Mortality, Symptoms, and Functional Impairment in Late-Life Depression

Christopher M. Callahan, MD, Fredric D. Wolinsky, PhD, Timothy E. Stump, MA, Nancy A. Nienaber, MA, Siu L. Hui, PhD, William M. Tierney, MD

OBJECTIVE: To determine whether depressive symptoms measured at baseline are associated with mortality and to describe the course of depressive symptoms and their relation to physical decline in patients over a 6-year period.

DESIGN: Prospective cohort study conducted from 1990 through 1996.

SETTING: Urban academic primary care group practice.

PATIENTS: A cohort of 3,767 patients aged 60 years and older screened for depressive symptoms during routine office visits using the Centers for Epidemiologic Studies Depression Scale (CES-D) participated in the mortality study. A subsample of 300 patients with CES-D scores 16 or above and a subsample of 100 patients with CES-D scores less than 16 participated in the study of the course of depressive symptoms and physical decline.

MEASUREMENTS AND MAIN RESULTS: Mortality by December 1995 was measured for all screened patients; reinterviewed patients completed the CES-D and the Sickness Impact Profile (SIP). The mean follow-up period was 45 months ($\pm$ SD 12.2 months); 561 (14.9%) of the patients died by December 1995. In proportional hazards models, age, gender, race, history of smoking, serum albumin value, and an ideal body weight in the lowest 10% were significant correlates of time to death, but the baseline CES-D was not. Patients with depressive symptoms had significantly worse physical and psychosocial functioning scores on the SIP than did patients without depressive symptoms. Using the generalized estimating equation method, the strongest predictor of the current CES-D score was the patient's prior CES-D score. However, worsening physical functioning score on the SIP was also independently correlated with worse CES-D scores ($p \leq .001$).

CONCLUSIONS: Symptoms of depression were not associated with mortality in this cohort of older adults. However, patients with depressive symptoms reported greater functional impairment than did those without depressive symptoms. Moreover, decline in physical functioning was independently correlated with a concurrent increase in depressive symptoms.

KEY WORDS: late-life depression; mortality; symptoms; functional impairment.

J GEN INTERN MED 1998;13:746-752.

identifying depressive symptoms among community-based populations have typically not found an excess mortality among those subjects with significant symptoms of depression, while studies identifying criteria-based disorders in specialty psychiatry populations have reported excess mortality among patients with these disorders.¹⁸ Other studies have reported that among patients with specific medical conditions, those with depression have poorer clinical outcomes, including mortality.²⁰⁻²³

The Medical Outcomes Study demonstrated that the functioning and well-being of depressed patients is compromised as severely as that of patients with major chronic medical conditions.¹ That study also reported that the combination of depression with chronic medical conditions is associated with twice the reduction in social functioning associated with either condition alone. Furthermore, patients with significant symptoms of depression who do not meet criteria for major depression have been shown to suffer significant morbidity from these symptoms.^{1-5,19}

Previous studies, however, have not elucidated the etiology of the relation between chronic medical illness, depressive symptoms, and functional impairment. Furthermore, it has proven difficult to determine whether patients with depressive symptoms and functional impairment have a greater risk of mortality than patients with similar functional impairment but no depression.^{24,25} Information on these issues would inform treatment of depression in patients with chronic medical illness with regard to whether it may improve functioning and survival as well as mood.

This study had two specific aims. First, we sought to determine if depressive symptoms at baseline identify a group of older primary care patients with greater mortality over 5 years. Second, we sought to describe the course of depressive symptoms and their relation to physical decline over a 6-year period.

Numerous studies have consistently described excess physical illness, functional impairment, and morbidity among patients with depressive symptoms.¹⁻¹⁹ However, previous studies addressing whether depression is a risk factor for early mortality have reported conflicting results. Some of these conflicting results may be explained by important differences among studies in definitions of depression, study populations, attention to confounding clinical variables, and length of follow-up. For example, studies

Received from the Regenstrief Institute for Health Care (CMC, TES, NAN, SLH, WMT); Indiana University Center for Aging Research (FDW); Richard L. Roudebush VAMC and the Indiana University School of Medicine (CMC, SLH, WMT), Indianapolis, Ind.; and Saint Louis University School of Public Health, St. Louis, Mo. (WMT).

The opinions expressed herein are solely those of the authors and not necessarily those of the supporting institutions and agencies.

