

## Depressive Symptoms and Risk of Stroke The Framingham Study

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**Background and Purpose**—Emerging evidence raises the possibility of an association between depression and stroke risk. This study sought to examine whether depressive symptoms are associated with an increased risk of cerebrovascular events in a community-based sample.

**Methods**—A prospective study was conducted on 4120 Framingham Heart Study participants aged 29 to 100 years with up to 8 years of follow-up. The Center for Epidemiologic Studies Depression Scale was used to measure depressive symptoms. Incident stroke and transient ischemic attack (TIA) events were assessed by uniform diagnostic criteria. The association between depressive symptoms and risk of stroke/TIA was analyzed with Cox proportional-hazards models, after adjusting for traditional stroke risk factors.

**Results**—In participants <65 years, the risk of developing stroke/TIA was 4.21 times greater ( $P<0.001$ ) in those with symptoms of depression. After adjusting for components of the Framingham Stroke Risk Profile (hazard ratio=3.43, 95% CI=1.60 to 7.36,  $P=0.002$ ) and education (hazard ratio=4.89, 95% CI=2.19 to 10.95), similar results were obtained. In subjects aged 65 and older, depressive symptoms were not associated with an increased risk of stroke/TIA. Taking antidepressant medications did not alter the risk associated with depressive symptoms.

**Conclusions**—In this community-based study, depressive symptoms were an independent risk factor for incident stroke/TIA in individuals <65 years. These data suggest that identification of depressive symptoms at younger ages may have an impact on the primary prevention of stroke. (*Stroke*. 2007;38:16-21.)

**Key Words:** depressive symptoms ■ stroke ■ transient ischemic attack ■ risk factors

Depression after stroke has long been recognized as a common condition with many negative effects.<sup>1-5</sup> Whether depression is an antecedent risk factor for stroke has not been extensively studied, and evidence of this association remains inconclusive.<sup>6,7</sup> Because depression has been associated with increased rates of cardiovascular disease<sup>8,9</sup> and mortality,<sup>8,10,11</sup> it raises the possibility that a similar relation may exist for cerebrovascular disease.

The relation between age, depression, and stroke has not been fully explored. However, substantial evidence has shown that depression is a common condition in the elderly<sup>12</sup> and that the incidence rates of stroke increase with age.<sup>13</sup> Because the incidence of both depression and stroke increases with age, we examined the association between antecedent depression symptoms and risk of stroke according to age.

The objective of the present study was to determine whether the presence of symptoms indicative of depression at baseline examination was associated with an increased risk of stroke/transient ischemic attack (TIA) in elderly and nonelderly participants.

## Subjects and Methods

### Study Sample

The Framingham Heart Study, an epidemiological study of cardiovascular disease including stroke, was established in 1948 as a longitudinal, community-based, population study. During 1948 to 1950, 5209 men and women (55% women), aged 28 to 62 years and representing a two-thirds sample of the town of Framingham, Mass, were enrolled in the study. Since the study's inception, surviving original cohort subjects have undergone regular biennial examinations. Beginning in 1971 to 1974, 5124 children of the original cohort and spouses (offspring cohort) enrolled in the study. Details of the study design, implementation, and criteria for diagnosis have been previously published.<sup>14,15</sup>

The sample for this study consisted of 918 attendees of the original cohort cycle 22 (1990 to 1992; mean age, 80 years) and 3202 attendees of the offspring cohort cycle 6 (1996 to 1998, mean age, 59 years) who were free of stroke at these examinations, had complete assessment of depressive symptoms (defined as at least 16+ items), and were available for follow-up of incident stroke/TIA. The Boston Medical Center institutional review board approved the study, and all participants provided informed consent.

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## Depressive Symptoms

Depressive symptoms were evaluated with the Center for Epidemiological Studies Depression scale (CES-D).<sup>16</sup> It was administered by a technician at cohort examination 22 (1990) and offspring examination 6 (1996) and is a 20-item scale documenting 4 factors: depressive affect, somatic complaints, positive affect, and interpersonal relations, with proven internal consistency, test-retest reliability, and construct validity.<sup>16,17</sup> Scores on the CES-D range from 0 to 60, with higher scores indicating more symptoms of depression. According to CES-D guidelines,<sup>16</sup> scores of 0 to 15 were indicative of nondepression, and scores of 16 to 60 were indicative of depressive symptomatology.

