

Depressive Symptomatology and Incident Cognitive Decline in an Elderly Community Sample

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Background: It is not known whether depression is a cause or consequence of progressive cognitive decline. We assessed the relationship between depressive symptoms and subsequent cognitive decline in the community-dwelling elderly population.

Methods: Data were from a population-based cohort study that enrolled 2812 noninstitutionalized elderly residents of New Haven, Conn, and followed them with in-home visits in 1982, 1985, 1988, and 1994. Cognitive function was assessed with the Short Portable Mental Status Questionnaire (SPMSQ). Response to the SPMSQ was scored as high, medium, and low, and cognitive decline was defined as a transition to a lower category. Depressive symptoms were measured with the Center for Epidemiological Studies Depression Scale.

Results: An elevated level of depressive symptoms was associated with an increased risk of incident cognitive de-

cline among medium SPMSQ performers (3-year odds ratio [OR], 1.72; 95% confidence interval [CI], 1.04-2.82, $P=.03$; 6-year OR, 2.40; 95% CI, 1.33-4.34; $P=.004$; 12-year OR, 1.65; 95% CI, 0.62-4.38; $P=.31$) but not among high performers (3-year OR, 0.93; 95% CI, 0.62-1.39; $P=.71$; 6-year OR, 1.03; 95% CI, 0.67-1.58; $P=.90$; 12-year OR, 1.26; 95% CI, 0.59-2.71; $P=.55$), after adjustment for age, sex, race, education, income, housing type, functional disability, cardiovascular profile, and alcohol use.

Conclusions: Depressive symptoms, particularly dysphoric mood, presage future cognitive losses among elderly persons with moderate cognitive impairments. However, the data do not provide support for the hypothesis that depressive symptoms are associated with the onset or rate of cognitive decline among cognitively intact elderly persons.

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IT IS NOT known whether depression, particularly at subclinical levels, contributes to the onset or course of cognitive decline in old age or instead is a consequence of cognitive impairment. Epidemiologic studies have been primarily limited to cross-sectional investigations that are consistent in showing a positive correlation between depressive symptoms and poorer cognitive performance in putatively nondemented individuals,¹⁻³ as well as between depressive symptoms and severe cognitive deficits indicative of dementia in population-based samples,⁴⁻⁷ but reveal little about the causal direction of this association.

estimated 15% of the United States population older than 65 years.⁸ Clinical and neuropathologic studies suggest that Alzheimer disease (AD) accounts for at least 50% of dementia cases.⁹ Caring for dementia patients imposes enormous psychosocial and economic burdens on family and other caregivers.¹⁰ In the United States, the total societal cost of caring for all persons first diagnosed with AD in 1991 alone has been estimated at \$67.3 billion.¹¹ Aside from age and genetic factors,¹² there are few established risk factors for AD.⁹

Case-control investigations of depression and cognitive function have focused on AD patients. A pooled reanalysis of studies conducted before 1990 suggests that a history of medically treated depression occurring at least 1 year prior to AD

See also page 1082

Dementia, defined as chronic and substantial decline in 2 or more areas of cognitive function sufficient to interfere significantly with work, social activities, and interpersonal relationships, affects an esti-

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SUBJECTS AND METHODS

RESPONDENTS

The study population was drawn from the New Haven, Conn, site of the Established Populations for Epidemiologic Studies of the Elderly (EPESE) project, described in detail elsewhere.¹⁸ The New Haven cohort is a multistage probability sample of 2812 noninstitutionalized persons 65 years and older living in New Haven in 1982. Samples were drawn from 3 housing strata: public housing for elderly persons (age- and income-restricted), private housing for elderly persons (age-restricted), and community housing. All eligible men were sampled; women were randomly subsampled to achieve roughly equal representation of both sexes. The response rate at baseline was 82%. Trained lay examiners interviewed the cohort in their homes in 1982, 1985, 1988, and 1994 and by telephone in intervening years.

MEASURES

Cognitive Function

Cognitive performance was measured during in-home interviews with the 10-item Short Portable Mental Status Questionnaire¹⁹ (SPMSQ). (The original item "What is the name of this place?" was changed to "What is your address?" as this seemed more appropriate for community-dwelling residents.) Correct answers receive 1 point; possible scores range from 0 to 10. If 4 or more items were refused or missing, the SPMSQ was not scored. Otherwise, refusals were scored as incorrect, and scores on missing items were imputed by assigning the mean of nonmissing items. For some analyses, we trichotomized scores into 3 categories: high (9-10), medium (7-8), and low (0-6).

Depressive Symptomatology

The Center for Epidemiological Studies Depression Scale²⁰ (CES-D), a self-report measure of current depressive symptomatology, was administered during in-home interviews. Possible scores range from 0 to 60; higher scores indicate more severe symptoms. The conventional cutpoint of 16 was used to classify respondents as "depressed" or "nondepressed." For some analyses, depressed respondents were further subdivided into cases of "severe" (CES-D score ≥ 26) vs "mild/moderate" ($16 \leq$ CES-D score ≤ 25) depression based on tertiles of the CES-D distribution. An alternative scoring approach employed a diagnostic algorithm²¹ designed to capture the presence of dysphoria (low mood), considered the essential feature of clinical depression.²²

Covariates

The following self-reported variables were viewed as potential confounders because of their associations with depressive symptoms or cognitive function among New Haven²³ or other community-dwelling elders,^{4,16} or because of their status as established risk factors for vascular dementia,²⁴ the most common cause of progressive cognitive decline in elderly persons after AD²⁵: age (coded as a continuous covariate); sex; race (white or nonwhite); education (≥ 12 or < 12 years); yearly income ($< \$5000$, $\geq \$5000$, or missing); housing; functional disability (defined as requiring assistance with 1 or more activities of daily living²⁶ [walking across a room, dressing, eating, bed-to-chair transferring, bathing, using toilet]); cardiovascular profile (low- or high-risk, where high-risk is defined as a history of physician-diagnosed stroke, diabetes, myocardial infarction, or a measured sitting blood pressure of at least 160/95 mm Hg); and cigarette and alcohol consumption.

