Depression and Risk of Heart Failure Among the Elderly: A Prospective Community-Based Study

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Objective: Although the association between depression and the incidence of coronary heart disease has been established in many studies, the impact of depression on the incidence of heart failure has not been previously investigated. Methods: We examined the effect of depression (assessed by means of the Center for Epidemiological Studies Depression Scale (CES-D) with a cutoff point of $\geq 21$) on the incidence of heart failure in a community sample of persons aged $\geq 65$ years who were participants in the New Haven cohort of the Established Populations for Epidemiological Studies in the Elderly. Results: At baseline 2501 individuals were free of heart failure. Of these, 188 (132 women and 56 men) scored as depressed. Depressed participants were significantly more likely to have hypertension, diabetes, and mobility-related functional limitations and were less likely to be male or married. During the 14-year follow-up period, 313 participants (146 men and 167 women) developed heart failure, defined as hospital admission for heart failure or mortality with heart failure as the underlying cause of death. After adjusting for baseline differences in demographic and comorbidity factors and functional status using Cox regression, depression tended to be associated with a greater risk of heart failure (hazard ratio (HR) = 1.52, 95% confidence interval (CI) = 0.94–2.43, $p = .09$). This effect was significant in women (HR = 1.96, 95% CI = 1.11–3.46, $p = .02$) but not in men (HR = 0.62, 95% CI = 0.23–1.71, $p = .05$ for the interaction term between sex and depression). Conclusions: Depression is an independent risk factor for heart failure among elderly women but not elderly men. Key words: heart failure, risk factors, aging, depression.

INTRODUCTION

The association between depression and coronary heart disease has been widely studied. Epidemiological studies have consistently described an influence of depression on mortality after the onset of coronary heart disease (1–5) and more recently on disease incidence (6). This relationship also exists for depressive symptoms in the absence of information on the possible clinical diagnosis of depression (7–9). Heart failure (HF) is a common and serious condition among elderly persons, and depression is highly prevalent among patients with HF (10, 11). Depressed individuals have elevated sympathoadrenal activation (12, 13), which has been shown to influence the progression of HF (14–17). Similar neurohormonal mechanisms may be involved in the clinical onset of decompensated HF in persons with ischemic or hypertensive heart disease. Although a few studies have demonstrated an association between depression and mortality after the onset of HF (18), as well as an association between depression and mortality due to HF in the general population (19), the role of depression on the incidence of HF is currently unknown. The present study sought to determine the importance of depression on HF incidence in a population-based sample of elderly persons followed for up to 14 years.

METHODS

Study Population

The present study was based on data from the Yale Health and Aging Project (YHAP), a prospective cohort study of noninstitutionalized individuals $\geq 65$ years of age. YHAP is one of the four cohorts of the Established Populations for Epidemiological Studies of the Elderly program conducted by the National Institute on Aging (20). The YHAP cohort was assembled in 1982 by obtaining a stratified probability sample of persons from three New Haven housing strata: public housing for the elderly, private housing for the elderly, and general housing in the community. Male participants were oversampled. Approximately 82% of eligible individuals participated in the baseline interview ($N = 2812$, 1169 men and 1643 women). The average age of women and men in the sample was 74.2 and 73.2 years, respectively. Of the 2812 participants, 175 who responded positively at baseline to two questions addressing orthopnea (“Do

BMI = body mass index; CES-D = Center For Epidemiological Studies Depression Scale; CI = confidence interval; CVD = cardiovascular diseases; DBP = diastolic blood pressure; HF = heart failure; HR = hazard ratio; ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification; MI = myocardial infarction; SBP = systolic blood pressure; SPMSQ = Short Portable Mental Status Questionnaire; YHAP = Yale Health and Aging Project.
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you get shortness of breath when you are lying down flat?” and “Does this shortness of breath improve when you sit up, or do you use extra pillows at night to prevent it?” and an additional 136 participants who used both loop diuretics and cardiac glycosides were considered to be potential HF cases and were excluded from the analyses.

Study Measures

Depressive symptoms at baseline were measured by means of the Center for Epidemiological Studies Depression Scale (CES-D), a 20-item scale of depressive symptoms with a potential total score ranging from 0 to 60 (21). If three or more items of the scale were missing, the sum score was set to missing. If one or two items were missing, the depressive symptom score was based on a weighted average of the nonmissing items. Although there is no standard cutoff point for use of this scale, a cutoff point of ≥21 was used to indicate symptom severity that approximates a clinical diagnosis of depression. When compared with a clinical diagnosis of depression based on DSM-III-R criteria, a score of 21 or more on the CES-D has a sensitivity (92%) and specificity (87%) (22). The term “depression” in this report denotes a depressive symptom score of 21 or more on the CES-D.

