ORIGINAL ARTICLE

Depressive Symptoms, Vascular Disease, and Mild Cognitive Impairment

Findings From the Cardiovascular Health Study

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Context: Depressive symptoms are common in patients with dementia and may be associated with increased risk of developing dementia. It has been hypothesized that depressive symptoms and dementia may be attributable to underlying vascular disease in some older persons.

Objectives: To test the hypotheses (1) that depressive symptoms are associated with increased risk of developing mild cognitive impairment (MCI), a preclinical state that often precedes dementia, and (2) that the association between depressive symptoms and MCI is attributable to underlying vascular disease.

Design: Prospective, population-based, longitudinal study.

Setting: Random sample of adults 65 years or older recruited from 4 US communities.

Participants: Subjects were 2220 participants in the Cardiovascular Health Study Cognition Study with high cognitive function at baseline. Depressive symptoms were measured at baseline using the 10-item Center for Epidemiological Studies Depression Scale and were classified as none (0-2 points), low (3-7 points), and moderate or high (≥8 points). Vascular disease measures at baseline included confirmed history of stroke, transient ischemic attack, diabetes mellitus, or hypertension; carotid artery stenosis; ankle-arm blood pressure index; and small or large infarcts or white matter disease on cerebral magnetic resonance imaging. Mild cognitive impairment was diagnosed after 6 years of follow-up based on the consensus of a team of dementia experts using standard clinical criteria.

Main Outcome Measure: Diagnosis of MCI.

Results: Depressive symptoms at baseline were associated with increased risk of MCI (10.0%, 13.3%, and 19.7% for those with no, low, and moderate or high depressive symptoms, respectively). This association was diminished only slightly by adjustment for vascular disease measures and demographics. Vascular disease measures also were associated with increased risk of MCI, and these associations were not diminished by adjustment for depressive symptoms or demographics.

Conclusion: Depressive symptoms were associated with increased risk of MCI, and this association was independent of underlying vascular disease.

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DEPRESSIVE SYMPTOMS ARE common in dementia and occur in approximately 30% of patients with dementia.[1] Investigators conducting longitudinal studies[2-8] have found that older persons with depressive symptoms have increased risk of cognitive decline and dementia, and the author of a meta-analysis[9] concluded that the risk of dementia is approximately doubled in older adults with depressive symptoms. However, it remains controversial whether depressive symptoms represent a risk factor for dementia, whether they are an early symptom of neurodegeneration, or whether they are a reaction to early cognitive deficits. For example, some studies have suggested that depressive symptoms appear to coincide with[10] or follow[11,12] the onset of dementia rather than precede it.

It is important to clarify the timing of the association between depressive symptoms and dementia. If depressive symptoms are a risk factor for or an early symptom of dementia in some older persons, it would suggest that older adults should be monitored more closely for new depressive symptoms. In addition, randomized controlled trials could be performed to determine whether older adults with depressive symptoms are less likely to develop dementia if they are treated with antidepressants, cholinesterase inhibitors, or other medications.

Mild cognitive impairment (MCI) is a newly recognized syndrome that often precedes dementia. It is characterized by abnormal cognitive function that reflects a decline from prior levels that is not severe enough to affect daily activities or to satisfy the criteria for dementia.[13] In a clinical setting, approximately 50% of patients with MCI convert to dementia within 3 years.[14]

Prior cross-sectional investigations have shown that depressive symptoms are common in patients with MCI.[1] One study[15] demonstrated that depressive symptoms were 1 of several risk factors for MCI, but the investigators did not exclude subjects with evidence of cognitive impairment at baseline. The primary objective of our study was to test the hypothesis that depressive symptoms are associated with increased risk of developing MCI in subjects with no evidence of cognitive impairment at baseline. To our knowledge, ours is the first study to examine the association between depressive symptoms and MCI longitudinally.