Address correspondence and reprint requests to Dr. Callahan: Regenstrief Institute for Health Care, 1001 W. 10th St., RG6, Indianapolis, IN 46202-2859.

METHODS

Mortality Study

The study site was an academic primary care group practice affiliated with the Indiana University School of Medicine. In 1991, this practice delivered primary care to more than 12,000 patients, resulting in approximately 40,000 outpatient visits per year.²⁶ The study was conducted in two phases from January 1991 to November 1996.

Phase 1 took place from January 1991 to June 1993. Of 4,413 patients aged 60 years and older making regularly scheduled primary care visits, 3,767 (85%) were screened for depression, dementia, and alcoholism. Prisoners were excluded, as were patients residing in a nursing home, those unable to speak English, and those who were hearing impaired. The screening instruments included the Center for Epidemiologic Studies Depression scale (CES-D),²⁷ the Short Portable Mental Status Questionnaire (SPMSQ),²⁸ and the CAGE alcoholism questionnaire.²⁹ Detailed methods and results of the screening program for these three conditions have been previously reported.^{19,30,31} Professional research assistants administered the study instruments in face-to-face interviews in the primary care clinic.

In addition to these screening data, we obtained clinical data from the Regenstrief Medical Record System.³² For screened patients, we determined history of smoking, the last available serum albumin level, and the percentage of ideal body weight using standard formulas and height and weight at the time of the baseline interview. These variables were chosen because of their reported association with mortality. Mortality for all 3,767 screened patients was determined as of December 1995 using hospital discharge condition, death summaries, autopsy reports, and the Indiana State Board of Health's death certificate files.

We used proportional hazards regression to determine if a baseline CES-D score of 16 or above was associated with mortality when controlling for age, gender, race, education, cognitive impairment (SPMSQ score ≥ 3 errors), evidence of alcohol dependency (CAGE score ≥ 2), history of cigarette smoking, serum albumin level, and percentage of ideal body weight. A score of 16 or greater on the CES-D indicates significant symptoms of depression (sensitivity, 80%; specificity, 72%) and is widely used as a screening threshold.^{27,33} We constructed three dummy variables for ideal body weight representing patients in the highest 10% of ideal body weight, the lowest 10%, and the 80% in the middle of the distribution. The middle range of ideal body weight was used as the reference category. The duration variable in the Cox proportional hazards model was the number of months from enrollment in the study until death or until December 1995, whichever came first. The main purpose of this Cox proportional hazards model was to determine if a patient's CES-D score was independently associated with mortality when

controlling for those variables previously reported in the literature to predict mortality among older adults.

Symptom Follow-up Study

Phase 2 of the study was conducted on a subsample of the original cohort of 3,767 patients described above in the mortality study. All patients who scored 16 or higher on the CES-D and a random sample of 100 patients who scored below 16 on the CES-D at baseline were invited to complete a second-stage extended interview within 2 weeks. Informed consent was obtained after explaining the risks and benefits of participation. The second-stage extended interview consisted of the Hamilton Depression Rating Scale (HAM-D)³⁴ and the Sickness Impact Profile (SIP).³⁵ The HAM-D is a 21-item questionnaire that measures severity of depressive symptoms. The range of scores on the HAM-D is 0 to 63 with scores of 10 to 20 indicating mild to moderate depression and scores above 20 suggesting more severe depression. We used the physical and psychosocial subscales of the SIP to measure the impact of illness on patients' quality of life and as a measure of overall functional status. The original SIP contains 140 items assessing 12 categories of functioning: sleep and rest, emotional behavior, body care and movement, home management, mobility, social interaction, ambulation, recreation and pastimes, communication, alertness behavior, work, and eating.

Of the 612 patients who exceeded the threshold on the CES-D, 300 (49%) agreed to participate in subsequent assessments. Eligible patients who declined to participate in the subsequent assessments did not differ significantly from enrollees by gender, race, education, percentage with cognitive dysfunction or evidence of alcohol dependency or mortality, but they were slightly older (68 vs 66 years, $p < .01$) and had slightly lower mean CES-D scores (24 vs 25, $p < .01$) than did study participants.¹⁹ Of the 3,155 patients who scored below 16 on the CES-D, we used a random list of patients to assemble a sample of 100 consecutively consenting patients (3%). Thus, a subsample of 400 patients in total participated in the follow-up study.

