Association Between Depression and Mortality in Older Adults

The Cardiovascular Health Study

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Background: Studies of the association between depressive symptoms and mortality in elderly populations have yielded contradictory findings. To address these discrepancies, we test this association using the most extensive array of sociodemographic and physical health control variables ever studied, to our knowledge, in a large population-based sample of elderly individuals.

Objective: To examine the relation between baseline depressive symptoms and 6-year all-cause mortality in older persons, systematically controlling for sociodemographic factors, clinical disease, subclinical disease, and health risk factors.

Methods: A total of 5201 men and women aged 65 years and older from 4 US communities participated in the study. Depressive symptoms and 4 categories of covariates were assessed at baseline. The primary outcome measure was 6-year mortality.

Results: Of the 5201 participants, 984 (18.9%) died within 6 years. High baseline depressive symptoms were associated with a higher mortality rate (23.9%) than low baseline depression scores (17.7%) (unadjusted relative risk [RR], 1.41; 95% confidence interval [CI], 1.22-1.63). Depression was also an independent predictor of mortality when controlling for sociodemographic factors (RR, 1.43; 95% CI, 1.23-1.66), prevalent clinical disease (RR, 1.25; 95% CI, 1.07-1.45), subclinical disease indicators (RR, 1.35; 95% CI, 1.15-1.58), or biological or behavioral risk factors (RR, 1.42; 95% CI, 1.22-1.65). When the best predictors from all 4 classes of variables were included as covariates, high depressive symptoms remained an independent predictor of mortality (RR, 1.24; 95% CI, 1.06-1.46).

Conclusions: High levels of depressive symptoms are an independent risk factor for mortality in community-residing older adults. Motivational depletion may be a key underlying mechanism for the depression-mortality effect.

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The link between depression and mortality in older persons continues to be a hotly debated issue, with some investigators demonstrating that depression is an independent risk factor for mortality and others failing to find this association. Although researchers may argue about the reasons for these inconsistent findings (measures of depression used, sample used, the length of the observation period for ascertaining mortality, and choice of covariates), individuals in both camps would agree that a fair test of the depression-mortality hypothesis requires that known demographic and physical health status predictors of mortality be controlled. Moreover, the better and more extensive the health controls used in a study, the more conclusive would be a finding linking depression to mortality.

The Cardiovascular Health Study (CHS), a large population-based study of older persons, affords a unique opportunity to test the association between depression and mortality because of the extensive array of sociodemographic, objective clinical disease, subclinical disease, and health risk factor variables available as covariates. The association between more than 70 predictor variables and 5-year mortality for this sample was recently reported by Fried and colleagues. While Fried and colleagues used an exploratory approach, relying on stepwise Cox proportional hazards regression procedures to determine the best predictors of mortality, we use a more theoretical, hypothesis-based approach in this article. We extend the work of Fried and colleagues by testing specific multivariate models linking depression to 6-year mortality in this sample. Five distinct mod-
PARTICIPANTS AND METHODS

STUDY POPULATION

The sample used for this study was from the CHS, a prospective, observational study designed to determine the risk factors for and consequences of cardiovascular disease in older adults. Beginning in 1989, a total of 5201 men and women aged 65 years or older were recruited in 4 US communities: Forsyth County (North Carolina); Washington County (Maryland); Sacramento County (California); and Allegheny County (Penn). Potential participants were identified from a random sample stratified by age group (65-74, 75-84, and ≥85 years) from the Health Care Financing Administration Medicare Enrollment Lists. All persons thus identified and age-eligible household members who were planning to reside in the community for at least 3 years were eligible to participate. Exclusion criteria included being wheelchair bound in the home, being unable to participate in the examination at the field centers, or undergoing active treatment for cancer. Additional information regarding sampling and recruitment for the CHS has been published previously.20,21 The length of follow-up for this group was 6 years for the analyses reported herein.

EVALUATION

Extensive demographic and health information was collected by trained interviewers or by clinical examination. Level of depressive symptoms at baseline was assessed with the 10-item version of the Center for Epidemiological Studies Depression Scale (CES-D22,23). Covariates to be included in the models tested were chosen from 4 categories—sociodemographic factors, prevalent clinical disease, subclinical disease, and biological or behavioral risk factors. For each of these categories, a subset of covariates was chosen based on previous findings in the CHS sample showing that these are important indicators of health status19,24 within each of these categories. Table 1 provides a listing of variables examined in this study and descriptive information for these variables.