diagnosis is associated with an elevated risk of dementia in persons 70 years and older.¹³ However, a recent case-control study that paid closer attention to the temporal ordering between depression and dementia found that treated depression occurring more than 1 year prior to earliest AD symptoms did not predict AD onset.¹⁴ Two recently published cohort studies of depression and subsequent cognitive impairment also yield discrepant results. Devanand et al¹⁵ report that depressed mood was strongly predictive of incident AD among 478 individuals identified through a New York City dementia registry and followed from 1 to 5 years. In contrast, Dufouil et al¹⁶ found that depressive symptoms were not associated with cognitive deterioration during a 3-year period in a community-based sample of 1600 elderly French persons.

Given the inconclusive evidence, additional population-based longitudinal investigations are needed. We determined whether an elevated level of depressive symptomatology is predictive of an increased incidence of cognitive impairment or a faster rate of cognitive decline in a cohort of community-dwelling elderly persons. Clarifying the temporal relationship between depressive states and cognitive dysfunction may be helpful in elucidating the etiology of these conditions. Furthermore, given the fail-

ure of many primary care physicians to recognize or treat depression in elderly patients,¹⁷ a positive finding would suggest the need to incorporate depression screening into medical practice to identify individuals at high risk for cognitive decline and should stimulate investigation of the efficacy of various treatments for depression in slowing the rate of progressive cognitive impairment.

RESULTS

In 1982, 2754 (98%) of the 2812 respondents had valid SPMSQ scores (**Table 1**). At the 3-year assessment, 2030 respondents (87% of those alive) completed the SPMSQ. After 6 years, 1447 respondents (80% of those alive) were retested, and 756 (73% of those alive) had valid SPMSQ scores at the 12-year assessment.

At baseline, 2412 individuals had high or medium scores on the SPMSQ and were therefore at risk of cognitive decline (**Table 2**). The 342 low-scoring respondents were significantly more likely to be older, female, nonwhite, poor, disabled, less educated, live in public housing, abstain from alcohol, and have an elevated CES-D score than were higher scorers. Compared with nondepressed respondents, depressed individuals had a greater odds of low cognitive performance at baseline (age-

ANALYSES

Outcomes of interest are (1) onset of cognitive impairment and (2) course of cognitive change during the study period.

Depression and Onset of Cognitive Impairment

Cognitive decline was defined as a transition to a lower SPMSQ category (high to medium or low, or medium to low) during a given interval. Respondents with low SPMSQ scores at the beginning of an interval were excluded from consideration during that period.

Incidence of cognitive decline by initial depression status and SPMSQ category was estimated during intervals of 3 lengths: 1982 to 1985 and 1985 to 1988 (3 years); 1982 to 1988 and 1988 to 1994 (6 years); and 1982 to 1994 (12 years). Polytomous logistic regression was used to estimate the relative risk of cognitive decline or death in depressed vs nondepressed respondents, controlling for potential confounders. The 3 outcomes—maintenance of cognitive function, cognitive decline, and death—were treated as unordered categorical variables. Preliminary analyses showed that the magnitude of the depression effect was comparable for the two 3-year intervals, as were results from the two 6-year intervals. Thus, data from intervals of equal length were combined to achieve maximal power.

Sociodemographic covariates were included in multivariate models. To maximize efficiency, health-related covariates were retained only if the covariate was a significant predictor ($P < .05$) of decline in multivariate modeling or if its inclusion changed the magnitude of the depression coefficient by at least 10%. Accordingly, only smoking status was not included in final models. Values of time-varying covariates were updated at the start of each interval; when missing data occurred, values from the previous interval were substituted.

Depression and Mean Cognitive Performance Over Time

Multiple linear regression was used to estimate mean SPMSQ scores at the end of an interval as a function of depression status at the start of an interval, controlling for initial cognitive performance and confounders. The hypothesis that depression is associated with a more rapid rate of decline was tested by inclusion of interaction terms between initial depression status and indicator variables for length of time elapsed. If any covariate exhibited significant interactions with time, then these interactions were included before introducing the depression \times time terms. High or medium SPMSQ scorers with at least 1 subsequent test contributed data to reported analyses. Restricting analyses to respondents with 4 valid SPMSQ scores yielded little change in parameter estimates.

To eliminate the possibility that observed associations between elevated CES-D scores and cognitive performance were due solely to poor physical health without underlying psychological disorder, we also estimated the effect of dysphoric mood alone on cognitive decline. To address dose-response issues, we examined whether severity of a depressive episode and consistency of depression history would affect the likelihood of decline. In separate logistic models, we examined the depression-decline association in younger vs older respondents to determine if the relationship was stronger at older ages, as suggested by case-control data.¹³ In addition, because the cognitive manifestation of AD may be accentuated in the presence of vascular disease,²⁷ data were stratified by cardiovascular profile.

Computing was done using the statistical package SUDAAN, version 7.0.²⁸ The estimating equations approach²⁹ was used to adjust standard errors for the clustering due to the sampling scheme and repeated measurements. Estimates were weighted to reflect differential sampling, coverage, and response rates within housing and sex strata.

adjusted odds ratio [OR], 1.75; 95% confidence interval [CI], 1.19-2.57; $P = .005$), although the association was somewhat attenuated when the above covariates were controlled (OR, 1.37; 95% CI, 0.92-2.05; $P = .12$).

