Article

Are Depressive Symptoms a Risk Factor for Mortality in Elderly Japanese American Men?: The Honolulu-Asia Aging Study

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Objective: This study determined the influence of depressive symptoms on subsequent mortality of all causes.

Method: The Honolulu Heart Program, established in 1965, is a prospective, community-based cohort of Japanese American men living in Hawaii. The analysis was based on 3,196 Japanese American men aged 71–93 at the time of the fourth examination in 1991–1993. Depressive symptoms were measured by use of an 11-question version of the Centers for Epidemiologic Studies Depression Scale questionnaire. All-cause mortality data were available for 6 years of follow up. Data were analyzed on the basis of presence or absence of chronic diseases.

Results: The overall prevalence of frequent depressive symptoms was 9.9%. Age-adjusted mortality rates at 3 years were 48.0 and 30.3 per 1,000 person-years for the depressed and nondepressed groups, respectively. At 6 years, the rates were 54.1 (depressed) and 41.5 (nondepressed) per 1,000 person-years. After adjustment for age, marital status, and antidepressant use, the relative risk for all-cause mortality associated with depressive symptoms was 1.53 for 3-year and 1.27 for 6-year mortality. Among participants who were healthy (without cognitive impairment, coronary heart disease, stroke, diabetes, or cancer), the association between depressive symptoms and mortality was greater (relative risk of 2.30 and 1.57 for 3- and 6-year mortality, respectively). Among participants with chronic disease, there were no significant associations between depressive symptoms and mortality.

Conclusions: Depressive symptoms are a risk factor for mortality in elderly people, particularly in physically healthy individuals.

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Depressive symptoms are common in community-dwelling elderly people (1). Yet the diagnosis of depression has often been missed and treatment inadequate (2). The result of ignoring depression has serious implications. Depression amplified the morbidity of disability, pain, drug side effects, and malnutrition and increased the need for health care in one study (3). Mortality was higher in community studies of depressed elderly persons (4–10) and especially in depressed elderly persons with coronary heart disease (11–14). A recent community study (15) noted a nearly twofold greater cardiac mortality for individuals with major depression than those with minor depression.

We present data on the contribution of depressive symptoms to mortality in elderly Japanese American men. We hypothesized that depressive symptoms would result in greater mortality and that these rates would be particularly high in the physically ill.

Method

Study Population

The Honolulu Heart Program began as a prospective cardiovascular study of 8,006 men of Japanese ancestry living on the island of Oahu, Hawaii, in 1965 who were born between 1900 and 1919. All men of Japanese ancestry identified by using World War II selective service registration cards were invited to participate (16). Since 1965 the cohort has been examined seven times. More recent examinations have focused on neurologic diseases and conditions associated with aging.

This analysis was based on the fourth examination of the cohort, conducted from 1991 to 1993, when 3,741 men aged 71–93 years were examined (80% of the 4,676 eligible cohort). All-cause mortality data were available for 6 years of follow-up. The study was approved by the institutional review board of Kuakini Medical Center, the procedures followed were in accordance with institutional guidelines, and after complete description of the study to the subjects, written informed consent was obtained.

Data Collection

The fourth examination included collection of demographic information, answers to medical and psychological questionnaires, assessment of cognitive function, fasting blood tests, a 2-hour glucose tolerance test, seated blood pressure and anthropometry measures that were collected in a standardized manner. Morbidity and mortality surveillance included monitoring of hospital discharge records, death records, and death certificates. For this report, all-cause mortality data were analyzed and matched with the national death index through December 1997. Mortality data collection was believed to be essentially complete; at the fourth examination, only five men were lost to follow-up.

TABLE 1. Demographic and Clinical Characteristics of Elderly Japanese American Men From the Honolulu-Asia Aging Study, by Presence or Absence of Depressive Symptoms

