Depressive Symptomatology and Incident Cognitive Decline in an Elderly Community Sample

Shari S. Bassuk, ScD; Lisa F. Berkman, PhD; David Wypij, PhD

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 decline 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.

Arch Gen Psychiatry. 1998;55:1073-1081

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, as well as between depressive symptoms and severe cognitive deficits indicative of dementia in population-based samples but reveal little about the causal direction of this association.

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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 estimated 15% of the United States population older than 65 years. Clinical and neuropathologic studies suggest that Alzheimer disease (AD) accounts for at least 50% of dementia cases. Caring for dementia patients imposes enormous psychosocial and economic burdens on family and other caregivers. 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. Aside from age and genetic factors, there are few established risk factors for AD.

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...
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. 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 sub-sampled 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 Questionnaire (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 Scale (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≤ CES-D score ≤25) depression based on tertiles of the CES-D distribution. An alternative scoring approach employed a diagnostic algorithm designed to capture the presence of dysphoria (low mood), considered the essential feature of clinical depression.

Covariates

The following self-reported variables were viewed as potential confounders because of their associations with depressive symptoms or cognitive function among New Haven others or other community-dwelling elders, or because of their status as established risk factors for vascular dementia, the most common cause of progressive cognitive decline in elderly persons after AD: age (coded as a continuous covariate); sex; race (white or nonwhite); education (≥12 or <12 years); yearly income (<$5000, ≥$5000, or missing); housing; functional disability (defined as requiring assistance with 1 or more activities of daily living [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.

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.

Computing was done using the statistical package SUDAAN, version 7.0.28 The estimating equations approach 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 X time interactions were not statistically significant. Stratification by initial SPMSQ performance again reveals that the detrimental effect of de-

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 X 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 underlyng psychologi-
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, 1.06; 95% CI, 0.30-1.16; 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 × 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, 1.08-4.83; P = .03) at 6 years, and 0.90 (95% CI, 0.27-3.02; P = .86) at 12 years. The depression × 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. 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>
<thead>
<tr>
<th>Table 1. Unweighted Distribution of Follow-up Status and Cognitive Performance on the Short Portable Mental Status Questionnaire (SPMSQ)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. (%)</strong></td>
</tr>
<tr>
<td>Valid SPMSQ</td>
</tr>
<tr>
<td>Partial/proxy interview</td>
</tr>
<tr>
<td>Not interviewed</td>
</tr>
<tr>
<td>Deceased</td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
<tr>
<td><strong>Among those with valid SPMSQ</strong></td>
</tr>
<tr>
<td><strong>SPMSQ category</strong></td>
</tr>
<tr>
<td>1982</td>
</tr>
<tr>
<td>1985</td>
</tr>
<tr>
<td>1988</td>
</tr>
<tr>
<td>1994</td>
</tr>
<tr>
<td><strong>Among high/medium scorers at baseline</strong></td>
</tr>
<tr>
<td>Mean ± SD SPMSQ score</td>
</tr>
<tr>
<td>Decline from baseline, %*</td>
</tr>
</tbody>
</table>

* Weighted percentages. NA indicates not applicable.

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Depressive symptoms, particularly dysphoric mood, were strongly predictive of subsequent decline among respondents with medium SPMSQ scores. However, this association 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, 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, 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. However, 2 well-designed cohort studies have examined the issue. Devanand et al 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 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).