## Stroke Case Ascertainment

Because the primary outcome of our study was the occurrence of an initial cerebrovascular event, we included TIAs along with completed strokes. Stroke was defined as a focal neurological deficit of sudden or rapid onset that persisted for >24 hours, and TIA, as a focal neurological deficit that fully resolved in <24 hours. Continuous surveillance for cerebrovascular events included daily hospital monitoring, tracking of medical encounters, and examination of those with possible stroke symptoms. All events were adjudicated by a panel of at least 2 neurologists, and verification of stroke was available for 90% of stroke cases by imaging. Stroke occurrence and characteristics, including subtypes, were determined at the end of the acute phase of the stroke according to uniform criteria<sup>18</sup> and a standardized protocol.<sup>19</sup>

## Statistical Analyses

Data from the original and offspring cohorts were pooled, and each subject contributed up to 8 years of follow-up from the baseline examination to the occurrence of stroke/TIA or censoring (at death, last examination, loss to follow-up, or 8 years). We considered 2 forms of the CES-D. First, we classified those with CES-D scores of at least 16 as indicative of depressive symptoms and those with a score 15 and below as not indicative of depressive symptoms. To substantiate increments of symptoms, we then used the continuous CES-D score to assess the risk of incident stroke/TIA associated with a 10-unit increase in CES-D. We used Cox proportional-hazards regression modeling to compare individuals with scores indicative of depressive symptoms with those with scores that were not indicative of depressive symptoms with respect to incident stroke/TIA and to estimate the hazard ratio (HR) associated with a 10-unit increase in CES-D score. Analyses were adjusted for age and sex and then additionally for components of the Framingham Stroke Risk Profile

(FSRP), including blood pressure, diabetes, atrial fibrillation, cardiovascular disease, left ventricular hypertrophy on the ECG, and current smoking.<sup>20</sup> Because the CES-D per se does not diagnose clinical depression and the use of antidepressant medication may have an effect on symptoms, we performed a supplementary analysis wherein the definition of depression was expanded to include those taking antidepressants, even if their current depressive symptoms were below the cutoff point. Treatment for depression with antidepressants was documented at baseline examination. Antidepressants included treatment with selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, tricyclic agents, modified cyclics, and other miscellaneous medications classified as antidepressants.

Anticipating that there might be an interaction between age and the effect of depressive symptoms on stroke, we performed a test of interaction. The results of the test confirmed a significant interaction; thus, all subsequent analyses were performed separately by age groups (<65 years and 65+ years). All statistical analyses were performed with SAS software (version 8.1).<sup>21</sup>

## Results

In this sample of 4120, the mean age was  $63.9 \pm 12.3$  years ( $n=2221$  <65 years,  $n=1899$   $\geq 65$  years), 56% were women, and the majority were married. During the 8-year follow-up period, there were 228 cerebrovascular events, corresponding to 144 incident stroke cases (22 hemorrhagic, 122 ischemic) and 84 TIAs occurring in 102 men and 126 women. For the total sample at baseline, the mean CES-D score was  $6.0 \pm 7.5$ , with 439 participants (10.7%) having a score of 16 or greater, indicative of depressive symptoms. Among those who had cerebrovascular events, 8.2% of ischemic strokes, 11.9% of TIAs, and 22.7% of hemorrhagic strokes had scores indicative of depressive symptoms at baseline examination. The distribution of characteristics within our sample at baseline, according to age and the presence or absence of depressive symptoms, are presented in Table 1. Among participants <65 years, those with scores indicative of depressive symptoms were more likely to be women, to be current smokers, to consume less alcohol, to be unmarried, and to be taking antidepressant medications. Among participants 65 years and older, those with scores indicative of depressive symptoms were more likely to be women; to have cardiovascular