The follow-up study took place from January 1994 to November 1996 and included yearly follow-up interviews of the 400 patients. These subsequent assessments were completed by telephone by professional interviewers affiliated with the Indiana University Public Opinion Laboratory. The telephone interview consisted of the CES-D and the physical and psychosocial subscales of the SIP. Because patients were enrolled in the study over a 3-year period from 1990 through 1993, the duration of follow-up ranges from 6 to 51 months and the number of follow-up interviews ranges from 1 to 4.

We used the generalized estimating equation method,³⁶⁻³⁸ to determine if a decline in physical functioning was independently associated with worse symptoms of depression at follow-up. The formula summarizing this analysis is shown below:

$$\text{CESD}_n = \beta(\text{CES-D}_{n-1}) + \beta[(\text{SIP}_{n-1} + \text{SIP}_n)/2] + \beta(\text{SIP}_n - \text{SIP}_{n-1}) + \beta(\text{other clinical variables}),$$

where n is the follow-up assessment at time 1, 2, 3, or 4, and $n - 1$ is the prior assessment.

We chose the generalized estimating equation method (with an unstructured working correlation matrix) because this method allows us to examine change over time in patients' depression scores while accounting for the correlation among an individual patient's repeated measures, variable lag times between patients' assessments (due to variable enrollment dates, missed reassessments, and loss to follow-up), and multiple covariates. Rather than modeling an average change over two points in time (as would be necessary in a linear regression), the generalized estimating equation allows for multiple observations per patient and the fact that an individual patient's scores move up and down on individual scales over the various observation windows.

RESULTS

Among the 3,767 patients screened, the mean age was 68 years (range 60–102 years), 68.8% were women, 63.4% were African American, 43.6% had 8 years or less of education, 15.7% had cognitive dysfunction (≥ 3 SPMSQ errors), 10.5% had evidence of alcohol dependency (≥ 2 positive responses on CAGE), and 612 (16.2%) exceeded the threshold for depression (CES-D ≥ 16).

The mean follow-up period was 45 months ($\pm$ SD 12.2 months); 561 (14.9%) of the patients died by December 1995. Figure 1 displays the survival curve for patients with depressive symptoms at baseline as compared with patients without these symptoms at baseline controlling for the other clinical variables. In Cox proportional hazards models, age, gender, race, history of smoking, serum albumin level, and an ideal body weight in the lowest 10% were significant predictors of time to death (Table 1). The baseline CES-D score as a dichotomous variable (CES-D

FIGURE 1. Survival curves for patients with and without depressive symptoms at baseline.

Table 1. Results of Multivariate Proportional Hazards Regression of Time to Death for Baseline Cohort of 3,767 Older Adults

Variable	Risk Ratio	95% Confidence Interval
History of smoking*	1.79	1.50, 2.14
Age (years)	1.04	1.02, 1.05
Female	0.60	0.50, 0.71
Low ideal body weight†	1.82	1.46, 2.26
Serum albumin <3.5 g/dL*	1.52	1.26, 1.84
African American	0.79	0.66, 0.94
Cognitive impairment‡	1.21	0.96, 1.51
Evidence of alcohol dependency§	1.18	0.92, 1.52
Depressive symptoms	1.14	0.91, 1.42
Education (years)	1.00	0.98, 1.03
High ideal body weight¶	1.17	0.84, 1.62

*As recorded in patients' electronic medical record at time of baseline interview.

†Lowest decile of ideal body weight at time of baseline interview.

‡Three or more errors on Short Portable Mental Status Questionnaire.

§Two or more positive responses on CAGE alcoholism questionnaire.

||Score of ≥ 16 on Centers for Epidemiologic Studies Depression scale.

¶Highest decile of ideal body weight at time of baseline interview.

≥ 16) was not a significant predictor of time to death either when controlling for these other clinical variables or when it is the only independent variable in the proportional hazards model. To explore the sensitivity of our results to dichotomizing the CES-D score, we repeated the proportional hazards model by including three dummy variables to indicated CES-D scores of 6–15 (36% of patients); 16–24 (9%); and above 24 (7%); a fourth reference category was subjects with CES-D score of 0–5 (48%). This also failed to demonstrate an independent relation between mortality and higher CES-D scores.