Information on a number of other baseline factors was collected and considered in our analyses. Baseline sociodemographic variables of interest included age, sex, years of education, race (white vs. nonwhite), and marital status. Self-reported history of physician-diagnosed myocardial infarction (MI), stroke, hip fracture, cancer, and diabetes were also assessed, as were smoking (current, past, never) and body mass index (BMI) (coded as follows: low, <23 kg/m²; intermediate, 24–27 kg/m²; or high, ≥28 kg/m²). An additional dummy variable was created for participants with missing BMI values (N = 199). Information on baseline functional status was measured by means of four items addressing mobility-related function, which is considered to be most closely associated with cardiovascular diseases (CVDs) (8). Two items were selected from an instrument for gross mobility (ability to climb one flight of stairs and walk half a mile) (23), and two were from the Katz index of basic activities of daily living (ability to walk across a room and to transfer from bed to chair) (24). Functional limitation was defined as the inability to perform at least one of these four functions. Cognitive function was also taken into consideration as a potentially confounding variable, given its association with depressive symptoms and CVD. The Short Portable Mental Status Questionnaire (SPMSQ) (25) was used to measure cognitive function. The SPMSQ score was used as a continuous variable.

In addition to the baseline factors noted above, we also collected information on the occurrence of incident MIs during follow-up. Incident MIs were based on the occurrence of hospitalizations for MI and were validated according to accepted criteria for MI diagnosis (26).

Study Outcome

Follow-up time started from the date of baseline interview in 1982 to the date of first hospitalization for HF, date of death due to HF as the underlying cause, or the end of follow-up period (December 31, 1996), whichever came first (27). In secondary analyses, we also examined survival time (for HF-specific mortality) and time to first hospitalization as separate outcomes. Information on hospital admissions for study participants was obtained from the Yale New Haven Hospital and Hospital of Saint Raphael, the two New Haven community hospitals. This information was collected through a surveillance system that conducted weekly reviews of all admissions to these two local hospitals. Additional information on hospitalizations in this cohort was obtained from federal data (Medicare Part A Beneficiary Bill History data from the Health Care Financing Administration [HCFA]). Only about 5% of hospitalizations identified through the HCFA data were missed from our surveillance and not included in the study.

Nonfatal HF events during follow-up were initially identified by reviewing the hospitalization records of study participants who were hospitalized between 1982 and 1986. When a given hospitalization record indicated that the primary discharge diagnosis or one of the first three secondary discharge diagnoses was HF (ICD-9-CM codes 428, 402.01, 402.11, 402.91, 404.01, 404.13, 404.91, and 404.93), the record was reviewed in detail. To qualify as a HF event, the hospitalization record had to indicate 1) the presence of shortness of breath accompanied by either physical signs or radiographic evidence of HF, 2) HF as one of the three major precipitating factors for hospitalization, and 3) HF-related symptoms occurring before or within 24 hours of hospital admission. Fatal HF events were identified by reviewing death certificates of all participants who died. A single nosologist coded all death certificates according to ICD-9-CM criteria. Deaths due to HF were identified by the same codes as those used for hospitalizations. Information on vital status was virtually complete (>99% of all cohort members).

We also considered an alternative method of defining HF events during follow-up. This alternative method defined HF on the basis of medication use during follow-up (ie, new use of both loop diuretics and cardiac glycosides) as determined by direct examination of medication bottles in the participant’s home at any of the follow-up interviews. This was done to shed light on HF events occurring outside the hospital.

Statistical Analysis

As the first step in our analysis, we examined bivariate associations between depression and other baseline factors. Next, we ran a Cox proportional hazards regression model, which assessed the unadjusted association between depression and HF. Similar Cox models were run to examine the unadjusted relationship between other baseline factors and risk of HF. Finally, we ran multivariable Cox models that assessed the association between depression and HF risk after adjustment for other factors. Initially, these multivariable models adjusted for baseline factors only. However, we also examined a multivariable model that adjusted for baseline factors as well as the occurrence of MI during follow-up as a time-dependent covariate. In all multivariable models, a backward elimination procedure was used. This procedure retained only those variables that were significant (p < .10) predictors of the outcome or that changed the point estimate for depression by ≥10% (depression, however, was always forced into the model).

To account for the complex nature of the YHAP sampling design, we used Survey Data Analysis (SUDAAN) software. SUDAAN applies the Taylor linearization procedure to estimate standard errors for regression coefficients. SUDAAN was used for all statistical analyses except the multivariable model that included a time-dependent covariate for MI during follow-up. For this model, we used SAS software because SUDAAN does not handle time-dependent covariates.