**TABLE 1. Baseline Characteristics Classified by Age and CES-D Score**

	Age <65 y, n=2221		Age $\geq 65$ y, n=1899	
	CES-D <16, n=1984	CES-D $\geq 16$ , n=237	CES-D <16, n=1697	CES-D $\geq 16$ , n=202
Men, %	48.4	31.2*	42.7	25.3*
Systolic blood pressure, mean $\pm$ SD, mm Hg	124.6 $\pm$ 17.0	123.2 $\pm$ 18.0	140.7 $\pm$ 19.9	139.2 $\pm$ 21.6
Hypertension, %	32.1	30.8	66.8	65.7
Diabetes, %	6.7	9.0	14.2	18.3
Current smoker, %	16.8	25.7*	8.1	12.4*
History of cardiovascular disease, %	5.8	8.0	22.5	33.2*
Atrial fibrillation, %	1.5	0.8	7.5	13.4*
Left ventricular hypertrophy on ECG, %	0.5	0.0	2.1	4.2
Any alcohol use, %	66.3	51.7*	51.9	32.5*
Not married, %	21.0	39.2*	36.4	55.0*
Nursing home resident, %	0.0	0.0	1.5	4.3*
Less than high school graduate, %	3.4	4.7	20.8	37.0*
Taking antidepressant medication, %	5.2	22.8*	3.8	13.4*

\*Significant difference between CES-D <16 and CES-D  $\geq 16$  within that age group at  $\alpha=0.05$ .

**TABLE 2. Results of Multivariable Cox Proportional-Hazards Regression Examining the Association Between Depressive Symptoms and the Risk of Stroke/TIA Among Subjects <65 Years Old**

	Adjusted for Age and Sex				Adjusted for Stroke Risk Factors*			
	Cases/N	HR	95% CI	P	Cases/N	HR	95% CI	P
CES-D $\geq 16$	37/2221	4.21	2.00–8.86	<0.001	37/2190	3.43	1.60–7.36	0.002
CES-D $\geq 16$ or taking antidepressant medication	37/2221	4.23	2.11–8.51	<0.001	37/2190	3.59	1.76–7.33	<0.001
Continuous CES-D†	37/2221	1.93	1.44–2.60	<0.001	37/2190	1.77	1.31–2.41	<0.001

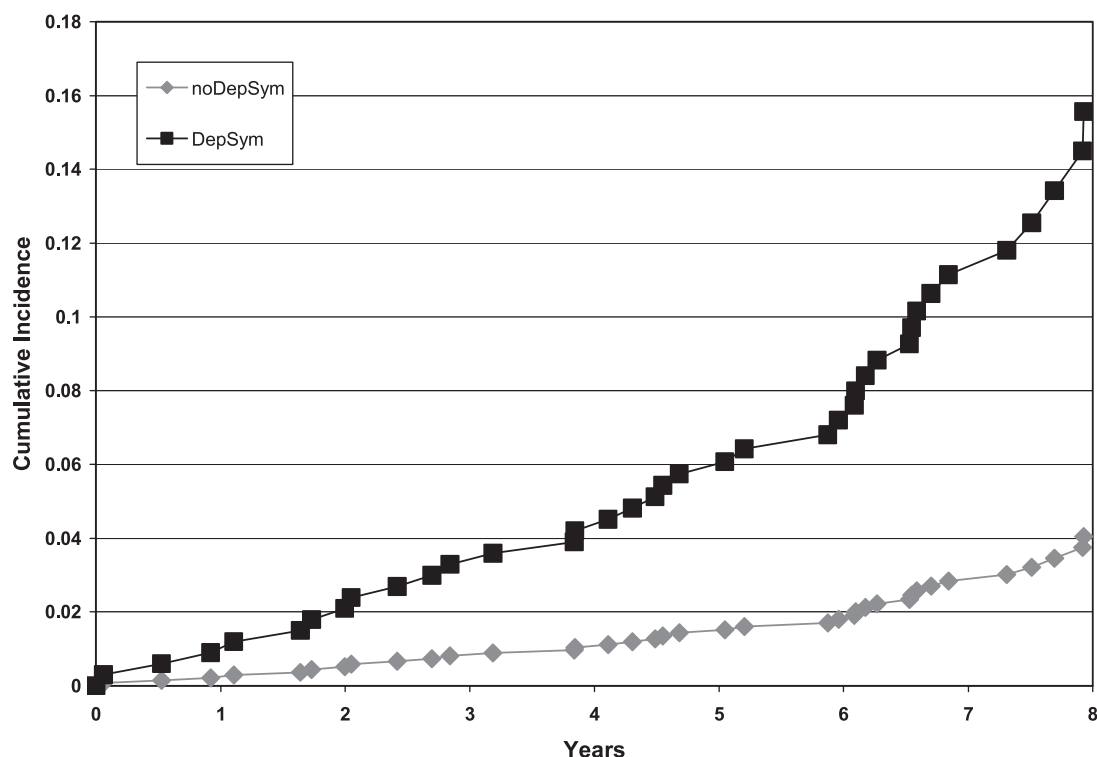
\*Age, sex, blood pressure, diabetes, atrial fibrillation, history of cardiovascular disease, left ventricular hypertrophy on the ECG, and current smoking; †with 10-point increments on the CES-D.