Variable	Men With Depressive Symptoms (N=317)[a]		Men Without Depressive Symptoms (N=2,879)[a]		Analysis		
	Mean	SD	Mean	SD	t	df	p
Age (years)	77.6	4.4	77.2	4.3	1.44	3194	0.15
Education (years)	10.8	3.2	10.7	3.1	0.53	3194	0.60
Body mass index (kg/m^2)	23.0	3.0	23.6	3.1	–3.01	3178	0.003[b]
Rating on Physical Activity Index[c]	30.4	4.3	31.1	4.6	–2.58	3185	0.01[b]
Alcohol (oz/month)	19.6	43.0	18.1	38.9	0.57	372	0.57
Blood pressure (mg Hg)							
Systolic	146.3	24.4	150.5	22.9	–3.03	3192	0.002[b]
Diastolic	78.4	10.4	80.7	11.0	–3.53	3191	<0.001[b]
	N	%	N	%	χ^2	df	p
Married	244	77.0	2,409	83.7	9.10	1	0.003[b]
Taking antidepressant medication	4	1.3	20	0.7	1.23	1	0.27
Taking antihypertensive medication	120	38.2	1,077	37.6	0.04	1	0.84
Current smoker	26	8.2	203	7.1	0.59	2	0.44
Chronic physical illness							
Diabetes mellitus	88	28.1	843	29.7	0.32	2	0.57
Coronary heart disease	53	16.7	418	14.5	1.10	1	0.29
Stroke	15	4.7	68	2.4	6.34	1	0.01[b]
Cancer	44	13.9	354	12.3	0.66	1	0.42
Cognitive impairment (score less than 74 on Cognitive Abilities Screening Instrument)	48	15.1	266	9.3	11.20	1	0.001[b]

[a] Group sizes vary owing to missing data.
[b] Significant difference between subjects with and subjects without depressive symptoms ($p \leq 0.05$).
[c] The measure used in the Framingham Study (21) and the Honolulu Heart Program (22); oxygen consumption for one of five activity levels is multiplied by the number of hours per day the subject engages in the task.

Depressive Symptoms

Participants were screened for depressive symptoms by using an 11-question version of the Centers for Epidemiologic Studies Depression (CES-D) Scale questionnaire (Appendix 1). Participants who did not answer three or more of the 11 depression questions were excluded from this analysis, leaving 3,196 participants to be studied. The standard CES-D Scale uses a cutoff score of 16 points for depressive symptoms (17). In this 11-question version, a score of 9 or greater was used (determined by extrapolation; $16/20 \times 11=8.8$, rounded up to 9). Shortened forms of the CES-D Scale have been found to be comparable with the full-scale version (18, 19). For convenience, we will refer to presence of depressive symptoms as "depression" or "depressed"; the term is not synonymous with clinical depression.

Other Key Variables

Covariates were selected because of their potential relationship with depressive symptoms or mortality. Diabetes mellitus was defined by World Health Organization criteria, by history (as told by the subject to a physician), by taking medications (insulin or oral hypoglycemics), by a fasting glucose level of 140 mg/dl or more, or by a 2-hour postload glucose of 200 mg/dl or more (20). Body mass index was defined as weight in kilograms divided by height in meters squared. The Physical Activity Index was based on the one used in the Framingham Study (21) and the Honolulu Heart Program (22), which multiplied the oxygen consumption of five different levels of activity with the numbers of hours a day engaged in that task.

Antidepressant medication use was determined by observation; participants brought in medications used in the previous 2 weeks. Cognitive function was measured with the Cognitive Abilities Screening Instrument (23), which was developed for cross-cultural studies of dementia. A score on the Cognitive Abilities Screening Instrument of less than 74 defined cognitive impairment. We tested the accuracy of a consensus panel of three physicians using DSM-III-R criteria for determination of dementia after a neurologist's examination and neuropsychological testing of 426 participants; when we used the cutoff point of 74, the sensitivity of the instrument for dementia was 80%, and the specificity was 90%.

Statistical Analysis

Subjects were divided into two groups on the basis of presence or absence of depressive symptoms, as defined. Means of variables were compared in these two groups by using two-sample t tests for continuous variables and chi-square tests for categorical variables. Age-adjusted mortality rates were calculated for 3-year and 6-year mortality per 1,000 person-years of follow-up. Dose-response relationships of depressive symptoms with mortality were studied for the six groups on the basis of the 11-item CES-D Scale score. Kaplan-Meier survival curves were plotted for 6-year mortality by using Wilcoxon's test for statistical significance.

Three separate Cox proportional hazards models assessed the association of depressive symptoms and mortality. Separate models for 3-year and 6-year mortality analyzed the immediate and long-term effects of depressive symptoms. The first model adjusted for age, marital status, and antidepressants. The second model added cardiovascular risk factors (body mass index, score on Physical Activity Index, systolic blood pressure, and presence of smoking and diabetes mellitus). The third model added chronic diseases (cognitive impairment, coronary heart disease, stroke, and cancer).