Previous literature suggests that the association between psychosocial factors and cardiovascular outcomes (7–9), as well as the association between biological risk factors and HF incidence (28), varies by gender. Therefore, analyses were conducted in the entire sample as well as separately by gender, and gender-related interactions were explored.
RESULTS

Among the 2812 participants at baseline, 311 subjects (122 men and 189 women) were either taking both digoxin and Lasix or had orthopnea and were therefore excluded, leaving 2501 disease-free individuals (1047 men and 1454 women). The average age of participants was 74 years. Study subjects were also predominantly non-Hispanic white.

Bivariate associations between baseline depression and other baseline factors under study are shown in Table 1. Depressed persons were significantly more likely to be hypertensive, diabetic, and to have mobility-related functional limitations. Depressed persons were significantly less likely to be male; among men, 56 (5.3%) were depressed at baseline, whereas among women, 132 (9.0%) were depressed. Depressed persons were also significantly less likely to be married and had significantly fewer years of education.

During the 14-year follow-up period, 313 (12.5%) participants had incident HF. Of these 313 events, 278 were hospitalizations for HF and 35 were deaths due to HF with no prior hospitalization for HF. The incidence of HF increased with age for both men and women and was higher in men compared with women in every age category. In a univariate Cox model, a CES-D score ≥21 was a significant risk factor for incident HF (HR = 1.69, 95% CI 1.19–2.39). Other univariate Cox models indicated that age, male gender, history of MI, history of diabetes, hypertension, pulse pressure, and cognitive impairment were significantly associated with increased risk of HF. Smoking status and obesity were not associated with HF risk in univariate models.

Next we conducted analyses to determine whether depression was associated with HF after adjustment for other factors. Figures 1 and 2 show that, compared with those who were not depressed, depressed participants at baseline had a lower probability of survival free of HF after adjustment for age. Table 2 presents the results of the multivariable Cox proportional hazards model, which assessed the relationship between depression and HF after adjustment for age and other baseline factors. The model selected depression, age, gender, diabetes, pulse pressure, hypertension, and functional status as independent predictors of increased HF risk. In this model, the adjusted relative risk of incident HF among depressed individuals, compared with those who were not depressed, was marginally significant (hazard ratio (HR) = 1.52, 95% confidence interval (CI) = 0.94–2.43, p = .086). Because BMI and smoking were found to be risk factors for HF in previous studies, we reran the model shown in Table 2 with additional adjustment for these two factors. We found, however, that this model yielded results that were nearly identical to those shown in

![Fig. 1. Age-adjusted cumulative probability of surviving free of heart failure among men according to depression status. Depression was defined as a score of 21 or more on the CES-D.](image)
created terms representing the interaction between depression and diabetes, pulse pressure, hypertension, and MI and added these interaction terms to the model. We failed to find, however, that any of these interactions were significant.

Despite the relatively small number of minority participants, analyses were done to see if race showed a major influence on risk. We did not detect any such effects. Race was neither a significant predictor of HF incidence \( (p = .15) \) nor a confounder of the association between depression and HF incidence. We also explored the interaction between race and depression in the multivariable model, but we found that this interaction was not significant \( (p = .97) \).

In additional secondary analyses, we examined whether perceived social and instrumental support, which were measured in this cohort \( (29) \), buffered the relationship between depression and HF, by examining the interaction between each type of support and depression. However, we found that neither of these interaction terms was significant in the multivariable model.

Depressed patients are more likely to have diminished health status and increased healthcare utilization \( (30) \). We therefore examined mortality and hospitalization separately. When analyzed separately, participants with a depressive symptom score \( \geq 21 \) were more likely to die of HF \( (HR = 1.78, 95\% CI = 1.34–9.24) \) than those who did not score as depressed, although the confidence interval was quite large and included 1. Similarly, those who had a depressive symptom score \( \geq 21 \) were more likely to be hospitalized for HF \( (HR = 1.65, 95\% CI = 1.02–2.67) \). The point estimate for the association between depression and HF was greater when mortality was considered as the outcome than when hospitalization was considered as the outcome. It is therefore unlikely that the observed association between depression and HF hospitalization is biased by the greater propensity of depressed individuals to seek medical attention. When HF medication use during follow-up was considered as a measure of HF incidence, the association with baseline depression showed similar trends, but these trends were less strong than those described above: for the total population, \( HR = 1.21 (95\% CI = 0.78–1.88) \); for women, \( HR = 1.26 (95\% CI = 0.73–2.19) \); and for men, \( HR = 0.95 (95\% CI = 0.44–2.05) \).

**DISCUSSION**

The present investigation supports the hypothesis that a high level of depressive symptoms is an independent risk factor for incident HF among elderly women but not elderly men. This finding is in agree-
ment with the finding of a previous study, in which depressive symptoms were associated with higher mortality due to HF (underlying cause) among older women (19). In the present study, controlling for HF risk factors (such as hypertension, diabetes, and history of MI) eliminated the association of interest in men but only attenuated it somewhat in women. This suggests that depressive symptoms are not likely to increase HF risk uniquely through these risk factors in women.