Table 2 displays the baseline characteristics of the random sample of 100 older adults with CES-D scores below 16 and the 300 older adults with CES-D scores of 16 or higher who participated in the follow-up study. Patients with depressive symptoms more often were white, more often had history of smoking, had higher HAM-D scores and had worse physical functioning and psychosocial functioning in each domain of the SIP.

Patients with CES-D scores of at least 16 had a slightly higher rate of reinterview (88.7% vs 82%, $p = .04$). There was no difference in mean duration of follow-up (Table 3). Of the 52 patients (13%) not reinterviewed, 10 died within 1 year of their baseline interview and 22 died prior to December 1995. Patients with elevated CES-D scores at baseline were more likely to have elevated CES-D scores at follow-up. These patients were also more likely to rate their health as fair or poor (75.1% vs 49.4%, $p < .001$). Both groups reported worse function at the end of

Table 2. Baseline Characteristics of Older Adults With and Without Depressive Symptoms

Characteristic	CES-D $\geq 16^*$ (n = 300)	CES-D < 16* (n = 100)	p Value
Mean age, years	65.6 ($\pm$ 5.9)	66.5 ($\pm$ 6.7)	.20
Female, %	73.6	65.4	.11
White, %	46.5	30.7	.005
Mean education, years ($\pm$ SD)	9.5 ($\pm$ 3.3)	9.6 ($\pm$ 3.6)	.76
Cognitive impairment [†] , %	12.0	10.9	.76
Evidence of alcohol dependency, [‡] %	15.4	11.9	.38
Serum albumin < 3.5 g/dL, § %	17.4	20.8	.44
Smoking history, [§] %	38.5	25.7	.02
Mean HAM-D score ($\pm$ SD)	17.8 ($\pm$ 7.0)	7.6 ($\pm$ 5.1)	.001
SIP physical scale score [¶] ($\pm$ SD)	23.2 ($\pm$ 14.2)	12.8 ($\pm$ 12.8)	.001
Subscale scores ($\pm$ SD)			
Body care and movement	41.8 ($\pm$ 29.6)	20.7 ($\pm$ 25.3)	.001
Mobility	13.0 ($\pm$ 13.0)	6.3 ($\pm$ 10.9)	.001
Activity	24.9 ($\pm$ 12.5)	17.0 ($\pm$ 13.0)	.001
SIP psychosocial scale score [¶] ($\pm$ SD)	32.2 ($\pm$ 18.5)	12.4 ($\pm$ 12.6)	.001
Subscale scores ($\pm$ SD)			
Emotional/behavioral	26.6 ($\pm$ 17.3)	7.8 ($\pm$ 9.9)	.001
Social interaction	43.9 ($\pm$ 37.7)	14.8 ($\pm$ 19.6)	.001
Alertness behavior	37.8 ($\pm$ 24.6)	16.6 ($\pm$ 19.7)	.001
Communication	17.3 ($\pm$ 16.3)	8.8 ($\pm$ 14.6)	.001

*Centers for Epidemiologic Studies Depression scale.

[†]Three or more errors on Short Portable Mental Status Questionnaire.

[‡]Two or more positive responses on CAGE alcoholism questionnaire.

[§]As recorded in patients' electronic medical record at time of baseline interview.

^{||}Hamilton Depression Rating scale.

[¶]Sickness Impact Profile.

the follow-up period, and patients with CES-D scores of 16 or higher at baseline continued to report greater impairment than those patients without significant depressive symptoms (Table 3). The magnitude of these differences in functioning were similar to those found at baseline.

In a model of the patient's CES-D score at the end of an observation interval as a function of the patient's CES-D score at the beginning of the observation interval, the change in SIP physical functioning score over that interval, the mean SIP score for that interval, and other baseline clinical variables, the strongest predictor of the current

Table 3. Last Reinterview Results Among Older Adults With and Without Depressive Symptoms Participating in Follow-up Study*