Among all at-risk respondents, those with elevated CES-D scores were more likely to decline cognitively in any given interval than were those with lower scores, though the increase in risk was statistically significant only for the 6-year interval (**Table 3**). On closer examination, the association between depression and subsequent decline seemed to be confined to respondents whose SPMSQ scores at the start of an interval were in the medium rather than high category. The significant association between depression and decline persisted in medium scorers after adjustment for potential confounders (**Table 4**). Depressed respondents were also more likely than nondepressed respondents to die than to maintain cognitive function, particularly during longer intervals.

To examine whether observed effects were related specifically to depressed mood rather than the cumulative number of symptoms, we performed the multivariate analyses with dysphoria as the predictor of interest. Among medium scorers, dysphoria was more strongly associated with cognitive decline than was an elevated total CES-D score. Compared with nondysphoric persons, medium scorers

with depressed mood had 1.76 times the odds of declining by the 3-year assessment (95% CI, 0.93-3.36; $P = .08$); such odds jumped to 2.57 by 6 years (95% CI, 1.30-5.08; $P = .007$), and to 2.91 by 12 years (95% CI, 1.00-8.42; $P = .05$). Among high scorers, there was no association between dysphoria and decline (3-year OR, 0.71; 95% CI, 0.44-1.15; $P = .16$; 6-year OR, 0.89; 95% CI, 0.52-1.51; $P = .66$; 12-year OR, 0.74; 95% CI, 0.30-1.80; $P = .50$).

To address the possibility that trichotomous classification of SPMSQ scores might have obscured small shifts in cognitive performance over time and to determine whether depression is associated with the rate of cognitive change, we also treated the SPMSQ as a continuous outcome variable in linear regression modeling. Initially depressed respondents turned in poorer cognitive performances at follow-up than did nondepressed respondents, though between-group differences were greatly attenuated after adjustment for covariates (**Table 5**). Consistent with the hypothesis that depression is associated with a more rapid rate of decline, the magnitude of the comparative deficit of the depressed group steadily increased with length of follow-up (from 0.15 to 0.20 to 0.44 SPMSQ points). However, depression \times time interactions were not statistically significant. Stratification by initial SPMSQ performance again reveals that the detrimental effect of de-

Table 1. Unweighted Distribution of Follow-up Status and Cognitive Performance on the Short Portable Mental Status Questionnaire (SPMSQ)

	No. (%)			
	Baseline, 1982	3-Y Follow-up, 1985	6-Y Follow-up, 1988	12-Y Follow-up, 1994
Valid SPMSQ	2754 (97.9)	2030 (72.2)	1447 (51.5)	756 (26.9)
Partial/proxy interview	58 (2.1)	136 (4.8)	224 (8.0)	186 (6.6)
Not interviewed	0 (0.0)	156 (5.5)	146 (5.2)	95 (3.4)
Deceased	0 (0.0)	490 (17.4)	995 (35.4)	1775 (63.1)
Total	2812 (100.0)	2812 (100.0)	2812 (100.0)	2812 (100.0)
Among those with valid SPMSQ				
SPMSQ category				
High	1643 (59.7)	1219 (60.0)	794 (54.9)	365 (48.3)
Medium	769 (27.9)	512 (25.2)	432 (29.9)	198 (26.2)
Low	342 (12.4)	299 (14.7)	221 (15.3)	193 (25.5)
Total	2754 (100.0)	2030 (100.0)	1447 (100.0)	756 (100.0)
Among high/medium scorers at baseline				
Mean \pm SD SPMSQ score	8.92 \pm 1.00	8.57 \pm 1.70	8.33 \pm 1.80	7.73 \pm 2.40
Decline from baseline, %*	NA	24.8	29.1	37.6

*Weighted percentages. NA indicates not applicable.

pression was observed exclusively among medium scorers. After adjustment for confounders, the main-effects estimate for depression among medium scorers was -0.44 points (95% CI, -0.78 to -0.09 ; $P=.01$); among high scorers, the corresponding estimate was -0.06 points (95% CI, -0.31 to 0.19 ; $P=.64$).

Severity of depressive symptoms did not exhibit a consistent relationship to the probability of cognitive decline across the 3 follow-ups. At the 3- and 6-year assessments, after adjustment for confounders, mildly to moderately depressed persons were at increased risk of decline compared with the nondepressed persons (3-year OR, 1.34; 95% CI, 0.95-1.89; $P=.09$; 6-year OR, 1.50; 95% CI, 1.04-2.16; $P=.03$), but severely depressed persons were not (3-year OR, 0.67; 95% CI, 0.39-1.16; $P=.15$; 6-year OR, 0.95; 95% CI, 0.43-2.13; $P=.91$). Conversely, by 12 years, the excess risk was confined to the severely depressed subgroup (OR, 3.32; 95% CI, 0.94-11.69; $P=.06$); mild/moderate depression was not associated with decline (OR, 1.02; 95% CI, 0.48-2.15; $P=.97$). These trends were far more pronounced among medium performers (data not shown).

Contrary to expectation, the depression-cognitive decline association was not stronger in respondents who exhibited a consistent history of depression (ie, who had high CES-D scores at 2 or more points prior to the interval during which cognitive change was assessed) as compared with those with only 1 prior elevated CES-D score (Table 6). Indeed, among medium performers, recent-onset depression (depression occurring at the start of an interval but not earlier) appeared to be as or more predictive of subsequent decline as a consistent history of depression. Furthermore, an isolated depressive episode occurring 3 to 6 years prior to the start of a given interval had less prognostic significance than recent-onset depression.

Stratified multivariate analyses of younger (65-74 years) and older (≥ 75 years) subgroups provide some support for the hypothesis that depression is a better predictor of cognitive decline in the older old, but only for

medium SPMSQ scorers. While depression was associated with an equivalent increase in risk after 3 years in both older (multivariate OR, 1.83; 95% CI, 0.92-3.61; $P=.08$) and younger medium scorers (OR, 1.80; 95% CI, 0.87-3.73; $P=.11$), the 6- and 12-year ORs jumped to 3.33 (95% CI, 1.51-7.34; $P=.003$) and 1.92 (95% CI, 0.37-10.10; $P=.44$), respectively, in the older subgroup but fell to 1.33 (95% CI, 0.55-3.19; $P=.53$) and 1.14 (95% CI, 0.31-4.16; $P=.84$) in the younger. However, depression \times age interactions were not statistically significant.

