ORIGINAL ARTICLE

Depressive Symptoms and Cognitive Decline in Nondemented Elderly Women

A Prospective Study

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Background: The association between depressive disorders and subsequent cognitive decline is controversial. We tested the hypothesis that elderly women (aged 65 years and older) without dementia but with depressive symptoms have worse cognitive function and greater cognitive decline than women with few or no symptoms.

Methods: As part of an ongoing prospective study, we evaluated 5781 elderly, mostly white, community-dwelling women. Women completed the Geriatric Depression Scale short form. Three cognitive tests—Trails B, Digit Symbol, and a modified Mini-Mental State Examination—were administered at baseline and approximately 4 years later. Baseline, follow-up, and change scores for the cognitive tests were analyzed by analysis of covariance and Kruskal-Wallis analysis; the odds of cognitive deterioration (≥3-point decline on the modified Mini-Mental State Examination) were determined by logistic regression.

Results: At baseline, 211 (3.6%) of the women had 6 or more depressive symptoms. Only 16 (7.6%) of these women were receiving antidepressant medication. Increasing symptoms of depression were associated with worse performance at baseline and follow-up on all 3 tests of cognitive function ($P<.001$ for all comparisons). For example, the baseline Digit Symbol score (mean ± SD) was 45.5 ± 10.7 among women with 0 to 2 symptoms of depression, 40.3 ± 10.7 for women with 3 to 5 symptoms, and 39.0 ± 11.3 for women with 6 or more symptoms. After adjusting for the baseline score, cognitive change scores were also inversely associated with the number of depressive symptoms ($P<.001$ for all comparisons). Odds ratios for cognitive deterioration using 0 to 2 symptoms as the reference were 1.6 (95% confidence interval, 1.3-2.1) for 3 to 5 symptoms and 2.3 (95% confidence interval, 1.6-3.3) for 6 or more symptoms. Results were similar after being adjusted for education, age, health status, exercise, alcohol use, functional status, and clinic site.

Conclusions: Depressive symptoms in older women are associated with both poor cognitive function and subsequent cognitive decline. Mechanisms underlying the association between these 2 common conditions need further exploration.

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ALTHOUGH DEPRESSION and cognitive impairment affect up to 25% of elderly people (age ≥65 years),[1-3] the association between these 2 conditions is complex. Many studies[4-6] have found that depression is associated with poor performance on cognitive testing, and depression may even cause a reversible dementia or "pseudodementia."[7] As many as 30% of patients with nonreversible dementia, such as Alzheimer disease or dementia associated with cerebrovascular disease, have depressive syndromes, ranging from depressive symptoms to major depressive disorder.[8-11]

Whether depressive disorders are associated with subsequent cognitive decline—either the development of dementia or milder cognitive impairment—is controversial. Several,[12-16] although not all,[17-20] studies have found that depressive disorders are associated with an increased risk of dementia. Some of these studies are limited by small sample sizes, retrospective designs, and non–population-based samples. Others[14-16] used a case-control design, making it difficult to determine cause and effect because as many as 30% of patients with dementia have symptoms of depression. In addition, results have been difficult to interpret because symptoms used to diagnose depression, such as disturbances in concentration, poor energy, changes in sleep patterns, and lack of interest in activities, often occur in patients with dementia.

We asked whether depressive symptoms are a risk factor for cognitive decline by prospectively studying a group of community-dwelling women without dementia. This study design allows for the determination of whether depressive symptoms are associated with poorer

SUBJECTS AND METHODS

STUDY SAMPLE

We studied 7511 women who were enrolled in the Study of Osteoporotic Fractures, a prospective study of risk factors for osteoporotic fractures.[21] Community-dwelling women aged 65 years and older were recruited between 1986 and 1988 from population-based listings in 4 areas of the United States: Baltimore, Md; Minneapolis, Minn; the Monongahela Valley near Pittsburgh, Pa; and Portland, Ore. Men and black women were excluded because of their low incidence of osteoporotic fractures, as were women who were unable to walk without assistance and those with bilateral hip replacements. No woman had a previous diagnosis of dementia. At the second (1988-1990) and fourth (1992-1994) study visits, the subjects were administered a depression scale and a cognitive battery. During the study, 645 of the original 7511 subjects died; of the survivors, 5781 (84.2%) had follow-up cognitive and depression measurements. Women who did not have follow-up measurements had lower baseline scores on cognitive testing and on the depression scale than those who did have follow-up measurements (data not shown; $P<.001$ for all comparisons). The 5781 subjects who completed these tests at both times are the subjects of our study; all women provided written informed consent, and the Study of Osteoporotic Fractures was approved by the committees on human research at each site.