disease, atrial fibrillation, and left ventricular hypertrophy on the ECG; to consume less alcohol; to be unmarried; to be nursing home residents; to have lower education; and to be taking antidepressant medications.

We compared the risk of stroke/TIA in those with and without depressive symptoms separately for participants <65 years and 65+ years. Among participants <65 years, those who had a CES-D score indicative of depressive symptoms (Table 2 and Figure 1) were more than 4 times as likely to have a stroke/TIA than those without depressive symptoms (HR=4.21, 95% CI=2.00 to 8.86,  $P<0.001$ ). When we adjusted for components of the FSRP (HR=3.43, 95% CI=1.60 to 7.36,  $P=0.002$ ) or for education (HR=4.89, 95% CI=2.19 to 10.95,  $P<0.001$ ), similar results were observed. To account for the use of antidepressant medications, we examined those with CES-D scores  $\geq 16$  or taking antidepressant medications and continued to find a significant association (HR=4.23, 95% CI=2.11 to 8.51,  $P<0.001$ ), which remained after adjusting for components of the FSRP

(HR=3.59, 95% CI=1.76 to 7.33,  $P<0.001$ ). To further elucidate the impact of antidepressants, an additional analysis excluding those taking antidepressants showed a continued association (HR=3.86, 95% CI=1.55 to 9.64,  $P=0.004$ ). To better determine incrementally the influence of depressive symptoms on risk of stroke/TIA, we examined the impact associated with a 10-point increase in CES-D score and found with each 10-point increment an almost doubling of risk for stroke/TIA (HR=1.93, 95% CI=1.44 to 2.60,  $P<0.001$ ). This remained after adjustment for components of the FSRP (HR=1.77, 95% CI=1.31 to 2.41,  $P<0.001$ ).

Men and women who were 65+ years and had CES-D scores indicative of depressive symptoms (Table 3 and Figure 2) were not at a significantly higher risk for stroke/TIA than those who were not depressed (HR=0.78, 95% CI=0.46 to 1.32,  $P=0.350$ ). After adjusting for components of the FSRP (HR=0.78, 95% CI=0.46 to 1.34,  $P=0.374$ ) or for education (HR=0.70, 95% CI=0.41 to 1.22,  $P=0.214$ ), similar results remained. When we examined the effect of CES-D scores



**Figure 1.** Kaplan-Meier plot, showing the cumulative incidence of stroke/TIA: comparison of those with and without baseline depressive symptoms in the age group <65 years.