Stratification by cardiovascular profile reveals that the association between depression and cognitive decline was stronger among persons with high-risk profiles, but again only for medium SPMSQ scorers and only at longer intervals. Among medium scorers with high-risk cardiovascular profiles, the relative odds of decline associated with depression were 1.70 (95% CI, 0.78-3.70; $P=.18$) at 3 years, 3.19 (95% CI, 1.21-8.35; $P=.02$) at 6 years, and 6.42 (95% CI, 1.06-38.80; $P=.04$) at 12 years. Among medium scorers with a low-risk profile, the corresponding estimates were 1.67 (95% CI, 0.86-3.26; $P=.13$) at 3 years, 2.29 (95% CI, 1.08-4.85; $P=.03$) at 6 years, and 0.90 (95% CI, 0.27-3.02; $P=.86$) at 12 years. The depression \times cardiovascular profile interaction was significant ($P=.03$) in the 12-year analysis.

The clinical relevance of a medium SPMSQ score is ambiguous without knowledge of premorbid performance.¹⁹ Some respondents (eg, the less educated) would probably have "tested medium" throughout adulthood; their scores may not reflect incident impairment. For others, medium scores represent decline from higher levels of functioning. To examine more closely the relationship between depression and decline among medium scorers, we subdivided respondents with medium scores in 1985 or 1988 according to their baseline (1982) SPMSQ category. Among medium scorers who had previously performed at a higher level, the association between depression and subsequent decline was striking. That is, among persons with medium scores in 1985 but high scores in 1982, depres-

Table 2. Baseline Characteristics of 2412 Respondents at Risk of Cognitive Decline*

Characteristic	No. (%)†
Age, y	
65-74	1412 (61.5)
75-84	813 (31.7)
>85	187 (6.8)
Sex	
Male	1026 (37.2)
Female	1386 (62.8)
Education, y	
<12	1546 (59.6)
≥12	827 (39.1)
Yearly income, \$	
0 to <5000	803 (26.9)
5000 to <15 000	1119 (48.0)
≥15 000	223 (13.4)
Race	
White	1937 (83.3)
Nonwhite (90% black)	475 (16.7)
Housing	
Public	584 (8.1)
Private	748 (14.1)
Community	1080 (77.8)
Physical disability	
Yes	285 (9.8)
No	2127 (90.2)
Cardiovascular profile	
High risk	799 (31.0)
Low risk	1613 (69.0)
Current smoker	
Yes	512 (19.9)
No	1898 (80.0)
Drink alcohol in past month	
Yes	1258 (55.0)
No	1152 (44.9)
CES-D‡ score	
≥16	372 (15.4)
<16	2009 (83.4)
Dysphoria	
Yes	248 (10.2)
No	2129 (88.3)

*Unweighted sample sizes are given. Percentages are from the weighted data.

†Total number for each covariate may sum to less than 2412 (and percentages may sum to less than 100%) because of missing values.

‡Center for Epidemiological Studies Depression Scale.²⁰

sion in 1985 predicted decline during 1985 to 1988 (3-year OR, 4.91; 95% CI, 1.64-14.64; $P=.004$); similarly, among persons with medium scores in 1988 but high scores in 1982, depression in 1988 predicted decline during 1988 to 1994 (6-year OR, 5.48; 95% CI, 1.47-20.43; $P=.01$). On the other hand, among medium scorers whose performance history did not indicate a prior drop in cognitive function (ie, who had also scored medium at baseline), such depression had little prognostic significance with respect to future decline (3-year OR, 1.08; 95% CI, 0.28-4.20; $P=.92$; 6-year OR, 1.87; 95% CI, 0.35-10.16; $P=.47$).

COMMENT

Depressive symptoms, particularly dysphoric mood, were strongly predictive of subsequent decline among respondents with medium SPMSQ scores. However, this asso-

ciation was most marked in those medium scorers who had already experienced a decrement in cognitive performance (ie, who had transitioned from a baseline high to a medium SPMSQ category). Our interpretation is that the depression did not clearly precede, and may in fact have been a reaction to, eroding cognitive capacities. Supporting this interpretation is the finding that, in medium performers, recent-onset depression was more strongly associated with subsequent decline than a distal or even multiple past depressive episodes. Moreover, an elevated CES-D score was not associated with decline in cognitive function among respondents with the best initial SPMSQ scores. Overall, the data do not provide convincing support for the hypothesis that depression is a risk factor for cognitive decline or that it plays an etiologic role in the development of AD.

Our study has many strengths, most notably a prospective design with multiple direct assessments of depressive symptomatology and cognitive status, a large population-based inception cohort, and minimal loss to follow-up even after 12 years. These features allowed us to examine in more detail issues raised by earlier studies, including the role of initial cognitive status, the dose-response gradient (ie, severity and consistency of depressive symptoms), and potential dependence of the depression-cognitive decline relationship on age and cardiovascular profile.

Case-control investigations suggest that medically treated depression is a risk factor for AD,¹³ but methodologic limitations preclude a rigorous assessment of depression's hypothesized etiologic role. Exposure information was often obtained by family report, raising the possibility of recall bias. The timing of depression in relation to onset (as opposed to clinical diagnosis) of dementia is unclear. The question of whether untreated or undiagnosed depression is associated with incipient dementia has generally not been addressed. If individuals with depression secondary to underlying dementia are more likely to seek treatment than those with depression occurring in the absence of nascent dementia, a likely scenario,³⁰ then the depression-AD association would be inflated in such studies.