To study the effect of illness on the association between depression and mortality, we created two groups: "physically ill" (cognitive impairment, coronary heart disease, stroke, diabetes, or cancer) and "healthy" (individuals without chronic diseases). We repeated the Cox proportional hazards models for those with and without chronic diseases. In this cohort, coronary heart disease, stroke, and cancer were known to be the three most frequent causes of death (24). All statistical analyses were performed using

TABLE 2. Mortality Rates of Elderly Japanese American Men From the Honolulu-Asia Aging Study, by Presence or Absence of Depressive Symptoms

Measure of Mortality	Total Group		Physically Ill Group[a]		Physically Healthy Group[b]	
	Men With Depressive Symptoms (N=317)	Men Without Depressive Symptoms (N=2,879)	Men With Depressive Symptoms (N=173)	Men Without Depressive Symptoms (N=1,472)	Men With Depressive Symptoms (N=144)	Men Without Depressive Symptoms (N=1,407)
3-year follow-up						
Number of deaths	38	223	21	156	17	67
Unadjusted mortality rate/1,000 person-years	48.7	30.1	49.2	41.6	48.2	18.4
Age-adjusted mortality rate/1,000 person-years	48.0	30.3	48.2	39.9	48.0	19.6
6-year follow-up						
Number of deaths	83	601	51	395	32	206
Unadjusted mortality rate/1,000 person-years	53.4	40.5	60.6	53.7	45.0	27.6
Age-adjusted mortality rate/1,000 person-years	54.1	41.5	60.0	53.1	47.5	29.4

[a] Included subjects with cognitive impairment, coronary heart disease, stroke, diabetes, or cancer at examination 4.
[b] Excluded subjects with cognitive impairment, coronary heart disease, stroke, diabetes, or cancer at examination 4.

SAS software (SAS Institute, Cary, N.C.). All of the statistical tests were two-tailed.

Results

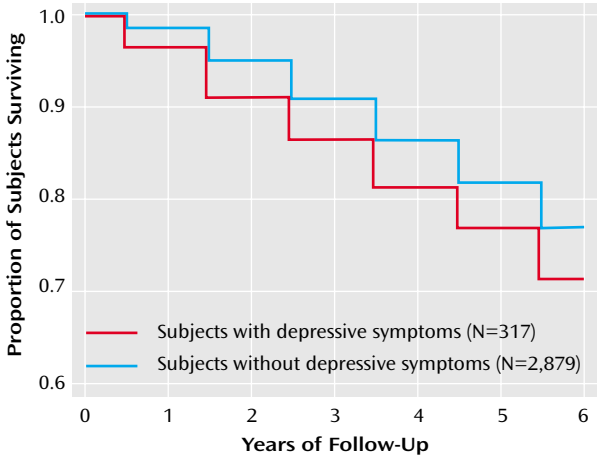
A total of 317 participants (9.9% of the cohort) had a score of 9 or greater on the 11-item CES-D Scale and were considered "depressed" (mean=3.73, SD=3.68, median=3.0, mode=3.0, range=0–26). The prevalence of depressive symptoms showed little variation among age groups (ages 71–74, 8.83%; ages 75–79, 10.5%; ages 80–84, 10.47%; ages 85 and older, 9.96%) (χ^2=2.05, df=3, p=0.56).

Those with depressive symptoms were significantly less likely to be married, had a lower body mass index, a lower rating on the Physical Activity Index, and lower systolic and diastolic blood pressure. They were more likely to have cognitive impairment and stroke (Table 1). The associations with age, education, smoking, use of antidepressants or antihypertensives, alcohol, diabetes, coronary heart disease, and cancer were not significant.

The follow-up interval was from the initial measure of depressive symptoms in 1991–1993 until December 1997. During this interval, there were 684 deaths in the cohort: 601 deaths among the nondepressed and 83 among the depressed (Table 2). Kaplan-Meier survival curves showed significantly greater mortality for men with depressive symptoms (Figure 1).