**TABLE 3. Results of Multivariable Cox Proportional-Hazards Regression Examining the Association Between Depressive Symptoms and the Risk of Stroke/TIA Among Subjects 65+ Years Old**

	Adjusted for Age and Sex				Adjusted for Stroke Risk Factors*			
	Cases/N	HR	95% CI	P	Cases/N	HR	95% CI	P
CES-D $\geq 16$	191/1899	0.78	0.46–1.32	0.350	179/1809	0.78	0.46–1.34	0.374
CES-D $\geq 16$ or taking antidepressant medication	191/1899	0.94	0.60–1.46	0.772	179/1809	0.93	0.59–1.47	0.759
Continuous CES-D†	191/1899	1.03	0.85–1.25	0.781	179/1809	1.01	0.82–1.24	0.930

\*Age, sex, blood pressure, diabetes, atrial fibrillation, history of cardiovascular disease, left ventricular hypertrophy on the ECG, and current smoking; †with 10-point increments on the CES-D.

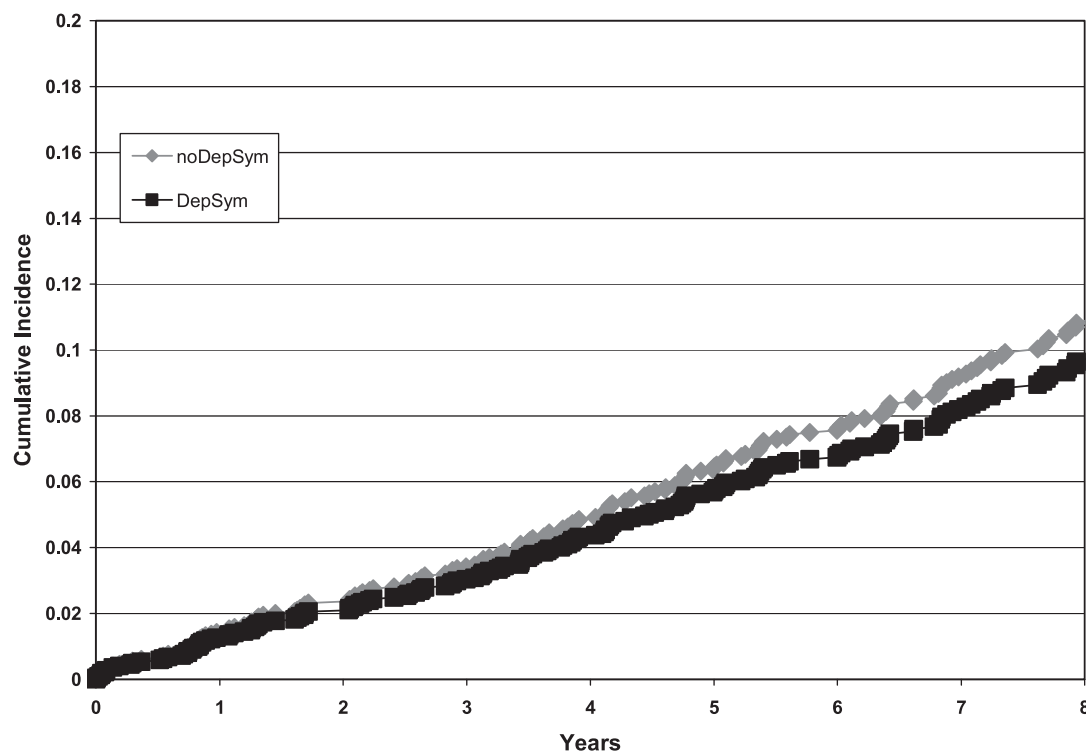
$\geq 16$  or antidepressant medication use, we found no association with incident stroke/TIA (HR=0.94, 95% CI=0.60 to 1.46,  $P=0.772$ ); we obtained similar results after adjustment for components of the FSRP (HR=0.93, 95% CI=0.59 to 1.47,  $P=0.759$ ). Last, analyzing the score as a continuous measure, we found no significant association with risk of stroke/TIA (HR=1.03, 95% CI=0.85 to 1.25,  $P=0.781$ ), and again we obtained similar results after adjustment for components of the FSRP (HR=1.01, 95% CI=0.82 to 1.24,  $P=0.930$ ).