MEASURING DEPRESSIVE SYMPTOMS

The Geriatric Depression Scale short form was administered during the second study visit (defined as the baseline examination in this study) and repeated approximately 4 years later. This is a validated and reliable self-report scale that detects depressive symptoms in elderly persons.[22] Scores range from 0 to 15, with higher scores indicating more symptoms of depression and a cutoff of 6 indicating depression. This cutoff has a sensitivity of 88% and specificity of 62% compared with a structured clinical interview for depression.[23] The scale was devised to minimize the measurement of nonspecific factors such as fatigue, sleep disturbance, and poor concentration that are more common in elderly persons and in those who are cognitively impaired.[24]

COGNITIVE TESTS

Three tests of cognitive function were administered by trained research assistants during the baseline (visit 2) and follow-up visits. Trails B was administered to test attention, sequencing, visual scanning, and mental flexibility. Scores are measured in seconds to completion, with higher scores indicating slower performance.[25] Digit Symbol was administered to measure attention, psychomotor speed, and perceptual organization.[26] Scores on Digit Symbol reflect the number correct within the timed trial; higher numbers indicate better performance. A modified version of the Mini-Mental State Examination (MMSE) with a maximum score of 26 was administered to measure global cognitive function, including components for orientation, concentration, language, praxis, and immediate and delayed memory. Lower scores indicate poorer performance.[27] To assess clinically meaningful cognitive changes, we defined cognitive deterioration as present if a woman's score declined 3 or more points on the modified MMSE. We also determined which women had been told by their physician that they had a diagnosis of dementia during the 4-year follow-up period.

OTHER VARIABLES

All participants completed a questionnaire, interview, and examination at baseline and again 4 years later at the clinic or in their home. At the baseline visit, we ascertained age, highest level of education, average weekly alcohol use in the past 30 days, smoking history, physical activity in the past week (kilocalories per week expended on exercise), and marital status. Subjects were asked to rate their overall health compared with other women as excellent, good, fair, poor, or very poor. Functional status was assessed for each of 13 activities (eg, preparing meals, shopping, dressing, bathing, and walking 2-3 blocks) based on a modified version of the Stanford Health Assessment Questionnaire.[28] We defined functional impairment as being present if the respondent reported much difficulty with 1 or more of these activities. During each clinic examination, we measured weight and height; body mass index was defined as weight in kilograms divided by the square of the height in meters. Systolic and diastolic blood pressures were measured at the right brachial artery using a standard procedure. Participants were asked about current use of antidepressant medications (within the past 30 days); reports of current medications were checked by examining the labels of drugs.

STATISTICAL ANALYSIS

We compared the characteristics of the women by the presence of depressive symptoms (0-2, 3-5, or $\geq$6) at baseline, using an analysis of variance for continuous variables and χ^2 test for dichotomous variables. For the normally distributed cognitive outcomes (Trails B and Digit Symbol scores and change scores on all 3 tests), we performed analyses of covariance, with depressive symptoms as the independent variable. Because the baseline and follow-up modified MMSE scores were skewed, we analyzed the scores by using a nonparametric Kruskal-Wallis analysis. To account for baseline cognitive function influencing the rate of cognitive decline, cognitive change scores were calculated as raw change scores and after adjusting for the baseline score. In addition, multivariate models were used to adjust for the effects of education, age, health status, exercise, alcohol use, functional status, and clinic site by entering them as stepwise covariates. We performed logistic regression analyses to determine the association between depressive symptoms and clinically significant cognitive deterioration or physician-diagnosed dementia, adjusting for potential confounders. All analyses were performed using commercial software (SAS; SAS Institute, Inc, Cary, NC). All P values are 2-sided, with $P<.05$ considered statistically significant. Continuous variables are reported as mean ± SD.