Longitudinal data on depression as a risk factor for dementia have been gathered primarily in small clinical samples of depressed patients already evincing pronounced cognitive deficits.³¹ However, 2 well-designed cohort studies have examined the issue. Devanand et al¹⁵ found that depressed mood was associated with a significant 2-fold risk of incident dementia, as diagnosed by standardized neuropsychological tests and evidence of impaired function. Excluding persons with moderate cognitive impairment at baseline did not attenuate the association; however, the relative risk that would have been observed had mildly impaired individuals, who comprised a disproportionate percentage of the sample, also been excluded was not reported. This study did not rule out depression as a prodromal feature of subclinical dementia. Dufouil et al¹⁶ reported no relationship between elevated CES-D scores and subsequent cognitive deterioration, defined as a drop of 5 or more points on the Mini-Mental State Examination.³² Unfortunately, the authors chose a conservative cutpoint (score ≥ 23) for clas-

Table 3. Depressive Symptomatology and Incidence of Cognitive Decline as Measured by a Transition to Lower Category on the Short Portable Mental Status Questionnaire (SPMSQ) Among Respondents Surviving to End of Designated Interval*

SPMSQ Category at Start of Interval	CES-D† Score ≥16		CES-D Score <16		Odds Ratio‡	95% Confidence Interval	P
	No.	% Decline	No.	% Decline			
3-y follow-up (1982-1985, 1985-1988)							
High or medium	433	28.6	2620	25.0	1.28	0.94-1.75	.12
High	247	29.6	1936	27.3	1.08	0.73-1.60	.70
Medium	186	27.3	684	17.4	1.77	1.10-2.84	.02
6-y follow-up (1982-1988, 1988-1994)							
High or medium	264	37.3	1697	29.8	1.55	1.11-2.15	.01
High	151	36.0	1248	32.3	1.23	0.82-1.86	.32
Medium	113	39.4	449	21.5	2.35	1.34-4.11	.003
12-y follow-up (1982-1994)							
High or medium	87	46.9	618	36.4	1.54	0.86-2.76	.15
High	59	49.6	468	37.7	1.55	0.78-3.11	.21
Medium	28	42.0	150	31.7	1.51	0.55-4.16	.42

*Unweighted sample sizes are given. Percentages and odds ratios are estimated from the weighted data.

†CES-D indicates Center for Epidemiological Studies Depression Scale.²⁰

‡Odds ratios are adjusted for age and SPMSQ category at start of interval.

Table 4. Adjusted Odds Ratios for Cognitive Decline or Death (vs Maintenance of Cognitive Function) According to Depression Status at Start of Interval (CES-D Score ≥16 vs CES-D Score <16)*

SPMSQ Category at Start of Interval	No.	Decline vs Maintain Function			Death vs Maintain Function		
		Odds Ratio†	95% Confidence Interval	P	Odds Ratio†	95% Confidence Interval	P
3-y follow-up (1982-1985, 1985-1988)							
High or medium							
Depressed	554	1.10	0.81-1.51	.54	1.13	0.81-1.58	.46
Nondepressed	3167						
High only							
Depressed	307	0.93	0.62-1.39	.71	1.32	0.85-2.05	.22
Nondepressed	2291						
Medium only							
Depressed	247	1.72	1.04-2.82	.03	1.02	0.64-1.61	.94
Nondepressed	876						
6-y follow-up (1982-1988, 1988-1994)							
High or medium							
Depressed	495	1.32	0.95-1.85	.10	1.61	1.18-2.20	.003
Nondepressed	2662						
High only							
Depressed	268	1.03	0.67-1.58	.90	1.61	1.06-2.44	.03
Nondepressed	1859						
Medium only							
Depressed	227	2.40	1.33-4.34	.004	1.70	1.08-2.67	.02
Nondepressed	803						
12-y follow-up (1982-1994)							
High or medium							
Depressed	341	1.40	0.76-2.56	.28	1.47	0.91-2.37	.11
Nondepressed	1799						
High only							
Depressed	196	1.26	0.59-2.71	.55	1.30	0.69-2.46	.41
Nondepressed	1261						
Medium only							
Depressed	145	1.65	0.62-4.38	.31	1.70	0.82-3.52	.15
Nondepressed	538						

*Unweighted sample sizes are given. Odds ratios are estimated from the weighted data. CES-D indicates Center for Epidemiological Studies Depression Scale.²⁰
 †Odds ratios are adjusted for age, Short Portable Mental Status Questionnaire (SPMSQ) category at start of interval, sex, race, education, income, housing type, functional disability, cardiovascular profile, and alcohol use.

Table 5. Effect of Depression (CES-D* Score ≥ 16) on Predicted Short Portable Mental Status Questionnaire (SPMSQ) Score Over Time Among Respondents With High or Medium SPMSQ Score at Start of Interval (Weighted Data)

	Adjusted for Age and Initial SPMSQ Category			Multivariate Model†		
	β	95% Confidence Interval	P	β	95% Confidence Interval	P
Interaction model						
Predicted difference in SPMSQ scores between subjects depressed and subjects not depressed at start of interval						
After 3 y	-.29	-0.52 to -0.06	.01	-.15	-0.37 to 0.07	.17
After 6 y	-.35	-0.65 to -0.06	.02	-.20	-0.49 to 0.09	.18
After 12 y	-.58	-1.26 to 0.10	.10	-.44	-1.09 to 0.22	.19
Predicted difference in effect of depressed mood at start of interval on SPMSQ score over time (depression \times time interaction)						
After 6 vs 3 y	-.06	-0.35 to 0.23	.69	-.05	-0.34 to 0.24	.75
After 12 vs 3 y	-.28	-0.96 to 0.39	.41	-.29	-0.94 to 0.37	.39
Main effects only model						
Predicted difference in SPMSQ score between subjects depressed and subjects not depressed at start of interval, averaged over all follow-up times						
	-.35	-0.57 to -0.12	.002	-.20	-0.42 to 0.01	.06

*CES-D indicates Center for Epidemiological Studies Depression Scale.²⁰

†Adjusted for age, initial SPMSQ category, sex, race, education, income, housing type, functional disability, cardiovascular profile, alcohol use, age \times time, and education \times time interactions.

sifying female respondents as depressed; if milder depressive episodes predict decline, as suggested by our and others' findings,^{13,15} then grouping individuals with mild symptoms and those with no symptoms into one unexposed category would dilute the observed association.