Prior studies also have demonstrated that depressive symptoms often co-occur with vascular disease[16,17] and that older adults with depressive symptoms have more evidence of vascular disease on magnetic resonance imaging (MRI).[18-20] This association has led to the "vascular depression" hypothesis, which proposes that vascular disease underlies mood disorders in some older adults.[16] Because there is a growing body of evidence that vascular disease also is associated with greater risk and severity of cognitive decline and dementia,[21-23] it has been proposed that vascular disease may be the link that underlies mood and cognitive disorders in some older persons.[24] Therefore, a secondary objective of our study was to test the hypothesis that the association between depressive symptoms and MCI, if present, is attributable to underlying vascular disease.

METHODS

THE CARDIOVASCULAR HEALTH STUDY

Subjects were participants in the Cardiovascular Health Study (CHS),[25] which is a prospective, population-based, longitudinal study of risk factors for coronary heart disease and stroke in 5888 adults 65 years or older: 5201 primarily African American and white subjects were enrolled in 1989-1990, and an additional 687 African Americans were enrolled in 1992-1993. Subjects were recruited from randomized Medicare eligibility lists in 4 US communities: Forsyth County, North Carolina; Washington County, Maryland; Sacramento County, California; and Pittsburgh, Pa. Subjects were considered eligible if they were 65 years or older, were noninstitutionalized, expected to remain in the area for at least 3 years, were able to give informed consent, did not require a proxy respondent, were not wheelchair bound, and were not receiving hospice treatment, radiotherapy, or chemotherapy.

The CHS included annual assessment of cognitive function beginning in 1989-1990 using the Modified Mini-Mental State Examination (3MS)[26] and the Digit Symbol Test.[27] The Benton Visual Retention Test[28] was added in 1994-1995. In addition, beginning in 1996-1997, the Telephone Interview for Cognitive Status[29] was performed when subjects were unable to come to the clinic; and the Informant Questionnaire on Cognitive Decline in the Elderly[30] and the Dementia Questionnaire[31] were performed in proxies if subjects were unable to participate in interviews on their own. Detailed data also were gathered at each annual visit on a wide range of other factors, including depressive symptoms, cardiovascular events, medication use, and ability to perform activities of daily living (ADL) and instrumental ADLs. In 1991-1994, cerebral MRI was performed in 3608 subjects.

THE CHS COGNITION STUDY

The CHS Cognition Study has been described previously in detail, including the methods of classification for MCI and dementia.[32,33] Briefly, in 1998-1999, the CHS administered a standardized protocol across the 4 sites to identify all participants who had prevalent dementia at the time of MRI in 1991-1994 or who developed subsequent incident dementia or MCI. The sample was limited to those participants who had MRI in 1991-1994 and a 3MS evaluation, for a total of 3608 participants. The results of a comparison between subjects who underwent MRI and those who did not have previously been reported.[34]

Each subject was classified as having normal cognition, dementia, or MCI based on a review of available data; dementia also was classified as being prevalent at the time of MRI or as being incident during follow-up. Information reviewed included all previous cognitive test data (3MS, Digit Symbol Test, Benton Visual Retention Test, Telephone Interview for Cognitive Status, Telephone Interview for Cognitive Status, and Dementia Questionnaire) and medical histories, ADL and instrumental ADL impairment, and medication use. In addition, more detailed neuropsychological, neurological, and psychiatric examinations were performed in a subset of subjects who were alive in 1998-1999 and considered high risk. All MCI and dementia cases were reviewed by an adjudication committee composed of expert neurologists and psychiatrists.

Dementia was defined as a progressive or static deficit in at least 2 cognitive domains that did not necessarily include memory and was of sufficient severity to affect the subjects' ADLs, combined with a history of normal intellectual function.[32,33,35] Individuals who did not meet dementia criteria but who exhibited poor cognitive function that reflected a decline from a prior level were classified as having MCI. The MCI category reflected a heterogeneous group and was not restricted to the MCI amnestic subtype. Subjects classified as having MCI did not have ADL impairment, but they may have had minor instrumental ADL impairment. This definition is consistent with that proposed in a recent international consensus statement on criteria for MCI.[13] This enabled classification of 3602 (99.8%) of 3608 subjects in the CHS Cognition Study, including those who had died during follow-up.