Table 1. Baseline Characteristics of 5781 Women by Number of Depressive Symptoms at Baseline*

Characteristics	No. of Depressive Symptoms 0-2 (n = 5005)	3-5 (n = 565)	≥6 (n = 211)
Age, y	72.8 ± 4.7	74.0 ± 5.2	73.5 ± 4.8
Education, y	12.9 ± 2.7	12.1 ± 2.8	11.8 ± 2.9
Married, %	49.0	41.1	36.0
Diastolic blood pressure, mm Hg	77 ± 9	77 ± 10	77 ± 10
Body mass index, kg/m^2	26.2 ± 4.4	26.7 ± 5.2	27.2 ± 5.4
Functional difficulty, %	28.0	51.0	61.1
Self-reported excellent or good health, %	90.0	67.1	57.8
Drinks per week, No.	1.9 ± 3.8	1.5 ± 3.4	1.4 ± 3.1
Exercise, kcal/wk	1791 ± 1682	1417 ± 1603	1148 ± 1644
Antidepressant use, %	1.3	3.0	7.6

**Data are given as mean ± SD unless otherwise indicated. All comparisons are significant (P<.001) except for diastolic blood pressure (P=.16) and drinks (P=.04).*

Table 2. Cognitive Function Scores According to Number of Depressive Symptoms at Baseline and at Follow-up 4 Years Later*

Cognitive Test	No. of Depressive Symptoms 0-2 (n = 5005)	3-5 (n = 565)	≥6 (n = 211)
Trails B, s			
Baseline	120 ± 53	144 ± 70	143 ± 66
Follow-up	141 ± 66	171 ± 83	176 ± 80
Change	21 ± 53	27 ± 68	32 ± 58
Digit Symbol, No. correct			
Baseline	45.5 ± 10.7	40.3 ± 10.7	39.0 ± 11.3
Follow-up	42.7 ± 11.3	37.0 ± 11.5	35.5 ± 11.8
Change	−2.8 ± 7.3	−3.2 ± 7.0	−3.5 ± 7.2
Modified MMSE, No. correct			
Baseline	24.9 ± 1.4	24.6 ± 1.7	24.6 ± 1.7
Follow-up	24.6 ± 1.8	24.0 ± 2.2	23.8 ± 2.4
Change	−0.4 ± 1.9	−0.6 ± 2.3	−0.8 ± 2.5

**Data are given as mean ± SD. MMSE indicates Mini-Mental State Examination. For Digit Symbol and the modified MMSE, a higher score represents better performance; for Trails B, a lower score represents better performance. All comparisons were significant (P<.001) except the change scores for Digit Symbol (P = .18).*

cognitive function at baseline and with subsequent cognitive decline during several years. We used a depression scale designed for elderly persons that de-emphasizes symptoms that may overlap with dementia and depression. Our hypothesis was that, compared with women with few or no depressive symptoms, women with several or many depressive symptoms would have worse cognitive function at baseline and more cognitive decline.

RESULTS

Compared with women with few or no baseline depressive symptoms (0-2), women with more depressive symptoms were older, less educated, and less likely to be married (**Table 1**). Subjects with fewer depressive symptoms exercised more, were more likely to self-report good to excellent health, and were less likely to have functional impairment. Of the 5781 women, 211 (3.6%) had 6 or more depressive symptoms, of whom 16 (7.6%) reported taking antidepressant medications.

DEPRESSIVE SYMPTOMS ASSOCIATED WITH COGNITIVE FUNCTION

At baseline, women with more depressive symptoms had lower cognitive test scores than women with few symptoms (**Table 2**). More symptoms of depression were associated with worse baseline cognitive scores. When adjusted for education, age, health status, exercise, alcohol use, functional status, and clinic site, these differences remained statistically significant (Trails B: $F_{2,5218} = 12.4$; Digit Symbol: $F_{2,5617} = 20.5$; and modified MMSE: $\chi^2_2 = 17.0$ [$P<.001$ for all comparisons]).

Cognitive scores declined during follow-up in all women (Table 2). Women with more baseline depressive symptoms also had worse follow-up cognitive scores. These differences remained after multivariate adjustments for education, age, health status, exercise, alcohol use, functional status, and clinic site (Trails B: $F_{2,5218} = 12.3$; Digit Symbol: $F_{2,5617} = 20.8$; and modified MMSE: $\chi^2_2 = 54.4$ [$P<.001$ for all comparisons]).