Variable	CES-D $\geq 16^†$ (n = 266)	CES-D < 16† (n = 82)	p Value
Mean length of follow-up, months ($\pm$ SD)	39.0 ($\pm$ 18.7)	37.5 ($\pm$ 12.7)	.39
CES-D [†] score ≥ 16 at last follow-up interview, %	48.5	16.0	.001
SIP physical scale score [‡] ($\pm$ SD)	26.1 ($\pm$ 15.9)	15.8 ($\pm$ 14.5)	.001
Subscale scores ($\pm$ SD)			
Body care and movement	44.6 ($\pm$ 34.1)	27.2 ($\pm$ 30.2)	.001
Mobility	20.5 ($\pm$ 16.6)	11.2 ($\pm$ 13.5)	.001
Activity	26.7 ($\pm$ 14.4)	17.8 ($\pm$ 14.3)	.001
SIP psychosocial scale score [‡] ($\pm$ SD)	35.9 ($\pm$ 22.6)	16.3 ($\pm$ 16.3)	.001
Subscale scores ($\pm$ SD)			
Emotional/behavioral	22.9 ($\pm$ 16.3)	10.9 ($\pm$ 11.0)	.001
Social interaction	47.3 ($\pm$ 39.1)	22.0 ($\pm$ 28.6)	.001
Alertness behavior	35.7 ($\pm$ 25.2)	14.7 ($\pm$ 18.1)	.001
Communication	19.7 ($\pm$ 19.7)	9.2 ($\pm$ 14.8)	.001

*Using data from last follow-up interview for patients with at least one follow-up interview.

[†]Center for Epidemiologic Studies Depression scale.

[‡]Sickness Impact Profile.

CES-D score was the patient's CES-D score at the previous interview (Table 4). Changes in SIP physical functioning score and mean SIP physical functioning score were also independently correlated with change in the CES-D score over that same interval (Table 4). In a similar model including the three subscale scores composing the SIP physical functioning score, only changes in the body care and movement subscale and the mobility subscale were independently correlated with change in the patient's CES-D score. We did not use the psychosocial subscales in these models because of the substantial overlap in individual items among these scales and the CES-D items.

DISCUSSION

This study had two major findings. First, depressive symptoms were not associated with mortality in a cohort of 3,767 primary care patients. Second, among a representative subsample of 400 of these older adults, patients with depressive symptoms at baseline reported nearly twice the functional impairment of older adults without depressive symptoms, and these patients were more likely to report depressive symptoms and functional impairment at subsequent reinterviews. Also, worse physical functioning and a reported decline in physical functioning were independently correlated with an increase in depressive symptoms, even when accounting for patients' prior level of depressive symptoms.

This study builds on the results of previous reports by following a large primary care sample of older adults for up to 6 years, explicitly documenting the change in depressive symptoms and functional impairment over time, and examining risk of mortality while controlling for a host of confounding clinical variables known to increase risk of death.

In a 1992 review, Thomas et al. suggested that prior studies reporting such an association between depressive symptoms and mortality among older adults tended to enroll patients from specialty psychiatry settings who meet criteria-based definitions of depressive disorders.¹⁸ These studies often failed to control for important clinical covariates such as comorbid conditions or smoking history.

Prior studies reporting no association between depression and mortality have tended to enroll community-based samples and measure depression severity using symptom-based scales. For example, in a study of 1,855 community-based older adults, Thomas et al. found no association between depressive symptoms at baseline and survival time over 3 years.¹⁸ Similarly, in a population-based study of 1,612 adults aged 50 years and older, Gallo et al. found no increase in the relative risk of 13-year mortality among patients with major depression or with depression syndrome with sadness.³⁹ In contrast, in a population-based study of 3,560 people, those with major depressive disorder determined using the Diagnostic Interview Schedule had an increased relative risk of death in proportional hazards models adjusted for age only.⁴⁰

The current study extends these prior reports by enrolling a large sample of primary care patients aged 60 years and older for whom we had access to several important clinical variables previously demonstrated to predict mortality in older adults.^{41–43} The patient sample enrolled in the current study is older and, because we enrolled subjects visiting primary care clinics, likely had a greater burden of medical illness. Thus, these patients have a higher expected mortality and multiple competing potential causes of death. Nonetheless, we found no association between depressive symptoms and mortality. The strongest predictors of mortality in this cohort were smoking history, greater age, male gender, and evidence of poor nutrition.

Although mortality rates did not differ between those with and those without depressive symptoms at baseline, patients with depressive symptoms did report significantly greater physical impairment. This impairment was reported for relatively high levels of functioning, such as communication and social interaction, as well as for more basic functioning such as body care. The disparity in functional impairment between those with and those without depressive symptoms persisted several years after the baseline interview.