Our analyses excluded subjects with prevalent dementia at the time of MRI. In addition, to minimize the potential for inclusion of subjects with MCI at baseline, we restricted our analyses to the 2220 subjects who had 3MS scores of 90 or higher in 1992-1993 and who were classified as having normal cognitive function or MCI in 1998-1999. This is more conservative than the cutoff point of a 3MS score lower than 78 that is typically used to screen for dementia.[36]

EVALUATION OF DEPRESSIVE SYMPTOMS

Depressive symptoms were measured annually as part of the main CHS using the Center for Epidemiological Studies Depression Scale 10-item questionnaire,[37] which has a maximum score of 30. We classified subjects as having moderate or high depressive symptoms if their scores were 8 or higher in 1992-1993. This cutoff point has been recommended by the CHS to reflect subjects at risk for clinical depression and has been used

by other investigators.[19] In addition, to determine whether there was a graded association between the number of depressive symptoms and MCI, we performed a Lowess smoothing curve (bandwidth, 0.8) of the percentage of subjects who developed MCI by the number of depressive symptoms in 1992-1993. This curve indicated that the risk of MCI began to increase in subjects with Center for Epidemiological Studies Depression Scale scores of 3 or higher, so we further classified the level of depressive symptoms at baseline as none (0-2 points), low (3-7 points), and moderate or high (≥8 points).

To examine the effects of treatment of depressive symptoms, we identified subjects who reported the use of antidepressants in 1992-1993. Medication use was assessed by asking subjects to show interviewers all prescription medications (including pills, dermal patches, eyedrops, creams, salves, and injections) that they had taken in the past 2 weeks, and the name, strength, and number of pills prescribed and taken were recorded. Medications were then classified into categories. We classified subjects as users of antidepressants if they reported the use of a tricyclic or tetracyclic antidepressant, nontricyclic antidepressant, or combination tricyclic antidepressant and antipsychotic or monoamine oxidase inhibitor at the 1992-1993 visit.

EVALUATION OF VASCULAR DISEASE

Vascular events, including stroke and transient ischemic attack (TIA), were identified as part of the main CHS study using a rigorous protocol.[38,39] Subjects were asked at their initial interview whether they had ever had a stroke or TIA, with stroke defined as an abrupt onset of neurologic deficit lasting at least 24 hours and with TIA defined as a rapid onset of focal neurologic deficit lasting less than 24 hours. All potential vascular events were validated either by physician questionnaire or by medical record review.[38] During follow-up, participants were asked to report all hospitalizations and outpatient cardiovascular events, which were investigated in detail. Incident vascular events were adjudicated by the CHS events subcommittee based on review of medical history, symptoms, course, and outcome using the definitions already given.[39] The adjudication process sometimes detected previously unreported prebaseline events.

Carotid artery atherosclerosis was measured using duplex ultrasonography performed using 2-dimensional brightness mode imaging to detect thickening of the arterial wall, disruption of normal wall surfaces, and development of focal plaques bilaterally.[25] Images were interpreted at the CHS ultrasound reading center by trained readers, and the degree of stenosis was classified as 0%, 1% to 24%, 25% to 49%, 50% to 74%, 75% to 99%, or 100% based on the most severely affected vessel.[40]

The ankle-arm blood pressure index was calculated by measuring blood pressure in the supine position after a 30-minute rest.[25] Duplicate measurements were performed in the right arm and in both ankles, and the ankle-arm blood pressure index was calculated by averaging the measurements taken at each site and by taking the lower of the 2 ankle-arm ratios.

Diabetes mellitus was defined based on American Diabetic Association guidelines[41] as a fasting glucose level of 126 mg/dL or higher (≥7.0 mmol/L) or the use of insulin or oral hypoglycemic agents. Hypertension was defined as a mean seated systolic blood pressure greater than 160 mm Hg, a mean seated diastolic blood pressure greater than 95 mm Hg, or a self-reported history of hypertension combined with the use of hypertensive medication.