EXTENT OF COGNITIVE DECLINE ACCORDING TO DEPRESSIVE SYMPTOMS

The change in cognitive scores was inversely associated with the number of baseline depressive symptoms (Table 2). Compared with women with 0 to 2 depressive symptoms, women with more depressive symptoms had a greater reduction in cognitive scores. These differences were significant after adjusting for baseline cognitive score (Trails B: $F_{2,5253} = 17.58$; Digit Symbol: $F_{2,5654} = 13.79$; and modified MMSE: $F_{2,5732} = 23.28$ [$P<.001$ for all comparisons]) and after adjusting for education, age, health status, exercise, alcohol use, functional status, and clinic site (Trails B: $F_{2,5217} = 3.64$ [$P = .03$]; Digit Symbol: $F_{2,5617} = 3.41$ [$P = .03$]; and modified MMSE: $F_{2,5693} = 8.44$ [$P<.001$]).

To minimize the effect of possible subclinical baseline cognitive impairments on our results, we repeated our analyses after excluding women who had a modified MMSE score of less than 20 (of a maximum score of 26) at baseline (n = 49) or who reported a history of physician-diagnosed stroke (n = 292), dementia (n = 89), or Parkinson disease (n = 57) at the time of follow-up testing. Excluding these women did not substantially affect the results.

BASELINE DEPRESSIVE SYMPTOMS AND CLINICALLY MEANINGFUL COGNITIVE OUTCOMES

To assess whether depressive symptoms were associated with greater clinically meaningful cognitive decline, we identified the women whose scores on the

Table 3. Association of Baseline Depressive Symptoms With Clinically Meaningful Cognitive Outcomes During the 4-Year Study: Results of the Unadjusted and Adjusted Analyses*

	Odds Ratio (95% CI)					
	Unadjusted			Adjusted		
	No. of Depressive Symptoms			No. of Depressive Symptoms		
Clinically Meaningful Outcome	0-2	3-5	≥6	0-2	3-5	≥6
≥3-Point decline on modified MMSE score (n = 653)	1.0	1.6 (1.3-2.1)	2.3 (1.6-3.3)	1.0	1.6 (1.2-2.1)	2.1 (1.4-3.1)
History of physician-diagnosed dementia at follow-up (n = 89)	1.0	2.3 (1.2-4.3)	3.0 (1.3-7.1)	1.0	1.7 (0.9-3.5)	2.3 (0.9-5.9)

**Adjusted for age, education, health status, exercise, alcohol use, functional status, and clinical site. CI indicates confidence interval; MMSE, Mini-Mental State Examination.*

modified MMSE declined 3 or more points. Compared with those whose scores declined less than 3 points, the 653 women whose scores showed a 3-point or more decline were older, less educated, and more functionally impaired ($P<.05$ for all comparisons, data not shown). Women with more than 2 symptoms of depression were more likely to have cognitive deterioration than those with few or no symptoms (**Table 3**). When adjusted for education, age, health status, exercise, alcohol use, functional status, and clinic site, the results were similar (Table 3). There was a "dose effect," with 3 to 5 symptoms having a small increased risk of cognitive deterioration and 6 or more symptoms having a greater risk of cognitive deterioration.

During the study, 89 women reported that their physician had told them that they had a diagnosis of dementia. A higher number of depressive symptoms was associated with greater odds of having a diagnosis of dementia (Table 3). Compared with women with 0 to 2 depressive symptoms, those with 3 to 5 symptoms had more than a 2-fold increase in dementia diagnosis, and those with 6 symptoms had a 3-fold increase in dementia diagnosis. Multivariate adjustments reduced the magnitude of this association somewhat, although the confidence intervals were wide (Table 3).

COMMENT

In this prospective study of elderly women without dementia, we found that women with depressive symptoms at baseline had poorer cognitive test performance, greater cognitive decline, and a greater risk of clinically meaningful cognitive deterioration at the 4-year follow-up. Because the subjects did not have dementia at baseline, we were able to demonstrate that the depressive symptoms preceded clinically significant cognitive impairment. We also demonstrated that there was a dose effect, with the number of depressive symptoms associated with a greater extent of cognitive impairment and decline.

Our results are supported by several studies[12-16,29] that have found an association of depression with a risk of dementia, but not by 2 studies[20,30] that investigated the association between depression and preclinical cognitive decline. In 1 of these studies,[30] depression was associated with worse cross-sectional cognitive scores in 1600 elderly subjects but not with a greater extent of cognitive decline. In that study, however, 34% of the surviving subjects did not have cognitive follow-up examinations, and the cognitive scores of subjects with follow-up improved during the 3-year study period. The lack of an association between depression and faster cognitive decline may have been due to a selection bias or to a practice effect.