Three separate Cox proportional hazards models were analyzed with all-cause mortality as the endpoint (Table 3). In the first model, after adjustment for age, marital status, and antidepressant medication use, the relative risk for all-cause mortality associated with depressive symptoms was 1.53 (Cox proportional hazards model, 95% confidence interval [CI]=1.09–2.16; χ^2=5.88, df=1, p=0.02) for 3-year mortality and 1.27 (Cox proportional hazards model, 95% CI=1.01–1.60, χ^2=4.26, df=1, p=0.04) for 6-year mortality. Adjustment for other factors known to influence mortality (model 2) did not appreciably alter the relative risk for either 3- or 6-year mortality. However, in model 3, the association no longer reached statistical significance after further adjustment for presence of chronic diseases.

FIGURE 1. Probability of Mortality in Elderly Japanese American Men From the Honolulu-Asia Aging Study, by Depressive Symptoms[a]



[a] Kaplan-Meier survival curves for 6-year mortality from all causes in relation to presence or absence of depressive symptoms at examination 4 (Wilcoxon's χ^2=6.71, df=1, p=0.01).

To avoid the influence of these diseases on depressive symptoms and mortality, Cox proportional hazards models were repeated separately for elderly men with and without chronic diseases (Table 3). As defined previously, the healthy group excluded participants with cognitive impairment, coronary heart disease, stroke, diabetes, or cancer. The physically ill group included participants with at least one of these diseases. Associations between depression and mortality were significant only in the healthy group. The associations were stronger for 3-year than for 6-year mortality. We found a significant interaction among health/physical illness, presence of depressive symptoms, and their association with 3-year mortality but no significant interaction for 6-year mortality (data not shown).

Discussion

Depressive symptoms predicted greater mortality in elderly Japanese American men, a risk that continued after

TABLE 3. Cox Proportional Hazards Models of Relation of Depressive Symptoms to 3-Year and 6-Year Mortality Rates in Elderly Japanese American Men From the Honolulu-Asia Aging Study

	Model 1[a]				Model 2[b]				Model 3[c]			
	Relative		Analysis		Relative		Analysis		Relative		Analysis	
Group	Risk	95% CI	χ^2 (df=1)	p	Risk	95% CI	χ^2 (df=1)	p	Risk	95% CI	χ^2 (df=1)	p
Total group (N=3,196)												
3-year mortality	1.53	1.09–2.16	5.88	0.02	1.45	1.02–2.06	4.21	0.04	1.42	0.99–2.02	3.71	0.05
6-year mortality	1.27	1.01–1.60	4.26	0.04	1.27	1.00–1.60	3.98	<0.05	1.21	0.96–1.53	2.49	0.11
Physically healthy group (N=1,551)[d]												
3-year mortality	2.30	1.33–3.95	9.01	0.003	2.17	1.25–3.77	7.59	0.006				
6-year mortality	1.57	1.08–2.29	5.46	0.02	1.56	1.06–2.29	5.10	0.02				
Physically ill group (N=1,645)[e]												
3-year mortality	1.19	0.75–1.87	0.54	0.46	1.08	0.67–1.73	0.10	0.76	1.08	0.67–1.73	0.10	0.75
6-year mortality	1.11	0.83–1.49	0.52	0.47	1.09	0.81–1.47	0.34	0.56	1.05	0.78–1.41	0.10	0.75

[a] Adjusted for age, marital status, and use of antidepressant medication (df=1).
[b] Adjusted for age, marital status, use of antidepressant medication, and cardiovascular risk factors (body mass index, rating on Physical Activity Index, systolic blood pressure, smoking, and diabetes (df=1).
[c] Adjusted for age, marital status, use of antidepressant medication, cardiovascular risk factors (body mass index, rating on Physical Activity Index, systolic blood pressure, smoking, and diabetes), and chronic diseases (cognitive impairment, coronary heart disease, stroke, and cancer) (df=1).
[d] Excluded subjects with chronic cognitive impairment, coronary heart disease, stroke, diabetes, or cancer at examination 4.
[e] Included subjects with chronic cognitive impairment, coronary heart disease, stroke, diabetes, or cancer at examination 4.

adjustment for age and chronic medical conditions. To our knowledge, this is the first community-based study of an Asian population in terms of depression and mortality. An extensive review showed that previous studies were predominantly among Caucasian populations (4). We found only one article that analyzed this association in Mexican Americans (5).