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)†‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
</tr>
<tr>
<td>65-74</td>
<td>1412 (61.5)</td>
</tr>
<tr>
<td>75-84</td>
<td>813 (31.7)</td>
</tr>
<tr>
<td>&gt;85</td>
<td>187 (6.8)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1026 (37.2)</td>
</tr>
<tr>
<td>Female</td>
<td>1386 (62.8)</td>
</tr>
<tr>
<td>Education, y</td>
<td></td>
</tr>
<tr>
<td>&lt;12</td>
<td>1546 (59.6)</td>
</tr>
<tr>
<td>≥12</td>
<td>827 (30.1)</td>
</tr>
<tr>
<td>Yearly income, $</td>
<td></td>
</tr>
<tr>
<td>0 to &lt;5000</td>
<td>803 (26.9)</td>
</tr>
<tr>
<td>5000 to &lt;15 000</td>
<td>1119 (48.0)</td>
</tr>
<tr>
<td>≥15 000</td>
<td>223 (13.4)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1937 (83.3)</td>
</tr>
<tr>
<td>Nonwhite (90% black)</td>
<td>475 (16.7)</td>
</tr>
<tr>
<td>Housing</td>
<td></td>
</tr>
<tr>
<td>Public</td>
<td>584 (8.1)</td>
</tr>
<tr>
<td>Private</td>
<td>748 (14.1)</td>
</tr>
<tr>
<td>Community</td>
<td>1080 (77.8)</td>
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<tr>
<td>Physical disability</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>285 (9.8)</td>
</tr>
<tr>
<td>No</td>
<td>2127 (90.2)</td>
</tr>
<tr>
<td>Cardiovascular profile</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>799 (31.0)</td>
</tr>
<tr>
<td>Low risk</td>
<td>1613 (69.0)</td>
</tr>
<tr>
<td>Current smoker</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>512 (19.9)</td>
</tr>
<tr>
<td>No</td>
<td>1898 (80.0)</td>
</tr>
<tr>
<td>Drink alcohol in past month</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1258 (55.0)</td>
</tr>
<tr>
<td>No</td>
<td>1152 (44.9)</td>
</tr>
<tr>
<td>CES-D† score</td>
<td></td>
</tr>
<tr>
<td>≥16</td>
<td>372 (15.4)</td>
</tr>
<tr>
<td>&lt;16</td>
<td>2009 (83.4)</td>
</tr>
<tr>
<td>Dysphoria</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>248 (10.2)</td>
</tr>
<tr>
<td>No</td>
<td>2129 (88.3)</td>
</tr>
</tbody>
</table>

*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
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

<table>
<thead>
<tr>
<th>SPMSQ Category at Start of Interval</th>
<th>CES-D† Score ≥16</th>
<th></th>
<th>CES-D Score &lt;16</th>
<th></th>
<th>Odds Ratio‡</th>
<th>95% Confidence Interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>High or medium</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>433</td>
<td>28.6</td>
<td>2620</td>
<td>25.0</td>
<td>1.28</td>
<td>0.94-1.75</td>
<td>.12</td>
</tr>
<tr>
<td>High</td>
<td>247</td>
<td>29.6</td>
<td>1936</td>
<td>27.3</td>
<td>1.08</td>
<td>0.73-1.60</td>
<td>.70</td>
</tr>
<tr>
<td>Medium</td>
<td>196</td>
<td>27.3</td>
<td>684</td>
<td>17.4</td>
<td>1.77</td>
<td>1.10-2.84</td>
<td>.02</td>
</tr>
<tr>
<td>High or medium</td>
<td>264</td>
<td>37.3</td>
<td>1697</td>
<td>29.8</td>
<td>1.55</td>
<td>1.11-2.15</td>
<td>.01</td>
</tr>
<tr>
<td>High</td>
<td>151</td>
<td>36.0</td>
<td>1248</td>
<td>32.3</td>
<td>1.23</td>
<td>0.82-1.86</td>
<td>.32</td>
</tr>
<tr>
<td>Medium</td>
<td>113</td>
<td>39.4</td>
<td>449</td>
<td>21.5</td>
<td>2.35</td>
<td>1.34-4.11</td>
<td>.003</td>
</tr>
<tr>
<td>12-y follow-up (1982-1994)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High or medium</td>
<td>87</td>
<td>46.9</td>
<td>618</td>
<td>36.4</td>
<td>1.54</td>
<td>0.86-2.76</td>
<td>.15</td>
</tr>
<tr>
<td>High</td>
<td>59</td>
<td>49.6</td>
<td>468</td>
<td>37.7</td>
<td>1.55</td>
<td>0.78-3.11</td>
<td>.21</td>
</tr>
<tr>
<td>Medium</td>
<td>28</td>
<td>42.0</td>
<td>150</td>
<td>31.7</td>
<td>1.51</td>
<td>0.55-4.16</td>
<td>.42</td>
</tr>
</tbody>
</table>