Cerebral MRI was performed according to a standard protocol, and images were interpreted by trained neuroradiologists who were blinded to subjects' age, sex, race or ethnicity, and other clinical information.[34,42-44] Infarcts on MRI were defined as lesions with an abnormal signal in a vascular distribution and no mass effect and were classified as small (<3 mm) or as large (≥3 mm). White matter disease was estimated as the total volume of periventricular and subcortical white matter signal abnormality on spin density–weighted axial images compared with 8 "reference" images and was classified on a scale ranging from grade 0 (none) to grade 9 (extensive). Intraclass correlation coefficients for repeated readings were 0.80 for white matter scores.[44]

We created 3 summary vascular disease measures, all of which reflected the 1992-1993 status. "Any history of vascular events" was defined as a confirmed history of stroke or TIA; "any subclinical vascular disease" was defined as a low ankle-arm blood pressure index (<1.0), high carotid artery stenosis (≥50%), or a confirmed history of diabetes mellitus or hypertension; and "any MRI evidence of vascular disease" was defined as the presence of large or small infarcts or a high white matter grade (≥4) on MRI.

STATISTICAL ANALYSIS

We first examined the association between the number of depressive symptoms and MCI graphically by performing a Lowess smoothing curve (bandwidth, 0.8) of the percentage of subjects who developed MCI by the number of depressive symptoms at baseline. To minimize the effect of small cell numbers, if there were fewer than 10 subjects with MCI with a given number of depressive symptoms, we combined them with an adjacent group and used the median number of depressive symptoms for the combined group in the Lowess smoothing curve. As already described, we used this curve to establish our cutoff points for no (0-2 points) and low (3-7 points) depressive symptoms and to confirm our a priori cutoff point for moderate or high (≥8 points) depressive symptoms.

We determined whether baseline characteristics of subjects with no, low, and moderate or high depressive symptoms differed in an ordinal manner using linear regression analysis for continuous variables and nonparametric tests for trend for categorical variables. We used logistic regression analysis to determine whether older persons with low and moderate or high depressive symptoms at baseline had increased odds of developing MCI during 6 years compared with those with no depressive symptoms at baseline. We also used logistic regression analysis to determine whether older persons with vascular disease had increased odds of developing MCI. In addition, we performed subgroup analyses in which we examined the association between moderate or high depressive symptoms and MCI in various subgroups of the study population (eg, women vs men, African Americans vs whites, users vs nonusers of antidepressant agents, and apolipoprotein E ε4 carriers vs noncarriers).

To determine whether the association between depressive symptoms and MCI was attributable to vascular disease, we performed a series of logistic regression models as follows: (1) unadjusted, (2) adjusted for demographic factors, (3) adjusted for vascular events, (4) adjusted for subclinical vascular disease, (5) adjusted for MRI evidence of vascular disease, and (6) adjusted for all of these variables. Vascular disease measures were examined individually (ie, stroke and TIA entered as separate variables) and using our summary measures (ie, any history of vascular events). We also performed a series of stratified analyses to determine whether the effects of depressive symptoms were similar in subjects who had and those who did not have a history of vascular disease and tested for interaction between depressive symptoms and vascular disease measures ($P<.20$).

Because depressive symptoms and vascular disease measures were independently associated with MCI in all of our analyses, we used backward stepwise logistic regression analysis ($P=.05$ to enter and $P=.10$ to remove) to determine which mea-

Table 1. Baseline Characteristics of 2220 Study Participants by Depressive Symptom Category*