### Discussion

In our community-based sample free of stroke or TIA at baseline, depressive symptoms were associated with a 4-fold increased risk of stroke/TIA in men and women <65 years but not in those 65+ years. With up to 8 years of follow-up, the association between depressive symptoms and risk of stroke/TIA was observed in those <65 years when depressive symptoms were treated as either a dichotomous or a contin-

uous measure, when adjusted for traditional risk factors or for education, or when those taking antidepressants were included in the depressive symptom group. To our knowledge, this is the first community-based study to examine the elderly and nonelderly groups separately and to document the association between depressive symptoms and stroke risk in those <65 years.

During the past decade, the association between depressive symptoms and stroke has been examined in a number of studies, with varying conclusions.<sup>7,22,23–29</sup> Several studies reported that baseline depressive symptoms predicted the risk of incident stroke,<sup>22,23,24</sup> ischemic stroke,<sup>7,25</sup> and stroke mortality.<sup>24,26</sup> Other studies concluded that depressive symptoms were not associated with an increased risk of stroke in general<sup>27,28</sup> or with nonfatal ischemic stroke or TIA.<sup>29</sup> We observed an association between antecedent depressive symptoms and risk of stroke/TIA but only in those below the age of 65 years. Our results are consistent with 2 previous studies documenting that baseline depression was not a risk



**Figure 2.** Kaplan-Meier plot, showing the cumulative incidence of stroke/TIA: comparison of those with and without baseline depressive symptoms in the age group 65+ years.



factor for stroke among individuals aged 60+ years<sup>28</sup> or 65+ years.<sup>27</sup> Our findings of an increased risk in the depressed nonelderly group support those of Gump et al,<sup>24</sup> who found an elevated risk of stroke among men aged 35 to 57 years; however, that study sample did not include either women or older men. In contrast, when Jonas and Mussolino<sup>22</sup> examined the risk of stroke in depressed individuals stratified by age (25 to 59 years and 60 to 74 years), a positive association was found in both age groups. However, the older age group in that study did not include individuals >74 years old, thus not inclusive of the oldest-old.

Previous studies have shown an inconsistent relation between antidepressants and stroke risk.<sup>30–33</sup> In our analysis, the inclusion of those taking antidepressants, even if their current depressive symptoms were below the cutoff point, did not significantly alter the risk of stroke/TIA associated with baseline depression in either age group. Also, the risk of stroke/TIA associated with baseline depression in those <65 years was not appreciably altered when those taking antidepressants were removed from the analysis.

Several mechanisms have been suggested in an attempt to explain the relation between antecedent depression and stroke. Multiple stroke risk factors may contribute to the association found between depressive symptoms and risk of stroke. However, when we examined the risk of stroke/TIA in the lowest quartile of the FSRP, a significant association remained (data not reported). Some genetic<sup>34</sup> and biological markers that have been implicated include increased levels of fibrinogen,<sup>35,36</sup> platelet activation,<sup>37,38</sup> and catecholamines.<sup>39</sup> More recently, inflammatory markers such as C-reactive protein have been suggested.<sup>40,41</sup> The association between depression and the risk of stroke may also be attributed to poor adherence to prescribed medical regimens, including medication, diet, and exercise. Depression has been found to be associated with low physical activity, smoking, and indulging in behavioral patterns that may increase vascular risk.<sup>22</sup>

The strengths of our investigation include its prospective design, duration of follow-up, large community-based sample, home/nursing home evaluations, and intensive stroke surveillance. Limitations include the lack of inclusion of diverse racial/ethnic groups and psychiatric documentation of depression and other mood disorders.

In conclusion, our study provides evidence supporting an association between depressive symptoms and an increased risk of stroke/TIA in individuals below the age of 65 years. Research is needed to determine the pathophysiological mechanisms leading to stroke in younger individuals who report depressive symptoms. Increased awareness of stroke risk in those exhibiting depressive symptoms may identify those who could benefit from primary stroke prevention.

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### Disclosures

None.

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