Study participants were followed up for an average of 6 years. Deaths were confirmed through reviews of obituaries, medical records, death certificates, and the Health Care Financing Administration health care use database for hospitations. Through these methods, and interviews of contacts and proxies for participants unavailable for follow-up, there was 100% complete follow-up ascertainment of mortality status.

ANALYTIC METHODS

The major focus of the analyses was the relation between depression and 6-year mortality, after controlling for other known demographic and physical health status predictors. Depression and the other covariates were assessed at baseline. To better understand potential modifiers of the depression-mortality link, we tested a series of Cox proportional hazards regression models in which covariates of 4 general types were also controlled (Table 1). Survival time was coded as number of days between the baseline interview and death or the last follow-up visit. Five models were tested: (1) the sociodemographic model, controlling for age, sex, race, educational level, marital status, and stressful life events; (2) the prevalent disease model, controlling for objectively measured prevalent clinical disease such as diabetes, congestive heart failure, and stroke; (3) the subclinical disease model, controlling for subclinical indicators of prevalent clinical disease such as claudication, major electrocardiographic abnormalities, and carotid stenosis; (4) the risk factor model, controlling for known biological and behavioral risk factors for mortality such as smoking status, fasting glucose level, and body mass index; and (5) the combined model, which controlled for all variables in the previous 4 models. Models 2 through 4, which proceed from the most proximal to more distal predictors of mortality, also controlled for sociodemographic variables. Models 1 through 4 were tested by entering all variables into the equation on a single step. The combined model (model 5) was tested by entering all variables except for depression on a first step, with significant predictors determined using a forward selection procedure (P=.05 for entry and P=.10 for removal), then forcing depression into the equation on a second step. Table 1 presents information for all variables used in the analysis, including coding schemes and descriptive statistics. Tables 2, 3, 4, 5, and 6 present results for the 5 Cox proportional hazards regression models tested, and show adjusted and unadjusted relative risk (RR) ratios (from a Cox proportional hazards model with only that variable as a predictor). Depression scores were dichotomized with a cutoff of 8 or higher, which corresponds to the cutoff of 16 or higher for risk for clinical depression on the 20-item version of the CES-D.

As seen in Table 1, there were differing levels of missing data on the various baseline indicators, with higher rates for subclinical disease and risk factor variables. Fried et al19 reported that variable estimates for their CHS mortality models were similar when using only participants with valid data vs replacing missing data and using all participants. Therefore, in the interests of clarity and simplicity, analyses were conducted only with participants who had no missing data, and thus the number of participants varies somewhat across models, ranging from 4710 (combined model) to 5173 (sociodemographic model). To test the proportional hazards assumption of the Cox proportional hazards model, the interaction of depression with survival time was computed and allowed to enter a model with all covariates. There was no violation of the assumption for depression.

The strength of this study lies in our ability to assess the relative risk of depression-related mortality in the context of specific classes of covariates that vary in their proximal relation to death, the careful measurement of predictors and outcome measures, and a large representative sample of community-residing older persons. In addition, 2 types of exploratory analyses are carried out to identify specific mecha-
nisms that might account for the depression-mortality effect.

**RESULTS**

For sociodemographic variables, participants ranged in age from 65 to 100 years at baseline (mean, 73 years); 57% were women, and 43% were men (Table 1). There was substantial variability on most of the prevalent disease, subclinical disease, and risk factor indicators. Approximately 20% of the sample met or exceeded the CES-D cutoff score for risk for clinical depression.

After 6 years of follow-up, there were 984 deaths, representing 18.9% of the total sample. There were 248 deaths (23.9%) among the 1036 participants with CES-D scores above the at-risk cutoff, while 734 (17.7%) of the 4156 participants below the cutoff had died within the follow-up period (unadjusted RR, 1.41; 95% confidence interval, 1.22-1.63). Depression scores for 2 of the persons who died were not available.