Characteristic	Depressive Symptom Category		
	None (n = 857)	Low (n = 916)	Moderate or High (n = 447)
Age, y	73.5 ± 4.2	73.8 ± 4.3	74.2 ± 4.8†
Female sex	431 (50.3)	569 (62.1)	319 (71.4)†
African American race or ethnicity	82 (9.6)	77 (8.4)	43 (9.6)
Educational achievement, y	15.6 ± 4.3	15.1 ± 4.3	14.6 ± 4.2†
Baseline Modified Mini-Mental State Examination score	95.3 ± 2.9	95.2 ± 2.9	95.3 ± 2.9
History of vascular events			
Stroke	19 (2.2)	29 (3.2)	23 (5.2)†
Transient ischemic attack	17 (2.0)	22 (2.4)	17 (3.8)
Any	32 (3.7)	43 (4.7)	31 (6.9)†
Subclinical vascular disease			
Ankle-arm blood pressure index <1.0	118 (14.2)	139 (15.7)	85 (19.8)†
Diabetes mellitus	109 (12.7)	102 (11.1)	66 (14.8)
Hypertension	100 (11.7)	84 (9.2)	61 (13.7)
Carotid artery stenosis ≥50%, %	37 (4.3)	34 (3.7)	17 (3.8)
Any	282 (33.7)	288 (32.3)	179 (41.4)†
Magnetic resonance imaging evidence of vascular disease			
Large infarcts	208 (24.3)	236 (25.8)	134 (30.0)†
Small infarcts	89 (10.4)	122 (13.3)	70 (15.7)†
High white matter grade ≥4	77 (9.0)	100 (10.9)	62 (13.9)†
Any	294 (34.4)	323 (35.4)	182 (40.8)†

*Data are reported as mean±SD or as number (percentage). Data were missing as follows: ankle-arm blood pressure index, n=73; hypertension, n=1; carotid artery stenosis, n=17; any subclinical vascular disease, n=60; large or small infarcts on magnetic resonance imaging, n=5; high white matter grade, n=10; and any magnetic resonance imaging evidence of vascular disease, n=7.

†Significant trend ($P<.05$) across the 3 depressive symptom categories based on linear regression analysis for continuous variables and on nonparametric test for trend for categorical variables.

sures were most strongly associated with increased odds of MCI. All demographic factors were retained to adjust for potential confounding.

All statistical analyses were performed using Stata (Intercooled, version 8.0; StataCorp LP, College Station, Tex). The final logistic regression model was evaluated for goodness of fit using the techniques of Hosmer and Lemeshow,[45] and sensitivity analyses were performed after excluding outlier, high leverage, and influential data points.[46]

HUMAN SUBJECTS

All study procedures were approved by institutional review boards at each site, and all participants signed an informed consent at study enrollment and periodically throughout the study. In addition, the secondary data analyses described herein were approved by the CHS steering committee; the committee on human research at the University of California, San Francisco; and the San Francisco Veterans Administration Medical Center research and development committee.

RESULTS

The 2220 study participants had a mean age of 74 years (age range, 64-92 years). Fifty-nine percent were women, 9% were African American, 84% had 12 or more years of education, and the mean±SD 3MS score at baseline was 95.2±2.9. Approximately 41% (n=916) had low depressive symptoms, and 20% (n=447) had moderate or high depressive symptoms at baseline.

Subjects with more depressive symptoms at baseline were slightly older, more likely to be female, and less educated than those with few depressive symptoms (**Table 1**). In addition, subjects with more depressive symptoms were more likely to have a history of vascular events, subclinical vascular disease, and MRI evidence of vascular disease. However, the percentages of subjects with no, low, and moderate or high depressive symptoms did not differ by race or ethnicity, and the mean cognitive test scores among the 3 groups in 1992-1993 were virtually identical.

Approximately 13% (n=296) of the subjects developed MCI during follow-up. Subjects with more depressive symptoms in 1992-1993 were more likely to develop MCI during the 6-year follow-up (**Figure 1**). The risks of MCI were 10.0%, 13.3%, and 19.7% for subjects with no, low, and moderate or high depressive symptoms, respectively (**Table 2**), and the unadjusted odds of MCI were increased by 40% in subjects with low depressive symptoms and more than doubled in subjects with moderate or high depressive symptoms. In addition, subjects with vascular disease in 1992-1993 were more likely to develop MCI during follow-up. The odds of MCI were consistently increased by 50% to 60% for subjects with a history of vascular events, subclinical vascular disease, or MRI evidence of vascular disease.

