
<tr>
<td>Diastolic BP, mean (SD), mmHg</td>
<td>84.92 (12.16)</td>
<td>84.16 (12.30)</td>
<td>84.24 (13.10)</td>
</tr>
<tr>
<td>Cholesterol, mean (SD), mg/dL</td>
<td>223.22 (47.76)</td>
<td>221.74 (46.00)</td>
<td>220.18 (45.94)</td>
</tr>
<tr>
<td>BP medication, n (%)†</td>
<td>115 (5.00)</td>
<td>100 (5.64)</td>
<td>143 (7.32)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)*</td>
<td>76 (3.32)</td>
<td>68 (3.84)</td>
<td>97 (4.96)</td>
</tr>
<tr>
<td>BMI, mean (SD), kg/m²</td>
<td>25.60 (4.56)</td>
<td>25.54 (4.88)</td>
<td>25.62 (5.32)</td>
</tr>
<tr>
<td>Physical activity, n (%)‡</td>
<td>Low</td>
<td>786 (34.24)</td>
<td>641 (36.22)</td>
</tr>
<tr>
<td>Moderate</td>
<td>993 (43.24)</td>
<td>791 (44.68)</td>
<td>711 (36.40)</td>
</tr>
<tr>
<td>High</td>
<td>517 (22.52)</td>
<td>338 (19.10)</td>
<td>303 (15.52)</td>
</tr>
<tr>
<td>Current smoker, n (%)‡</td>
<td>787 (34.28)</td>
<td>647 (36.56)</td>
<td>818 (41.88)</td>
</tr>
<tr>
<td>Alcohol use, n (%)*</td>
<td>None</td>
<td>571 (24.86)</td>
<td>411 (23.22)</td>
</tr>
<tr>
<td>≤2 drinks/d</td>
<td>1572 (68.46)</td>
<td>1249 (70.56)</td>
<td>1342 (68.72)</td>
</tr>
<tr>
<td>&gt;2 drinks/d</td>
<td>153 (6.66)</td>
<td>110 (6.22)</td>
<td>125 (6.40)</td>
</tr>
<tr>
<td>Incident stroke cases, n (%)</td>
<td>173 (7.54)</td>
<td>111 (6.28)</td>
<td>135 (6.92)</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; and BP, blood pressure. Significant difference between tertiles: *P<0.05; †P<0.01; and ‡P<0.001.
US population. In fact, results indicated a dose–response relation between anxiety and stroke. Moreover, the observed association between anxiety and stroke was independent of standard cardiovascular risk factors and of depressive symptoms. Exploratory analyses suggest that behavioral factors, particularly smoking and physical activity, may be important pathways to consider.

The scarcity of studies examining anxiety as a risk factor for stroke is surprising in light of accumulating evidence that...
anxiety is associated with increased risk for coronary heart disease.\textsuperscript{20,21} Although our findings differ from Surtees et al.,\textsuperscript{22} who reported no association between generalized anxiety disorder and incident stroke, we considered the spectrum of anxiety symptoms rather than focusing only on 1 anxiety disorder per se. Moreover, our results may differ from Jonas et al.,\textsuperscript{23} who reported no association between anxiety and stroke when both anxiety and depression were considered in the same model, for the following reasons: (1) we considered the unique contribution of anxiety without depression in the model; (2) we explicitly addressed the issue of multicollinearity between anxiety and depression, and did so in several ways; and (3) we considered anxiety symptoms as a continuous variable, allowing for greater power. Notably, anxiety symptoms remained significantly associated with incident stroke in all models which points to the importance of considering anxiety in its own right in relation to stroke.

Poor health behaviors may be a pathway linking anxiety with stroke risk. In the present study, behaviors (particularly smoking and physical activity) had the most sizable attenuating effect on the relationship between anxiety and incident stroke. However, because these behaviors did not account fully for the association between anxiety and incident stroke, direct biological effects of anxiety should also be considered. Chronic anxiety could lead to excess activation of the hypothalamic-pituitary-adrenal axis and sympathetic nervous system that may increase the risk for stroke.\textsuperscript{24} Anxiety could also contribute to stroke or other cardiovascular disease by lowering the threshold for arrhythmia or by reducing heart rate variability.\textsuperscript{25}

We controlled for several demographic, cardiovascular, and behavioral risk factors in our analyses. However, residual confounding may have occurred. For example, we controlled for education as an indicator of socioeconomic status, but this may not fully reflect the subject’s financial strain or perceived social status that may be important for stroke risk. It is worth nothing, however, that other work has identified anxiety as strongly influenced by socioeconomic and other social factors, and as possibly mediating effects of the social environment on health.\textsuperscript{26} Personality traits (e.g., neuroticism) not measured here may also be relevant to consider in these associations. We would conceptualize personality, a generally stable trait over the lifespan, as giving rise to more proximal psychiatric symptomatology such as anxiety. Thus, it is possible that anxiety acts as a mediator of the association between neuroticism and stroke. Although we could not address this issue in the present study (because of the lack of assessment of personality traits), this question merits future study. Moreover, given the limited number of studies in this area additional work is needed to elucidate the precise mechanisms whereby anxiety may be associated with an increased risk for stroke, including the role of other forms of distress.

The study had several limitations. Baseline history of stroke and coronary heart disease were self-reported. Possible bias may have occurred because of excluding individuals lost to follow-up or with missing data. We could not formally test mediation because of insufficiencies in temporal ordering of data collection. Stroke cases were identified based on discharge reports/death certificates and were not confirmed by imaging or a neurologist. In addition, we may not have accurately captured silent strokes (resulting in an underestimate of cases in the population), although such misclassification would likely bias results toward the null. Stroke is a heterogeneous condition and future work should consider the impact of anxiety on specific types of stroke. Finally, although the GWB-A subscale is correlated with other measures of anxiety,\textsuperscript{18} it has not been well validated against clinical diagnosis of anxiety disorders. However, given the diversity in anxiety disorders, and the continuum on which anxiety symptoms occur in the general population, anxiety symptoms are likely most relevant when considering cardiovascular risk.

The study had notable strengths. We considered anxiety symptoms as a risk factor for incident stroke with adjustments for numerous previously identified stroke risk factors. Furthermore, we carefully considered the role of depression in our analyses. Incident stroke events were confirmed by medical records/death certificates, which avoid self-report or retrospective reporting bias. We also considered subgroups defined by sex and race, with findings similar across groups. Finally, we examined the relationship between anxiety and incident stroke in a nationally representative sample of the US population followed up for 22 years.

In conclusion, higher anxiety symptoms were associated prospectively with an increased risk for incident stroke in a representative sample of the US population. Associations were independent of other cardiovascular risk factors including depression. Given anxiety is highly prevalent in the population,\textsuperscript{9} our findings suggest that assessing anxiety symptoms may contribute to developing more effective preventive and intervention strategies for reducing stroke risk.

Sources of Funding
This study was funded by the National Heart, Lung, and Blood Institute (T32 HL07560) and the National Institute of Mental Health (MH092707-01) of the National Institutes of Health.

Disclosures
None.

References
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Stroke. 2014;45:438-443; originally published online December 19, 2013;
doi: 10.1161/STRKEAHA.113.003741
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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