The sociodemographic model (Table 2) showed that participants who were older, male, less educated, and divorced, widowed, or separated were more likely to die. Controlling for sociodemographic characteristics, participants with a CES-D score higher than the cutoff score were also more likely to die. Similar to the unadjusted risk estimate, those with high depression scores had risks of mortality 43% higher than those with low depression scores. The prevalent disease model, shown in Table 3, revealed that participants with baseline angina, congestive heart failure, intermittent claudication, stroke, diabetes, and hypertension had higher mortality rates than...
participants without prevalent disease. Controlling for sociodemographic variables and prevalent clinical disease, individuals with high levels of depressive symptoms were more likely to die (25% higher risk). The subclinical disease model (Table 4) revealed that 6 of 7 subclinical disease indicators were independently predictive of 6-year mortality. Individuals with intermittent claudication, a lower forced expiratory volume, lower ankle-arm ratios, abnormal left ventricular ejection fractions, a major electrocardiographic abnormality, or carotid stenosis were more likely to die. Once again, controlling for sociodemographic factors and subclinical

<table>
<thead>
<tr>
<th>Variable</th>
<th>Descriptive Statistics*</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension‡</td>
<td>5185 (100.0)</td>
<td>...</td>
</tr>
<tr>
<td>Normotensive (reference)</td>
<td>2273 (43.8)</td>
<td>...</td>
</tr>
<tr>
<td>Borderline hypertensive</td>
<td>774 (14.9)</td>
<td>Random zero seated blood pressure: average systolic blood pressure of 140-159 mm Hg or diastolic blood pressure of 90-94 mm Hg</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>2138 (41.2)</td>
<td>Random zero seated blood pressure: average systolic blood pressure of &gt;160 mm Hg or diastolic blood pressure of &gt;95 mm Hg, or self-reported diagnosis by a physician and antihypertensive medication</td>
</tr>
<tr>
<td>Rose questionnaire for claudication‡</td>
<td>100 (1.9)</td>
<td>Positive or negative result for claudication at baseline</td>
</tr>
<tr>
<td>Rose questionnaire for angina‡</td>
<td>320 (6.2)</td>
<td>Positive or negative result for angina at baseline</td>
</tr>
<tr>
<td>Forced expiratory volume at 1 s, mL (N = 5111)</td>
<td>Mean, 2.1 (range, 0.3-4.5); SD, 0.7; median, 2.0</td>
<td>Measured during the baseline pulmonary function test</td>
</tr>
<tr>
<td>Ankle-arm ratio</td>
<td>5087 (100.0)</td>
<td>Minimum measure of right and left ankle-arm ratio measured in the clinic</td>
</tr>
<tr>
<td>0-0.9</td>
<td>4455 (87.6)</td>
<td>...</td>
</tr>
<tr>
<td>1-0.9</td>
<td>632 (12.4)</td>
<td>...</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td>5152 (100.0)</td>
<td>Based on echocardiographic readings by trained technicians</td>
</tr>
<tr>
<td>0 (normal or borderline)</td>
<td>4962 (96.3)</td>
<td>...</td>
</tr>
<tr>
<td>1 (abnormal)</td>
<td>190 (3.7)</td>
<td>...</td>
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<tr>
<td>Major electrocardiographic abnormality‡</td>
<td>1461/5028 (29.1)</td>
<td>Measured during the baseline electrocardiogram, any of the following: ventricular conduction defects, major Q- or QS-wave abnormalities, left ventricular hypertrophy, isolated major ST- or T-wave abnormalities, atrial fibrillation, or first-degree atrioventricular block</td>