The observation of excess physical disability among the patients with depressive symptoms presents a paradox. Because previous studies have demonstrated that functional impairment is associated with survival, one

Table 4. Results of Generalized Estimating Equation Method of Measuring the Association Between Various Factors and the CES-D Score at Follow-up*

Variable	Estimate	SE	z Score	p Value
Intercept	10.20	3.7	2.7	.007
CES-D score [†]	0.39	0.03	13.9	.000
Change in physical scale score [‡]	0.24	0.02	9.5	.000
Mean physical scale score [‡]	0.20	0.02	8.9	.000

*Model 1, using physical functioning scale summary score. Variables included in models but not significant: age, gender, race, ≥ 3 errors on Short Portable Mental Status Questionnaire, ≥ 2 positive responses on CAGE alcoholism questionnaire.

[†]Centers for Epidemiologic Studies Depression score at beginning of follow-up interval.

[‡]Change in Sickness Impact Profile scale score over the follow-up interval.

would have expected to find that patients with depressive symptoms had excess mortality at least in part due to their reported excess functional impairment.⁴¹⁻⁴³ The SIP instructions specifically ask if it is because of the patients' health that they are unable to perform the activity.³⁵ The fact that we did not find this association raises the question of whether these patients' depressive symptoms caused them to overestimate their physical impairment⁴⁴—a possibility that merits future research.

One reason for overestimating physical impairments may be the patients' attempts to explain or express their impairment on the basis of physical rather than psychiatric illness. Alternatively, their physical impairment could be quite real, but because part of the etiology of this impairment is an affective disorder, the excess physical impairment may not confer the same excess mortality attributable to physical impairment due to chronic medical illness.

There are several limitations with these data. First, we measured symptoms of depression rather than criteria-based diagnoses. It is possible that patients with criteria-based major depressive disorder do have excess mortality due to their affective disorder; these data cannot address this issue. Also, it is conceivable that patients with depressive symptoms were more likely both to move out of state and to die, thereby causing misclassification bias. Second, among the reinterview sample, some patients have longer follow-up and more reinterviews and thus contribute more observations to the analysis using the generalized estimating equation method. However, we repeated our analyses limiting the data to only one observation per patient, and the results were unchanged. Third, our study of the relation of depressive symptoms to function is limited to 400 of the larger screened sample of 3,767 older adults. Finally, we did not determine whether worsening function preceded an increase in depressive symptoms, or vice versa.

Consistent with previous studies, the best predictor of future severity of depressive symptoms was prior level of depressive symptoms.^{8,10,13,25,45-52} However, declining functional status was also associated with worsening depressive symptoms. Thus, there were aspects of depressive symptoms and functional disability that were not associated with excess mortality. Future studies should seek to determine if successful treatment of late-life depression results not only in a reduction in depressive symptoms, but also improvement in physical function. This is especially important among the cohort of older adults treated in primary care settings because these patients typically suffer from multiple chronic medical illnesses that contribute to functional impairment. Finally, consideration must be given to the possibility that psychiatric and physical symptoms each simply occur together and contemporaneously to some degree in each patient.⁵³ This possibility places a premium on treatment strategies and health systems capable of addressing the full range of patients' problems simultaneously.^{54,55}

Dr. Callahan was supported by grant K08 AG00538-04 from the National Institute of Health and a Paul Beeson Physician Faculty Scholar in Aging Research Award. Dr. Wolinsky was supported by grant R37 AG09692 from the National Institutes of Health. Dr. Tierney was supported by grants HS07632 and HS07763 from the Agency for Health Care Policy and Research.