The association between depressive symptoms and MCI was similar in a wide range of subgroups of the study population (eg, women vs men, African Americans vs whites, those with <12 vs ≥12 years of education, and apolipoprotein E ε4 carriers vs noncarriers) (**Table 3**). The use of antidepressant agents in 1992-1993 also did

not alter the association between depressive symptoms and MCI.

The association between depressive symptoms and MCI was not altered by adjustment for any of the vascular disease measures, alone or in combination (**Figure 2**). Similarly, the association between vascular disease measures and MCI was not altered by adjustment for depressive symptoms. There was no evidence of interaction between depressive symptoms and vascular disease measures (range, P=.32 to P=.98 for interaction).

In our final multivariate logistic regression model, depressive symptoms and vascular disease measures were independently associated with greater odds of developing MCI, and the magnitudes of the associations were similar to those from unadjusted models (**Table 4**). The vascular disease measures that were most strongly associated with greater odds of MCI were large or small infarcts on MRI and a history of diabetes mellitus. Results were unchanged if variables were modeled as continuous rather than categorized (eg, carotid artery stenosis, ankle-arm blood pressure index, and white matter grade) and were not affected by the side on which the lesion was located.

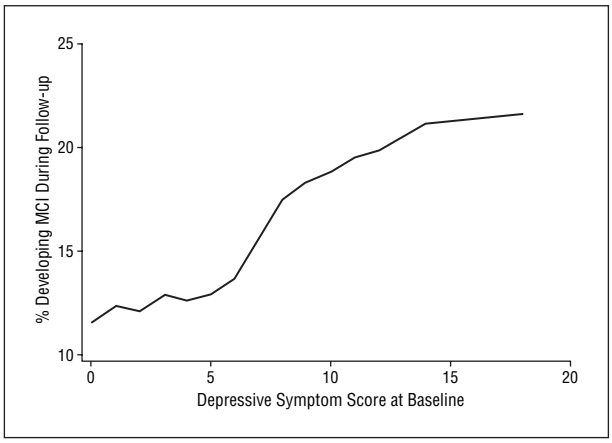

Figure 1. Percentages of subjects who developed mild cognitive impairment (MCI) during follow-up by depressive symptom score at baseline. A Lowess smoothing curve (bandwidth, 0.8) was used to examine the association between depressive symptom score at baseline and risk of developing MCI during the 6-year follow-up.

COMMENT

In older adults with normal cognitive function, the risk of MCI increased with the number of depressive symptoms at baseline. The odds of developing MCI were more than doubled in those with moderate or high depressive symptoms (≥8 points on the 10-item Center for Epidemiological Studies Depression Scale) at baseline, which is consistent with the findings of a meta-analysis[9] of the association between depressive symptoms and increased risk of dementia.

In addition, the association between moderate or high depressive symptoms and MCI was similar in all of the subgroups we examined (eg, women vs men, African Americans vs whites, younger vs older subjects, those with <12 vs ≥12 years of education, and apolipoprotein E ε4 carriers vs noncarriers) and was not altered by the use of antidepressant agents. This finding is in contrast to the results of some prior studies in which the association between depressive symptoms and dementia was limited to specific subgroups, such as men[47] or those with higher education.[8] This discrepancy may be explained by differences in study characteristics, such as differential loss to follow-up. The procedure used to diagnose MCI in the CHS Cognition Study resulted in virtually no loss to follow-up (0.2% with insufficient data) even among subjects who died, whereas the other studies[8,47] experienced greater losses to follow-up that differed among the subgroups studied.

Our results support the findings of prior studies[2-9] in which high depressive symptoms were associated with increased risk of cognitive decline and dementia. In addition, they are consistent with the hypothesis that depressive symptoms may be a symptom of ongoing neurodegeneration in some older persons.

To our knowledge, ours is the first study to examine the association between depressive symptoms and MCI longitudinally. Two prior studies[1,15] of the association between depressive symptoms and MCI among the CHS Cognition Study participants included cross-sectional data, in whole or in part.