Instead, depressed mood may affect HF risk through biological pathways possibly involving the neuroendocrine system. Emotional factors have long been hypothesized to precipitate hospitalization for HF patients (31). Psychological stress is believed to impair left ventricular function through various mechanisms, including the induction of transient changes of the electrophysiological properties of the myocardium and subsequent ventricular arrhythmia (32) and the occurrence of wall-motion abnormalities and a subsequent drop in ejection fraction (33, 34). Furthermore, patients with dilated cardiomyopathy and HF have shown impairment in left ventricular function during psychological stress (35). Emotional factors may increase the risk of HF through activation of the sympathetic nervous system (12, 13), which may contribute to progression of left ventricular dysfunction and renal sodium retention. Given the limited data available, however, these biological mechanisms remain speculative.

It is also possible that depression may act to increase risk through behavioral mechanisms. For example, investigators have reported that depressed persons are less likely to adhere to medical therapies (30), and failure to adhere to medical therapies could, presumably, increase the risk of developing HF. Unfortunately, this study did not have information on adherence to medical therapies; therefore, we were unable to determine if this factor explained the observed relationship between depression and increased HF risk.

It is unclear why depression was associated with increased HF risk among women but not men. The lack of association between depression and HF among men may be due to the underrepresentation of men who might have been susceptible to the adverse effects of depression, because these men might have died before the inception of the study. This may be true when dealing with an older cohort as in the present study. This hypothesis is supported by previous studies, which indicated a greater association between depression and CVD in younger men compared with older men (1, 3, 4) and a greater association between depression and CVD in older women compared with older men (8). It may also be that depressed women are simply more likely to seek hospitalization for HF than are men. Most of the HF events we observed in this study were hospitalizations. If women were more likely than men to go to the hospital for their HF symptoms, then the gender difference we observed in the association between depression and HF events may simply have been indicative of a difference in medical attention-seeking behavior between depressed men and women. However, when we defined HF based on medication use instead of hospitalization, we still found that depression increased HF risk in women but not men. This argues against the claim that the gender difference we observed simply reflects a greater willingness of depressed women to go to the hospital. One could speculate that that the gender difference we observed has a pathophysiological basis. If depression increases HF risk through sympathoadrenal activation, it may be that depression leads to a greater degree of sympathoadrenal activation in women compared with men or that the effects of such activation are more deleterious in women as opposed to men.

The current analysis has a number of limitations. First, we did not have information on serum lipoprotein levels. However, serum lipoprotein levels are not likely to have changed the association of interest because they do not seem to differ markedly according to the presence or absence of depressed mood (7), and if they do, they are lower rather than higher in depressed individuals (36). Second, the identification of incident cases by hospitalization and mortality in the present study may have excluded less severe cases of disease. Only persons who were hospitalized or those who were symptomatic (ie, in whom HF had undergone decompensation) were included as cases. However, decompensated HF is likely to have a greater impact on the clinical course and quality of life of patients than HF at an earlier stage. Therefore, this is a reasonable method of outcome ascertainment. Nevertheless, because information on medication intake was available at follow-up, we also considered this as a measure of HF incidence. The association between baseline depression and HF incidence as measured by medication use showed similar trends but was less strong, suggesting that depression may affect primarily incidence of HF defined by hospitalization and mortality rather than by medication use. However, measuring the outcome by medication use is less accurate. Although we have the exact date for mortality and hospital admission, we do not know the exact date for the initiation of drug therapy during the 3-year follow-up intervals. This may dilute the association between depression and HF when the outcome is measured by drug use. Third, we were unable to assess how treat-
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...ment for depression during follow-up, and adherence to medical treatment recommendations, may have altered the relationship between depression and HF.

Despite its limitations, this study has several advantages. This is the first longitudinal study to examine the effect of depression on HF incidence among the elderly, who comprise the majority of HF patients. The strengths of this study include complete and validated ascertainment of end points, prospective design, and control for various established risk factors for HF. Lastly, the present study is based on a random sample of community-dwelling elderly persons. The New Haven population is ethnically and socioeconomically diverse and as such should be representative of the elderly population in many communities of the United States.

Our findings indicate that the presence of depressed mood should alert clinicians to a higher risk of not only ischemic heart disease but also HF in their patients. Early diagnosis and treatment of depression may reduce the burden of morbidity and mortality due to HF in the elderly and reduce the public health costs associated with HF treatment. The results of this study affirm the importance of current clinical guidelines from the Agency for Health Care Policy and Research for diagnosis and treatment of depression (37), including routine use of screening for depression in the elderly.

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REFERENCES

25. Pfeiffer E. A short portable mental status questionnaire for the...