REFERENCES

1. Wells KB, Stewart A, Hays RD, et al. The functioning and well-being of depressed patients. *JAMA*. 1989;262(7):914-9.
2. Broadhead WE, Blazer DG, George LK, Tse CK. Depression, disability days and days lost from work in a prospective epidemiologic survey. *JAMA*. 1990;264(19):2524-8.
3. Johnson J, Weissman MM, Klerman GL. Service utilization and social morbidity associated with depressive symptoms in the community. *JAMA*. 1992;267:1478-83.
4. Ormel J, Von Korff M, Ustun TB, Pini S, Korten A, Oldehinkel T. Common mental disorders and disability across cultures. Results from the WHO Collaborative Study on Psychological Problems in General Health Care. *J Am Med Assoc*. 1994;272:1741-8.
5. Spitzer RL, Kroenke K, Linzer M, et al. Health-related quality of life in primary care patients with mental disorders. *JAMA*. 1995;274:1511-7.
6. Hirshfield RMA, Keller MB, Panico S, et al. The National Depressive and Manic-Depressive Association Consensus Statement on the Undertreatment of Depression. *JAMA*. 1997;277:333-40.
7. Bruce ML, Seeman TE, Merrill SS, Blazer DG. The impact of depressive symptomatology on physical disability. *Am J Public Health*. 1994;84:1796-9.
8. Rapp SR, Parisi SA, Wallace CE. Comorbid psychiatric disorders in elderly medical patients: a 1-year prospective study. *Am Geriatr Soc*. 1991;39:124-31.
9. Berkman LF, Berkman CS, Kasl S, et al. Depressive symptoms in relation to physical health and functioning in the elderly. *Am J Epidemiol*. 1986;124:372-88.
10. Kukull WA, Koepsell TD, Inui TS, et al. Depression and physical illness among elderly general medical clinic patients. *J Affect Disord*. 1986;10:153-62.
11. Katz IR. On the inseparability of mental and physical health in aged persons. Lessons from depression and medical comorbidity. *Am J Geriatr Psychiatry*. 1996;4:1-6.
12. Callahan CM, Wolinsky FD. Hospitalization for major depression among older Americans. *J Gerontol*. 1995;50A:M196-202.
13. Callahan CM, Hui SL, Nienaber NA, Musick BS, Tierney WM. Longitudinal study of depression and health services use among elderly primary care patients. *J Am Geriatr Soc*. 1994;42:833-8.
14. Borson S, Barnes RA, Kukull WA, et al. Symptomatic depression in elderly medical outpatients. Prevalence, demography, and health utilization. *J Am Geriatr Soc*. 1986;34:341-47.
15. Farmer ME, Locke BZ, Moscicki EK, Dannenberg AL, Larson DB, Radloff LS. Physical activity and depressive symptoms: the NHANES I Epidemiologic Follow-up Study. *Am J Epidemiol*. 1988;128:1340-51.
16. Katon W, Berg A, Robins AJ, et al. Depression: medical utilization and somatization. *Western J Med*. 1986;144:564-68.
17. Manning WG, Wells KB. The effects of psychological distress and psychological well-being on use of medical services. *Med Care*. 1992;30:541-53.
18. Thomas C, Kelman HR, Kennedy GJ, Ahn C, Yang C. Depressive symptoms and mortality in elderly persons. *Gerontol Soc Sci*. 1992;47(2):S80-7.
19. Callahan CM, Hendrie HC, Dittus RS, Brater DC, Hui SL, Tierney WM. Improving treatment of late life depression in primary care: a randomized clinical trial. *J Am Geriatr Soc*. 1994;42:839-46.
20. Rovner BW, German PS, Brant LJ, Clark R, Burton L, Folstein MF.