* 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)*

<table>
<thead>
<tr>
<th>SPMSQ Category at Start of Interval</th>
<th>Decline vs Maintain Function</th>
<th>Death vs Maintain Function</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Odds Ratio‡</td>
</tr>
<tr>
<td>High or medium</td>
<td>554</td>
<td>1.10</td>
</tr>
<tr>
<td>Depressed</td>
<td>3167</td>
<td></td>
</tr>
<tr>
<td>Nondepressed</td>
<td>307</td>
<td>0.93</td>
</tr>
<tr>
<td>High only</td>
<td>2291</td>
<td></td>
</tr>
<tr>
<td>Depressed</td>
<td>247</td>
<td>1.72</td>
</tr>
<tr>
<td>Nondepressed</td>
<td>876</td>
<td></td>
</tr>
<tr>
<td>High only</td>
<td>495</td>
<td>1.32</td>
</tr>
<tr>
<td>Depressed</td>
<td>2662</td>
<td></td>
</tr>
<tr>
<td>Nondepressed</td>
<td>288</td>
<td>1.03</td>
</tr>
<tr>
<td>High only</td>
<td>1859</td>
<td></td>
</tr>
<tr>
<td>Medium only</td>
<td>237</td>
<td>2.40</td>
</tr>
<tr>
<td>Depressed</td>
<td>803</td>
<td></td>
</tr>
<tr>
<td>Nondepressed</td>
<td>341</td>
<td>1.40</td>
</tr>
<tr>
<td>High only</td>
<td>1799</td>
<td></td>
</tr>
<tr>
<td>Depressed</td>
<td>196</td>
<td>1.26</td>
</tr>
<tr>
<td>Nondepressed</td>
<td>1261</td>
<td></td>
</tr>
<tr>
<td>Medium only</td>
<td>145</td>
<td>1.65</td>
</tr>
<tr>
<td>Depressed</td>
<td>538</td>
<td></td>
</tr>
<tr>
<td>Nondepressed</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 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.
Multivariate Model†

the cohort for 12 years; because the median of cognitive change did not occur. Furthermore, we suggest that a major nondifferential misclassification might be surmised from our findings.

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. While the SPMSQ has good stability in the ostensible absence of true cognitive change, 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%.32

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.34 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. Moreover, depression increases the risk of other adverse outcomes (recurrence 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 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)

<table>
<thead>
<tr>
<th>Interaction model</th>
<th>Adjusted for Age and Initial SPMSQ Category</th>
<th>Multivariate Model†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>95% Confidence Interval</td>
</tr>
<tr>
<td>Predicted difference in SPMSQ scores between subjects depressed and subjects not depressed at start of interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After 3 y</td>
<td>−.29</td>
<td>−.52 to −.06</td>
</tr>
<tr>
<td>After 6 y</td>
<td>−.35</td>
<td>−.65 to −.06</td>
</tr>
<tr>
<td>After 12 y</td>
<td>−.55</td>
<td>−1.28 to 0.10</td>
</tr>
<tr>
<td>Predicted difference in effect of depressed mood at start of interval on SPMSQ score over time (depression × time interaction)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After 6 vs 3 y</td>
<td>−.06</td>
<td>−.35 to 0.23</td>
</tr>
<tr>
<td>After 12 vs 3 y</td>
<td>−.28</td>
<td>−.96 to 0.39</td>
</tr>
<tr>
<td>Main effects only model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predicted difference in SPMSQ score between subjects depressed and subjects not depressed at start of interval, averaged over all follow-up times</td>
<td>−.35</td>
<td>−.57 to −0.12</td>
</tr>
</tbody>
</table>

* CES-D indicates Center for Epidemiological Studies Depression Scale.30
† Adjusted for age, initial SPMSQ category, sex, race, education, income, housing type, functional disability, cardiovascular profile, alcohol use, age × time, and education × time interactions.
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, although it is unclear whether dementia predisposes to depression more than other illnesses. 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. For example, degenerative changes in the locus ceruleus are observed more frequently in AD patients with depression than in their nondepressed counterparts, a finding consistent with the catecholaminergic deficit hypothesis of depression. We regard these as important areas for further examination.

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

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

* Unweighted sample sizes are given. Odds ratios are estimated from the weighted data.
† CES-D indicates Center for Epidemiological Studies Depression Scale.
‡ 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.
Accepted for publication September 23, 1997.
This research was supported by grant T32-MH11719 (National Research Service Award to Dr Bassuk) from the National Institute of Mental Health, Rockville, Md, and by grants R01-AG11042, N01-AG02105, and N01-AG12102 from the National Institute on Aging, Bethesda, Md.

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