Most community studies showed greater mortality in depressed patients (4–6, 8–10), although there was no association between depressive symptoms and mortality in the Piedmont Health Survey (7). A literature review (4) noted an average relative risk of 1.7 (range=1.6–1.8). Others reported excess mortality for all psychiatric disorders (25) and a relative risk of 1.5–2.5 in elderly persons with organic mental disorders, mood disorders, and psychotic disorders (26).

The most unexpected finding was that the physically healthy, depressed elderly men had a stronger association with mortality compared with the physically ill group—a result opposite to that of previous reports (4–14). We believe we are the first investigators to divide the patient cohort into healthy and physically ill groups, thus building in a comparison group. Others have either used physically healthy groups alone, controlling for medical burden, or analyzed a pure physically ill cohort (4–14).

We wondered about possible explanations. Perhaps depression was a marker for undiagnosed comorbid medical illness. The additive effect of depression on mortality may be minimal compared with the burden of chronic disease. Differences in the genetic composition and psychosocial environment of Japanese Americans in Hawaii could have major differences on the course of depression. As another example, strong associations between depression and cardiovascular illness (11–15), cerebrovascular disease (27), and diabetes (28) have been reported. Our study showed a relationship of depression with only cerebrovascular disease.

Limitations of the Study

This study analyzed only male elderly patients of Japanese ancestry in a community population. Although we controlled for the effect of gender and ethnicity, these findings may not be generalizable to other groups or settings. Compared with other study groups, our cohort was essentially homogeneous in terms of gender, age, and ethnicity. Furthermore, most of the Japanese population in Hawaii arrived from rural southern Japan at the turn of the century (29), so there may be similarities, even at the genetic level.

We were concerned that 545 participants were excluded from the study because of incomplete or invalid answers on the 11-item CES-D Scale questionnaire. We postulated that such individuals were unable to answer questions because of more severe cognitive impairment and/or medical burden. In addition, there were 935 survivors (20%) in the cohort that did not participate in examination 4; this group was most likely less healthy than the participants. Indeed, we found that mortality rates were more than double in those who participated in examination 4 but did not complete a valid 11-item CES-D Scale questionnaire and more than triple in those who did not participate at all in examination 4 (data not shown). These two excluded groups probably had the most severe medical burden and perhaps a high rate of depression. The elimination of these groups from the analysis could have skewed our evaluation of depression in the physically ill cohort.

Perhaps the most significant limitation of this study was that depression was measured at one point in time and followed prospectively. Depression-related mortality may have occurred before the measurement of depressive

symptoms. Unfortunately, data on depressive symptoms were not collected at earlier time points. Nonetheless, the deleterious effect of depression on mortality may not occur until middle age. Vaillant (30) showed no differences in health in a cohort of college-educated men until age 50. By age 70, there were significant differences in the mortality of healthy versus depressed men.

Conclusions

In summary, our study confirmed the hypothesis that depressive symptoms result in greater mortality for Japanese American elderly men, a group not previously studied, to our knowledge. Compared with other studies, our cohort was particularly homogenous. We felt that dividing the cohort into "healthy" and "physically ill" groups represented a novel way of studying the relationship among depression, health, and medical burden. Other databases could be analyzed in a similar manner to see if our findings could be replicated.

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APPENDIX 1. Centers for Epidemiologic Studies Depression Scale Questionnaire (11-item version)

The following is a list of the ways you might have felt or behaved. Please indicate how often you have felt this way during the **past week**.

Would you say in the last week…. [show cue card]	Rarely or None of the Time (less than 1 day)	Some or a Little of the Time (1–2 days)	Occasionally or a Moderate Amount of the Time (3–4 days)	Most of the Time
1. You were bothered by things that usually don't bother you.	0	1	2	3
2. You did not feel like eating; your appetite was poor.	0	1	2	3
3. You had trouble keeping your mind on what you were doing.	0	1	2	3
4. You felt that everything you did was an effort.	0	1	2	3
5. You felt depressed.	0	1	2	3
6. You felt hopeful about the future.	3	2	1	0
7. You felt fearful.	0	1	2	3
8. Your sleep was restless.	0	1	2	3
9. You were happy.	3	2	1	0
10. You felt lonely.	0	1	2	3
11. You could not get going.	0	1	2	3

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