One possible explanation for the apparent discrepancy between our results and those of Devanand et al is that we used an epidemiologic screening instrument rather than clinical assessment to ascertain cognitive status. The limitations of using brief screeners to detect mild cognitive dysfunction are well known.³³ While the SPMSQ has good stability in the ostensible absence of true cognitive change,¹⁹ its responsiveness to small changes in cognition over time is unclear. Nevertheless, using the SPMSQ, we detected strong relationships between other known risk factors (eg, age, lack of education) and cognitive decline (data not shown, but see White et al³⁴), suggesting that a major nondifferential misclassification of cognitive change did not occur. Furthermore, we followed up the cohort for 12 years; because the median time from AD onset to death is 8 to 10 years,³⁵ many incident cases would have presumably progressed to moderate or severe dementia and thus been detected with high probability. The SPMSQ's validity as a measure of cognitive impairment has been assessed in a subsample of respondents at another EPESE site.³⁶ Participants received a detailed medical examination to determine the presence and severity of impairment. When the middle SPMSQ and mild impairment categories were excluded, the SPMSQ's sensitivity in identifying moderate or severe impairment was 85% and the specificity was 96%.³⁷

Although the SPMSQ seems to capture the presence of at least moderate cognitive dysfunction, it provides no indication of the underlying medical condition responsible for such impairment. However, AD and vascular dementia account for the majority of irreversible pathologic

cognitive decline in elderly populations.²⁴ Among medium performers, we found that the relationship between depression and decline was stronger in the presence of a high-risk cardiovascular profile. A history of hypertension has been linked to the development of AD as well as vascular dementia,³⁸ and cerebrovascular disease may potentiate the clinical expression of pathologic features of AD.²⁷ Moreover, depression increases the risk of other adverse outcomes (reoccurrence or death) in myocardial infarction³⁹ and stroke⁴⁰ patients. Given these findings, the observed interaction between depression and cardiovascular profile is not surprising. That we failed to detect any association between depressive symptoms and decline among those high SPMSQ performers at greatest risk for the outcome—either because of their cardiovascular history or advanced age—supports the conclusion that depression is not a risk factor for dementia among elderly respondents with no apparent cognitive impairment at baseline.

While the CES-D may be useful in quantifying the severity of depressive states, it does not yield clinical diagnoses, such as major depression, dysthymia, or transient grief reactions. When we employed a diagnostic rather than the traditional approach to scoring the CES-D, the association between depressive symptoms and cognitive decline was enhanced. That this occurred only among medium SPMSQ scorers, however, implies that lack of diagnostic specificity is not a compelling explanation for the negative findings among their higher-scoring counterparts. Furthermore, we observed no noticeable increase in risk of decline among high-scoring respondents with a consistent as opposed to a sporadic history of depressive symptoms. However, additional prospective investigations using comprehensive clinical assessments of both mood and dementing disorders are necessary to determine whether there are stronger relationships between specific clinical syndromes than might be surmised from our findings.

Table 6. Adjusted Odds Ratios for Cognitive Decline (vs Maintenance of Cognitive Function) on the Short Portable Mental Status Questionnaire (SPMSQ) According to Consistency of Depression History*

SPMSQ Category at Start of Interval	CES-D† Score ≥ 16 in Year(s)	Depression History	No.	Odds Ratio‡	95% Confidence Interval	P		
3-y follow-up (1985-1988)	High or medium	1982 and 1985	Consistent	66	0.98	0.45-2.13	.96	
		1982 only	Sporadic, past	92	1.74	0.97-3.11	.06	
		1985 only	Sporadic, recent	91	1.52	0.84-2.75	.16	
		No year	None	965	1.00	...		
	High only	1982 and 1985	Consistent	39	0.59	0.23-1.52	.28	
		1982 only	Sporadic, past	66	1.85	0.95-3.63	.07	
		1985 only	Sporadic, recent	48	1.19	0.57-2.50	.64	
		No year	None	736	1.00	...		
	Medium only	1982 and 1985	Consistent	27	3.00	0.86-10.51	.09	
		1982 only	Sporadic, past	26	2.49	0.64-9.67	.19	
		1985 only	Sporadic, recent	43	3.65	1.12-11.87	.03	
		No year	None	229	1.00	...		
	6-y follow-up (1988-1994)	High or medium	1982/1985§ and 1988	Consistent	35	1.54	0.54-4.36	.42
			1982/1985 only	Sporadic, past	70	0.95	0.46-1.94	.88
			1988 only	Sporadic, recent	49	1.28	0.61-2.70	.51
			No year	None	462	1.00	...	
High only		1982/1985 and 1988	Consistent	19	1.23	0.25-6.02	.80	
		1982/1985 only	Sporadic, past	51	0.88	0.41-1.90	.74	
		1988 only	Sporadic, recent	24	0.72	0.25-2.11	.55	
		No year	None	321	1.00	...		
Medium only		1982/1985 and 1988	Consistent	16	2.34	0.64-8.54	.20	
		1982/1985 only	Sporadic, past	19	1.01	0.18-5.78	.99	
		1988 only	Sporadic, recent	25	3.00	0.90-9.97	.07	
		No year	None	141	1.00	...		