Contrary to our hypothesis, the association between depressive symptoms and MCI was independent of un-

Table 2. Depressive Symptoms and Vascular Disease Measures at Baseline and Odds of Developing Mild Cognitive Impairment (MCI)

Characteristic	No. of Participants	Developed MCI, %	Unadjusted Odds Ratio (95% Confidence Interval)
Depressive symptom category*			
None, 0-2 points	857	10.0	1.00 (Referent)
Low, 3-7 points	916	13.3	1.38 (1.03-1.85)
Moderate or high, ≥8 points	447	19.7	2.20 (1.59-3.03)
Vascular disease measures			
No history of vascular events	2114	13.1	1.00 (Referent)
Any history of vascular events	106	18.9	1.55 (0.94-2.56)
No subclinical vascular disease	1411	11.6	1.00 (Referent)
Any subclinical vascular disease	749	16.7	1.53 (1.19-1.97)
No MRI evidence of vascular disease	1414	11.2	1.00 (Referent)
Any MRI evidence of vascular disease	799	17.2	1.63 (1.28-2.09)

Abbreviation: MRI, magnetic resonance imaging.
*Measured using the 10-item Center for Epidemiological Studies Depression Scale.

Table 3. Association Between High Depressive Symptoms and Mild Cognitive Impairment (MCI) in Subgroups

Subgroup	No. of Participants	Developed MCI, %		Odds Ratio (95% Confidence Interval)*
		No or Low Depressive Symptoms	Moderate or High Depressive Symptoms	
Sex				
Female	1319	11.2	19.1	1.87 (1.33-2.64)
Male	901	12.4	21.1	1.89 (1.17-3.03)
Age, y				
<75	1416	9.5	17.3	1.99 (1.38-2.89)
≥75	804	15.8	23.3	1.62 (1.08-2.45)
Race or ethnicity				
African American	202	30.8	46.5	1.95 (0.98-3.88)
White	2018	9.8	16.8	1.85 (1.36-2.52)
Baseline Modified Mini-Mental State Examination score				
90-94	901	16.0	26.9	1.94 (1.32-2.84)
95-100	1319	8.8	14.7	1.78 (1.19-2.66)
Educational achievement, y				
<12	353	16.1	25.0	1.73 (0.95-3.16)
≥12	1867	10.9	18.5	1.85 (1.36-2.52)
Apolipoprotein E ε4 alleles†				
0	1613	11.2	18.2	1.76 (1.26-2.45)
≥1	448	13.5	22.6	1.88 (1.04-3.40)
Antidepressant use†				
Yes	97	14.8	25.0	1.93 (0.68-5.42)
No	2122	11.6	19.2	1.81 (1.36-2.41)

*Odds ratios are unadjusted and compare odds of developing MCI in subjects with moderate or high depressive symptoms with those with no or low depressive symptoms. None of the interaction terms was statistically significant.
†Numbers do not sum to 2220 because of missing data.

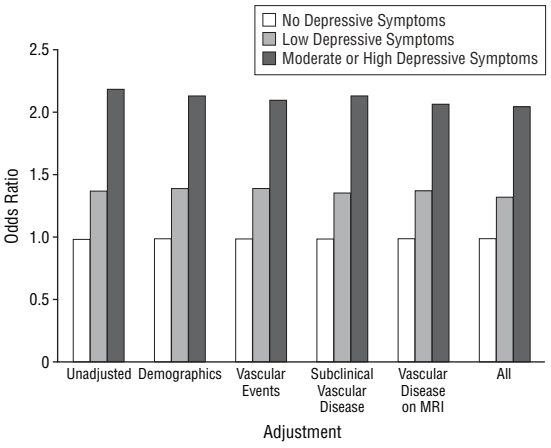

Figure 2. Odds of mild cognitive impairment (MCI) before and after adjustment for demographic and vascular disease variables. The figure shows the association between depressive symptom category and odds of MCI from unadjusted and adjusted logistic regression analyses. Subjects with no depressive symptoms served as the reference group (odds ratio, 1.0). Associations were unchanged by adjustment for demographic and vascular disease measures, suggesting that the association between depressive symptoms and MCI is independent of these factors. MRI indicates magnetic resonance imaging.