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<tr>
<td>Carotid stenosis‡</td>
<td>2540/5171 (49.1)</td>
<td>Measured during baseline carotid ultrasonography as either of the following for left or right: carotid stenosis, &gt;25th percentile</td>
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<tr>
<td>Systolic blood pressure, mm Hg (N = 5191)†</td>
<td>Mean, 135.8 (range, 77-230); SD, 21.5; median, 134</td>
<td>Average of 2 readings, zero muddler systolic blood pressure</td>
</tr>
<tr>
<td>Total cholesterol level, mmol/L (mg/dL) (N = 5173)†</td>
<td>Mean, 5.55 (214.6) (range, 62-433); SD, 1.02 (39.3); median, 5.51 (213.0)</td>
<td>...</td>
</tr>
<tr>
<td>Low-density lipoproteins, mg/dL (N = 5101)†</td>
<td>Mean, 133.1 (range, 28-340); SD, 35.7; median, 131.0</td>
<td>...</td>
</tr>
<tr>
<td>Fasting glucose level, mmol/L (mg/dL) (N = 5165)†</td>
<td>Mean, 6.1 (110.2) (range, 2.9-36.5); SD, 1.9 (34.6); median, 5.6 (101)</td>
<td>...</td>
</tr>
<tr>
<td>Triglyceride level, mmol/L (mg/dL) (N = 5173)†</td>
<td>Mean, 1.61 (142.70) (range, 0.42-14.94 (37-1323)); SD, 0.89 (78.5); median, 1.39 (123)</td>
<td>...</td>
</tr>
<tr>
<td>Smoking status§</td>
<td>5198 (100.0)</td>
<td>Self-report at baseline</td>
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<tr>
<td>Never smoker (reference)</td>
<td>2397 (46.1)</td>
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</tr>
<tr>
<td>Former smoker</td>
<td>2200 (42.3)</td>
<td>...</td>
</tr>
<tr>
<td>Current smoker</td>
<td>601 (11.6)</td>
<td>...</td>
</tr>
<tr>
<td>Body mass index (N = 5185)¶</td>
<td>Mean, 26.4 (range, 14.7-53.2); SD, 4.5; median, 25.9</td>
<td>...</td>
</tr>
<tr>
<td>Alcohol consumption, drinks per week</td>
<td>5183 (100.0)</td>
<td>Number of alcoholic beverages (beer, wine, or liquor) consumed per week at baseline</td>
</tr>
<tr>
<td>0 (reference)</td>
<td>2489 (48.0)</td>
<td>...</td>
</tr>
<tr>
<td>1-7</td>
<td>2026 (39.1)</td>
<td>...</td>
</tr>
<tr>
<td>&gt;7</td>
<td>668 (12.9)</td>
<td>...</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) of participants unless otherwise indicated. Percentages may not total 100 because of rounding.
†Continuous variable.
‡Categorical or indicator variable.
§Categorical or dummy variable.
¶Dummy variable.
| Calculated as weight in kilograms divided by the square of height in meters.
disease, a high baseline depression score was an independent predictor of 6-year mortality (35% higher risk than those with low depression scores). The biological and behavioral risk factors model (Table 5) showed that individuals with a higher systolic blood pressure, those with higher levels of fasting glucose, current and former smokers, those with a lower body mass index, and those who consumed no alcoholic beverages had higher 6-year mortality rates. Consistent with the previous 3 models, once sociodemographic and risk factor variables were controlled, high depression scores were predictive of mortality (42% higher risk). Results from the combined model, shown in Table 6, revealed that even after controlling for the best predictors from all 4 classes of covariates (selected using a Cox proportional hazards regression forward selection technique), a high baseline depression score was an independent risk factor for 6-year mortality (24% higher risk than those with low depression scores). Table 6 also serves as a summary of the best overall predictors of 6-year mortality across all classes of variables.