*Unweighted sample sizes are given. Odds ratios are estimated from the weighted data.

†CES-D indicates Center for Epidemiological Studies Depression Scale.²⁰

‡Odds ratios are adjusted for age, SPMSQ category of start of interval, sex, race, education, income, housing type, functional disability, cardiovascular profile, and alcohol use. Results of logistic regression (deaths not included) were used.

§1982/1985 indicates at least 1 CES-D score of 16 or higher in 1982 or 1985.

The occurrence of missing data due to mortality and nonresponse is an inherent feature of longitudinal studies of elderly populations. In our sample, both depressive symptoms and lower cognitive scores at baseline were significantly associated with death; among survivors, lower cognitive performance was also associated with subsequent missing SPMSQ scores. If depression was a stronger predictor of (unobserved) decline among respondents who died or refused reinterview than among those who were retested, our estimates will be biased downward. Several procedures were used to evaluate the effect of the potential bias. When decline and death were combined into 1 category, or, alternatively, when respondents with partial or proxy interview at follow-up were assumed to have declined cognitively, the pattern of results remained essentially unchanged from that of Table 4.

The prevalence of depression among AD patients is markedly higher than in the general elderly population,³¹ although it is unclear whether dementia predisposes to depression more than other illnesses.⁴¹ Both psychosocial and physiologic explanations could account for this relationship. Depression could develop in reaction to the realization of one's failing capacities or could arise as a result of neuroanatomic damage in the brain.⁴² For

example, degenerative changes in the locus ceruleus are observed more frequently in AD patients with depression than in their nondepressed counterparts,⁴³⁻⁴⁵ a finding consistent with the catecholaminergic deficit hypothesis of depression.⁴⁶ We regard these as important areas for further examination.

In conclusion, the data from this population-based longitudinal study do not indicate that depressive symptoms are associated with the onset or rate of cognitive decline among cognitively intact community-dwelling elderly persons. On the other hand, the results do show that dysphoric mood strongly presages future cognitive losses among elderly persons with questionable cognitive status, ie, who may already be evincing some difficulties. Although the depression may be a consequence rather than cause of progressive decline, these data may be of use in forecasting the service needs and designing interventions for aged persons with mild or moderate cognitive deficits. Targeted depression screening of this subgroup may be warranted. However, while treatment for depression has other documented benefits for elderly persons with⁴⁷ and without⁴⁸ cognitive impairment, our findings should restrain expectations that such treatment will delay the onset of dementia or prevent future cognitive decline.