- Depression and mortality in nursing homes. *JAMA*. 1991;265(8):993-6.
21. Ruberman W. Psychosocial influences on mortality of patients with coronary heart disease. *JAMA*. 1992;267(4):559-60.
22. Lyketsos CG, Hoover DR, Guccione M, et al. Depressive symptoms as predictors of medical outcomes in HIV infection. *JAMA*. 1993;270(21):2563-7.
23. Spiegel D, Bloom JR, Kraemer HC, Gottheil E. The effect of psychosocial treatment on survival of patients with metastatic breast cancer. *Lancet*. 1989;2:888-91.
24. Callahan CM, Kesterson JG, Tierney WM. The association of symptoms of depression with diagnostic testing among older adults. *Ann Intern Med*. 1997;126:426-32.
25. Aneshensel CS, Frerichs RR, Huba GJ. Depression and physical illness: a multiwave, nonrecursive causal model. *J Health Soc Behav*. 1984;25:350-71.
26. Tierney WM, Miller ME, Hui SL, McDonald CJ. Practice randomization and clinical research. The Indiana experience. *Med Care*. 1991;29:JS57-64.
27. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas*. 1977;1:385-401.
28. Pfeiffer E. A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients. *J Am Geriatr Soc*. 1975;23:433-41.
29. Mayfield D, McLeod G, Hall P. The CAGE questionnaire: validation of a new alcoholism screening instrument. *Am J Psychiatry*. 1974;131:1121-3.
30. Callahan CM, Hendrie HC, Tierney WM. Documentation and evaluation of cognitive impairment in elderly primary care patients. *Ann Intern Med*. 1995;122:422-9.
31. Callahan CM, Tierney WM. Health services use and mortality among older primary care patients with alcoholism. *J Am Geriatr Soc*. 1995;43:1378-83.
32. McDonald CM, Tierney WM, Martin DK, Overhage JM. The Regentrief Medical Record System: 20 years experience in hospital outpatient clinics and neighborhood health centers. *MD Comput*. 1992;9:206-17.
33. Mulrow CD, Williams JW, Gerety MB, Ramirez G, Montiel OM, Kerber C. Case-finding instruments for depression in primary care settings. *Ann Intern Med*. 1995;122:913-21.
34. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23:56-62.
35. Bergner M, Bobbitt RA, Carter WB, Gilson BS. The Sickness Impact Profile: development and final revision of a health status measure. *Med Care*. 1981;19(8):787-805.
36. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics*. 1986;42:121-30.
37. Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika*. 1986;73:13-27.
38. Karim MR, Zeger SL. GEE: A SAS Macro for Longitudinal Data Analysis. Baltimore, Md: Department of Biostatistics, The Johns Hopkins University. Technical report 674.
39. Gallo JJ, Rabins PV, Lyketsos CG, Tien AY, Anthony JC. Depression without sadness: functional outcomes of nondysphoric depression in later life. *J Am Geriatr Soc*. 1997;45:570-8.
40. Bruce ML, Leaf PJ, Rosal GPM, et al. Psychiatric status and 9-year mortality data in the New Haven Epidemiologic Catchment Area study. *Am J Psychiatry*. 1994;151:716-21.
41. Corti MC, Guralnik JM, Salive ME, Sorkin JD. Serum albumin level and physical disability as predictors of mortality in older persons. *JAMA*. 1994;272:1036-42.
42. Guralnik JM, LaCroix AZ, Branch LG, Kasl SV, Wallace RB. Morbidity and disability in older persons in the years prior to death. *Am J Public Health*. 1991;81(4):443-7.
43. Reuben DB, Rubenstein LV, Hirsch SH, Hays RD. The value of functional status as a predictor of mortality: results of a prospective study. *Am J Med*. 1992;93:663-9.
44. Waxman HM, McCreary G, Weinrit RM, Carner EA. A comparison of somatic complaints among depressed and non-depressed older persons. *Gerontologist*. 1985;25:501-7.
45. Phifer JF, Murrell SA. Etiologic factors in the onset of depressive symptoms in older adults. *J Abnorm Psychol*. 1986;95:282-91.
46. Kennedy GJ, Kelman HR, Thomas C. The emergence of depressive symptoms in late life: the importance of declining health and increasing disability. *J Community Health*. 1990;2:93-103.
47. Hankin JR, Locke BZ. The persistence of depressive symptomatology among prepaid group practice enrollees: an exploratory study. *Am J Public Health*. 1982;72:1000-7.
48. Lin N, Ensel WM. Depression-mobility and its social etiology: the role of life events and social support. *J Health Soc Behav*. 1984;25:176-88.
49. Sargeant K, Bruce ML, Florio LP, Weismann MM. Factors associated with 1-year outcome of major depression in the community. *Arch Gen Psychiatry*. 1990;47:519-26.
50. Kennedy GJ, Kelman HR, Thomas C. Persistence and remission of depressive symptoms in late life. *Am J Psychiatry*. 1991;148:174-8.
51. Wells KB, Burnam MA, Rogers W, Hays R, Camp P. The course of depression in adult outpatients. *Arch Gen Psychiatry*. 1992;49:788-94.
52. Turner JR, Beiser M. Major depression and depressive symptomatology among the physically disabled. *J Nerv Ment Dis*. 1990;178:343-50.
53. McWhinney IR, Epstein RM, Freeman TR. Rethinking somatization. *Ann Intern Med*. 1997;126:747-50.
54. Callahan CM, Hendrie HC, Tierney WM. The recognition and treatment of late life depression: a view from primary care. *Int J Psychiatry Med*. 1996;26:155-71.
55. Sturm R, Wells KB. How can care for depression become more cost-effective? *JAMA*. 1995;273:51-8.