To further explore the depression-mortality link, the Cox proportional hazards models were run using the 10 individual items from the CES-D in place of the single dichotomous variable. Depressive symptoms are rated for their frequency of occurrence in the week before the interview on a 4-point scale ranging from 0 (rarely or none of the time) to 3 (most of the time). We were interested in whether there were specific aspects of depression that were more predictive of mortality. These models consistently showed that there were 2 CES-D items that were independently predictive of 6-year mortality: (1) “I felt that everything I did was an effort” was a significant predictor of mortality in all 5 models (RR range, 1.12-1.32) and (2) “I felt blue most of the time” was also a significant predictor (RR range, 1.15-1.30).
(1.19), and (2) “I could not get going” was a significant independent predictor of mortality in 3 of the 5 models (RR range, 1.04-1.17). An additional attempt to help interpret the depression-mortality findings involved an exploratory analysis of other subjective self-assessments known to be related to mortality, such as self-assessed health status: “How would you say your health is?” Possible answers were (1) excellent, (2) very good, (3) good, (4) fair, or (5) poor. Interestingly, when this single indicator was included as a covariate in the combined model, the depression effect disappeared (RR, 1.11, \( P = .21 \)).

**COMMENT**

Using the most extensive array of sociodemographic and physical health control variables ever studied, to our knowledge, in a large population-based sample of elderly individuals, we show that depression is an independent risk factor for mortality in all 5 models tested. The risk of mortality was 25% to 43% higher among individuals with high levels of depressive symptoms in analyses examining the effects of depression on mortality in the context of sociodemographic factors, prevalent clinical disease, subclinical disease, and health risk factors, separately. When all predictors were combined, depression remained an independent risk factor for mortality (RR, 1.24). The full model showed that being older, male, less educated, and divorced, separated, or widowed were independent risk factors for mortality. Also, having hypertension, congestive heart failure, or stroke increased the risk of dying. Subclinical diseases, including intermittent claudication, a lower forced expiratory volume, a lower ankle-arm ratio, an abnormal left ventricular ejection fraction, a major electrocardiographic abnormality, and carotid stenosis, were also strong risk factors for mortality. Finally, 3 biological or behavioral risk factors, elevated fasting glucose level, being a current smoker, and low body mass index, were also risk factors for mortality.

Consistent with the observations of Lesperance and Frasure-Smith, our data show that older individuals do not need to have major depression to be at increased risk for mortality.
of mortality. Even milder or subthreshold forms of depression increase the risk of death in older persons.

What might mediate the relation between depression and mortality? A follow-up analysis of specific items of our depression measure showed that the depression-mortality effect is accounted for by a few items reflecting motivational depletion (I could not get going and I felt that everything I did was an effort). Similar items were identified in a study by Anda et al., who reported that wanting to give up and feeling that “I don’t have what it takes anymore” were independent predictors of mortality. These findings are consistent with a growing number of reports in the literature suggesting that factors such as vital exhaustion and decreased emotional vitality are linked to functional decline and mortality in older persons. Behavioral and pathophysiological mechanisms are plausible explanations for the link between affective or motivational states and mortality. Individuals who “give up” are likely to disengage from preventive and potentially restorative health behaviors and supportive relations. At the same time, or as a consequence of these behavioral changes, the neuroendocrine system may become disregulated and homeostatic immune functioning may be compromised. It is important that we pursue the mechanisms that account for the depression-mortality effect, and our pursuit of this goal would be facilitated by a better understanding and measurement of the affective and motivational states that underlie the depression-mortality link.

Although our data clearly support a depression-mortality link, we were also interested in identifying factors that might explain why some studies do not find this relation. There are many reasons why a specific study may not find a relation between depression and mortality, including the sample size, mortality rate, method for assessing depression, completeness of follow-up, length of the follow-up period, and choice of covariates. Our data suggest that one overlooked factor concerns the extent to which other self-report measures of health and functioning are included in the analysis. To the extent that the depression-mortality effect is driven by an underlying psychological state that includes elements of affect and motivation, we would expect its effects to be shared and diluted among a broad range of self-assessments, including perceived health, self-assessed functional status, and other indicators of subjective well-being. In general, studies that fail to find a depression-mortality link include multiple self-report indicators of functioning and other indicators of subjective well-being. In contrast, studies that show a significant association between depression and mortality typically rely on assessments of health and functioning based on relatively objective tests, ratings of study participants by an external evaluator, or both. This pattern is supported by our own data as well. As we would expect, once other self-report indicators of functioning and health are added to our multivariate model (eg, self-ratings of health), the significant depression effect disappears. This does not mean that the depression-mortality link is a statistical artifact, but rather it suggests that depression is one of several interrelated constructs that reflect the motivational and affective status of the individual and that these factors are in turn related to mortality.

From a clinical perspective, the findings from this study indicate that subthreshold levels of depression as measured by existing screening instruments should be taken seriously and further evaluated for possible treatment. Behavioral and medical interventions can be used to reduce these depressive symptoms and enhance quality of life and longevity in older persons.

Although this study represents a significant advance over existing literature in this area, it also has some limitations. First, we did not have available clinical diagnoses of depression or the psychiatric history of our respondents. The relation between clinical depression and mortality may actually be stronger than the relation between depressive symptoms and mortality observed in this study. Second, there is increasing evidence that depression...
pression may be linked specifically to cardiovascular mortality. Future analysis should focus on linking depression to specific causes of death, and this in turn will help us better understand the possible mechanisms linking depression to mortality. Finally, the limited psychosocial and behavioral data available in this study preclude a thorough exploration of the social and behavioral mechanisms underlying the depression-mortality effect. Identifying specific psychosocial and biological mechanisms that cause depressed persons to die prematurely should receive high priority in the next generation of studies in this area.

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