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REFERENCES

1. Rabbitt P, Donlan C, McInnes L, Watson P, Bent N. Unique and interactive effects of depression, age, socioeconomic advantage, and gender on cognitive performance of normal healthy older people. *Psychol Aging*. 1995;10:307-313.
2. LaRue A, Swan GE, Carmelli D. Cognition and depression in a cohort of aging men: results from the Western Collaborative Group Study. *Psychol Aging*. 1995; 10:30-33.
3. Jones KJ, Albert MS, Duffy FH, Hyde MR, Naeser M, Aldwin C. Modeling age using cognitive, psychosocial, and physiologic variables: the Boston Normative Aging Study. *Exp Aging Res*. 1991;17:227-242.
4. Scherr PA, Albert MS, Funkenstein HH, Cook NR, Hennekens CH, Branch LG, White LR, Taylor JO, Evans DA. Correlates of cognitive function in an elderly community population. *Am J Epidemiol*. 1988;128:1084-1101.
5. O'Connor DW, Pollitt PA, Roth M. Coexisting depression and dementia in a community survey of the elderly. *Int Psychogeriatr*. 1990;2:45-53.
6. Fuhrer R, Antonucci RC, Gagnon M, Dartigues JF, Barberger-Gateau P, Alperovitch A. Depressive symptomatology and cognitive functioning: an epidemiological survey in an elderly community sample in France. *Psychol Med*. 1992;22:159-217.
7. Forsell Y, Jorm AF, Winblad B. Association of age, sex, cognitive dysfunction, and disability with major depressive symptoms in an elderly sample. *Am J Psychiatry*. 1994;151:1600-1604.
8. Larson EB, Kukull WA, Katzman RL. Cognitive impairment: dementia and Alzheimer's disease. *Annu Rev Public Health*. 1992;13:431-449.
9. Bretelet MMB, Claus JJ, van Duijn CM, Launer LJ, Hofman A. Epidemiology of Alzheimer's disease. *Epidemiol Rev*. 1992;14:59-81.
10. George LK, Gwyther LP. Caregiver well-being: a multidimensional examination of family caregivers of demented adults. *Gerontologist*. 1986;26:253-259.
11. Ernst RL, Hay JW. The US economic and social costs of Alzheimer's disease revisited. *Am J Public Health*. 1994;84:1261-1264.
12. Plassman BL, Breitner JCS. The genetics of dementia in late life. *Psychiatr Clin North Am*. 1997;20:59-76.
13. Jorm AF, van Duijn CM, Chandra V, Fratiglioni L, Graves AB, Heyman A, Kokmen E, Kondo K, Mortimer JA, Rocca WA, Shalut SL, Soininen H, Hofman A. Psychiatric history and related exposures as risk factors for Alzheimer's disease: a collaborative re-analysis of case-control studies. *Int J Epidemiol*. 1991;20(suppl):43-47.
14. Speck CE, Kukull WA, Brenner DE, Bowen JD, McCormick WC, Teri L, Pfanschmidt ML, Thompson JD, Larson EB. History of depression as a risk factor for Alzheimer's disease. *Epidemiology*. 1995;6:366-369.
15. Devanand DP, Sano M, Tang MX, Taylor S, Gurland BJ, Wilder D, Stern Y, Mayeux R. Depressed mood and the incidence of Alzheimer's disease in the elderly living in the community. *Arch Gen Psychiatry*. 1996;53:175-182.
16. Dufouil C, Fuhrer R, Dartigues JF, Alperovitch A. Longitudinal analysis of the association between depressive symptomatology and cognitive deterioration. *Am J Epidemiol*. 1996;144:634-641.
17. Woolley DC. Geriatric psychiatry in primary care. *Psychiatr Clin North Am*. 1997; 20:241-260.
18. Cornoni-Huntley J, Ostfeld AM, Taylor JO, Wallace RB, Blazer D, Berkman LF, Evans DA, Kohout FJ, Lemke JH, Scherr PA, Korper SP. Established Populations for Epidemiologic Studies of the Elderly: study design and methodology. *Aging Clin Exp Res*. 1993;5:27-37.
19. Pfeiffer E. A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients. *J Am Geriatr Soc*. 1975;23:433-441.
20. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas*. 1977;1:385-401.
21. Schoenbach VJ, Kaplan BH, Grimson RC, Wagner EH. Use of a symptom scale to study the prevalence of a depressive syndrome in young adolescents. *Am J Epidemiol*. 1982;116:791-800.
22. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington, DC: American Psychiatric Association; 1994.
23. Berkman LF, Berkman CS, Kasl S, Freeman DH, Leo L, Ostfeld AM, Cornoni-Huntley J, Brody JA. Depressive symptoms in relation to physical health and functioning in the elderly. *Am J Epidemiol*. 1986;124:372-388.
24. Hebert R, Brayne C. Epidemiology of vascular dementia. *Neuroepidemiology*. 1995; 14:240-257.
25. Skoog I. Risk factors for vascular dementia: a review. *Dementia*. 1994;5:127-144.
26. Katz S, Downs TD, Cash HR, Grotz RC. Progress in the development of an index of ADL. *Gerontologist*. 1970;10:20-30.
27. Snowden DA, Grenier LH, Mortimer JA, Riley KP, Grenier PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer's disease. *JAMA*. 1997; 277:813-817.
28. Shah BV, Barnwell BG, Bieler GS. *SUDAAN User's Manual, Version 7.0*. Research Triangle Park, NC: Research Triangle Institute; 1996.
29. Zeger SL, Liang KY, Albert PS. Models for longitudinal data: a generalized estimating equation approach. *Biometrics*. 1988;44:1049-1060.
30. Henderson AS. Co-occurrence of affective and cognitive symptoms: the epidemiological evidence. *Dementia*. 1990;1:119-123.
31. Teri L, Wagner A. Alzheimer's disease and depression. *J Consult Clin Psychol*. 1992;60:379-391.
32. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975; 12:189-198.
33. Colsher PL, Wallace RB. Epidemiologic considerations in studies of cognitive function in the elderly: methodology and nondementing acquired dysfunction. *Epidemiol Rev*. 1991;13:1-27.
34. White L, Katzman R, Losonczy K, Salive M, Wallace R, Berkman L, Taylor J, Filenbaum G, Havlik R. Association of education with incidence of cognitive impairment in three established populations for the epidemiologic studies of the elderly. *J Clin Epidemiol*. 1994;47:363-374.
35. Walsh JS, Welch HG, Larson EB. Survival of outpatients with Alzheimer-type dementia. *Ann Intern Med*. 1990;113:429-434.
36. Albert MS, Smith LA, Scherr PA, Taylor JO, Evans DA, Funkenstein HH. Use of brief cognitive tests to identify individuals in the community with clinically diagnosed Alzheimer's disease. *Int J Neurosci*. 1991;57:167-178.
37. Field TS. Risk factors for change in the ability to perform basic activities of daily living among the elderly [dissertation]. Boston, Mass: Boston University School of Public Health; 1993.
38. Skoog I, Lernfelt B, Landahl S, Palmertz B, Andreasson L, Nilsson L, Persson G, Oden A, Svanborg A. 15-year longitudinal study of blood pressure and dementia. *Lancet*. 1996;347:1141-1145.
39. Carney RM, Freedland KE, Rich MW, Jaffe AS. Depression as a risk factor for cardiac events in established coronary heart disease: a review of possible mechanisms. *Ann Behav Med*. 1995;17:142-149.
40. Morris PLP, Robinson RG, Andrzejewski P, Samuels J, Price TR. Association of depression with 10-year poststroke mortality. *Am J Psychiatry*. 1993;150:124-129.
41. Alexopoulos GS, Abrams RC. Depression in Alzheimer's disease. *Psychiatr Clin North Am*. 1991;14:327-340.
42. Liston EH, Jarvik LF, Gerson S. Depression in Alzheimer's disease: an overview of adrenergic and cholinergic mechanisms. *Compr Psychiatry*. 1987;28: 444-457.
43. Zweig RM, Ross CA, Hedreen JC, Steele C, Cardillo JE, Whitehouse PJ, Folstein MF, Price DL. The neuropathology of aminergic nuclei in Alzheimer's disease. *Ann Neurol*. 1988;24:233-242.
44. Zubenko GS, Moosy J. Major depression in primary dementia: clinical and neuropathologic correlates. *Arch Neurol*. 1988;45:1182-1186.
45. Forstl H, Burns A, Luthert P, Cairns N, Lantos P, Levy R. Clinical and neuropathological correlates of depression in Alzheimer's disease. *Psychol Med*. 1992; 22:877-884.
46. Schildkraut JJ. The catecholamine hypothesis of affective disorders: a review of supporting evidence. *Am J Psychiatry*. 1965;122:483-497.
47. American Psychiatric Association. Practice guideline for the treatment of patients with Alzheimer's disease and other dementias of late life. *Am J Psychiatry*. 1997;154(suppl):1-33.
48. Blazer DG. Depression in the elderly: myths and misconceptions. *Psychiatr Clin North Am*. 1997;20:111-119.