Table 4. Model Terms Independently Associated With Greater Odds of Mild Cognitive Impairment

Model Term	Odds Ratio (95% Confidence Interval)*
Depressive symptom category	
Moderate	1.37 (1.00-1.88)
High	2.09 (1.46-2.97)
Vascular disease	
Large infarcts	1.67 (1.24-2.23)
Small infarcts	1.47 (1.01-2.14)
Diabetes mellitus	1.42 (0.98-2.04)
Age	1.09 (1.05-1.12)
Education, y	
<12	0.75 (0.51-1.10)
≥12	0.62 (0.43-0.89)
Male sex	1.14 (0.87-1.50)
African American race or ethnicity	5.36 (3.71-7.75)
Baseline Modified Mini-Mental State Examination score	0.93 (0.89-0.98)

*Odds ratio is for a 1-year increase in age and a 1-point increase in baseline Modified Mini-Mental State Examination score.

derlying vascular disease. Our findings differ from those of a recent study[47] in which the risk of dementia was greatest in depressed men with hypertension. However, this finding was based on a few subjects (97 men with dementia), and it may have reflected random variation due to the small numbers in the subgroups examined. Our findings are consistent with those of a recent study[48] in which depressed patients who had and those who did not have cognitive impairment did not differ in the levels of vascular disease or Alzheimer-type pathologic features observed at autopsy.

If the association between depressive symptoms and MCI is not attributable to vascular disease, what is the

underlying mechanism? One hypothesis is that development of late-life depressive symptoms may reflect an underlying neuropathologic condition that manifests as cognitive decline over time. Therefore, depressive symptoms in the absence of overt cognitive impairment may reflect the early signs of a neurodegenerative disease. An alternative explanation is that the symptoms of depression may overlap to some extent with the symptoms of cognitive deterioration. For example, statements such as "I have trouble keeping my mind on what I am doing," which is part of the Center for Epidemiological Studies Depression Scale, reflect aspects of mood and cognition.

Another hypothesis is that depression leads to damage in the hippocampus through a glucocorticoid cascade.[9] This hypothesis is supported by research showing that older adults with high or rising cortisol levels during 5 years have poorer memory and greater hippocampal atrophy.[49] There also may be a genetic link between depressive symptoms and dementia in some patients. For example, a study[50] of women at high risk of carrying the presenilin 1 mutation for dementia showed that carriers of this mutation had significantly more depressive symptoms than noncarriers and were more likely to have sought help from a psychiatric professional. All of these hypotheses, and perhaps others, await testing.

Strengths of our study include its large sample size, minimal loss to follow-up (0.2%), inclusion of African American and white subjects, and detailed evaluation of cardiovascular disease, including adjudicated vascular events, measures of subclinical disease, and cerebral MRI. In addition, subjects in all 3 depressive symptom categories had similar levels of cognitive function at baseline, which minimizes the potential for diagnostic bias among subjects with depressive symptoms.

A limitation of our study was that we were unable to determine the year of onset for MCI. In particular, it would have been informative to determine the mean amount of time between depressive symptoms and development of MCI. In addition, to exclude subjects with evidence of cognitive impairment at baseline, we used the 3MS, which may be insensitive to very mild cognitive deficits. An additional limitation is that we did not formally diagnose subjects as having clinical depression, although our results suggest that even low levels of depressive symptoms are associated with slightly increased risk of MCI.

CONCLUSIONS

We found that older adults with normal cognitive function and moderate or high levels of depressive symptoms at baseline were twice as likely to develop MCI during 6 years of follow-up and that this association was independent of underlying vascular disease. Our findings support the hypothesis that depressive symptoms may be a risk factor for or an early symptom of dementia in some older persons, and they suggest that older adults with depressive symptoms should be monitored closely for development of MCI and dementia.

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