Several methodological limitations of our study deserve comment. Nearly 16% of subjects did not have follow-up cognitive testing, and these women had lower cognitive function and a greater number of depressive symptoms at baseline. The women who did have follow-up testing were, therefore, more likely to be functioning at a higher level and less likely to have had significant baseline cognitive impairment. Although we used 3 standard scales to measure cognitive function and a standard scale for depressive symptoms, we did not examine women specifically to detect depression or cognitive decline. We doubt that such an evaluation would have changed our results because we used conservative criteria for clinically meaningful cognitive deterioration, and depressive symptoms are the hallmark of a diagnosis of clinical depression. Our study included ambulatory women, nearly all of whom were white, and we cannot determine whether our results apply to nonwhite women, less healthy women, or men. We are uncertain of the clinical implications of some of our results. For example, although small changes in cognitive test scores are of questionable clinical significance, we found depressive symptoms to be associated with 2 measures of cognitive decline, a history of a diagnosis of dementia or a decline in scores on the modified MMSE of 3 or more points, which have clearer clinical relevance.

What explains the association of depressive symptoms with greater cognitive decline? Patients with cognitive impairment, especially early dementia, may have depressive symptoms as a reaction to the loss of function associated with the cognitive deficits.[9] This may explain the high rate of depressive symptoms in patients with dementia, especially early in the course of their illness. We doubt that this is the explanation for our findings because the subjects in our study did not have dementia and were community-dwelling and ambulatory, and the association between depression and cognitive decline remained after adjusting for indices of health and functional status. Furthermore, when

we adjusted for baseline cognitive scores, those women with more depressive symptoms had greater change in cognitive scores.

Alternatively, depression can cause cognitive impairments (pseudodementia) and affect neuropsychological test results, which may resolve after the depression is treated.[5] If this were the explanation for our findings, we would have not have expected that those women with more depressive symptoms would have greater cognitive decline than those with fewer symptoms, once the cognitive change scores were adjusted for baseline score.

It is also possible that an underlying central nervous system alteration may cause both depressive symptoms and cognitive decline. Results from several research studies support an overlapping mechanism for dementia and depression in elderly persons. As many as 30% of patients with vascular dementia or Alzheimer disease have depressive symptoms.[9,31] Patients with Alzheimer disease with depression have more neuronal degeneration in brain areas implicated in depression (the locus ceruleus and raphe nuclei) than those without depression.[32] Changes in brain cortical areas have also been implicated in depression. Positron emission tomographic and single photon emission computed tomographic studies[33,34] have demonstrated a reduction in frontal lobe and limbic system blood flow in patients with primary and secondary depression, including those with depression and dementia. Elderly depressed patients have more white matter and other subcortical abnormalities on brain magnetic resonance images.[35,36] A neurodegenerative process such as Alzheimer disease, Parkinson disease, or vascular dementia may begin in frontal and limbic regions or involve serotonergic and noradrenergic pathways, and patients with one of these disorders may present with depressive symptoms early in the disease. Thus, depressive symptoms may be a prodromal or early symptom of a neurodegenerative disease. Or they might be a manifestation of a separate process that is associated with an increased risk for cognitive decline. We cannot distinguish between these 2 possibilities.

High levels of cortisol may be associated with depression and may also lead to neuronal death and cognitive decline.[37,38] Women with high cortisol levels or other manifestations of hypothalamic-pituitary-adrenal axis dysregulation might have depressive symptoms and poor cognitive function. It is also possible that depressive symptoms and cognitive decline are both due to an underlying genetic predisposition. For instance, the apolipoprotein E ε4 allele is a risk factor for Alzheimer disease and preclinical cognitive decline.[39,40] Some studies,[41] but not all,[20,42] have also found that apolipoprotein E ε4 is associated with an increased risk of geriatric depression.

The treatment of depressive symptoms may not only lessen the depression but also improve cognitive function and possibly other health outcomes. Few of our subjects, however, were taking antidepressants. Most elderly depressed patients are underdiagnosed and undertreated.[43] Studies[6,44] have found that the treatment of depression in elderly patients, whether it be pharmacological, behavioral, or other modalities, improves cognitive function. Whether the treatment of depressive symptoms can delay or prevent cognitive decline remains to be studied. In any case, depressive symptoms in elderly persons must be detected, and these patients should be observed closely, especially because of their increased risk for cognitive decline. Mechanisms underlying the association between these 2 common conditions—depressive symptoms and cognitive decline—need further exploration.

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