Depression and Risk of Coronary Heart Disease in Elderly Men and Women

New Haven EPESE, 1982-1991

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Background: Results of several recent studies suggest that depression is predictive of incident coronary disease. However, few studies have examined this relationship in the elderly, the age at which most coronary heart disease (CHD) becomes clinically manifest.

Methods and Results: Data are from the New Haven, Conn, cohort (N = 2812) of the Established Populations for the Epidemiologic Studies of the Elderly project. Baseline information on depressive symptoms and CHD risk factors was collected during an in-person interview in 1982. Nonfatal myocardial infarctions were identified through monitoring of admissions to local hospitals and were validated by medical chart review. Cause of death was obtained from death certificates for all deceased participants. Outcomes were defined as CHD deaths (n = 255) and total incident CHD events (n = 391) between January 1, 1982, and December 31, 1991. There was no association between depressive symptoms and CHD outcomes in men. Among women, depressive symptoms were associated with an age-adjusted relative risk of 1.03 (per unit increase on the symptom scale) for CHD mortality (P = .001) and total CHD incidence (P = .002). These associations were largely unaffected by adjustment for established CHD risk factors but were reduced to nonsignificant levels after additional adjustment for impaired physical function. Additional analysis showed a significant association for depressive symptoms among women who had no physical function impairments or who survived at least 3 years without an event.

Conclusion: Depressive symptoms may not be independent risk factors for CHD outcomes in elderly populations in general but may increase risk among relatively healthy older women.

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There is mounting evidence that depression among patients with existing coronary heart disease (CHD) is associated with adverse outcomes, such as mortality and recurrent coronary events. Whether depression also constitutes a risk factor for incident CHD events is somewhat less clear. Although some studies8-13 have found no association between depression and incidence of CHD, the results of several recent studies11-13 suggest that depression may increase risk for incident CHD outcomes. However, few studies have examined the role of depression in predicting CHD in the elderly despite the steep increase in CHD incidence in old age, especially among women. In addition, standard risk factors often show inconsistent associations with CHD among the elderly and are therefore somewhat less useful to identify high-risk individuals than they are in middle age.16-18 Other risk factors, however, may become more important in older age. For example, results of recent studies19,20 suggest that impaired physical function poses a significant risk for CHD death and survival after myocardial infarction (MI) in the elderly. Because depressive symptoms are often a corollary of declining health and impaired function,21 it is important to investigate whether depression is associated with CHD outcomes independent of impaired physical function.

Another largely unresolved issue in this research is whether the adverse effect of depression is limited to those with “severe” depression, for example, clinically diagnosed depressive disorder, or whether the risk increases linearly with increasing symptom levels. Although results of some studies1-4,13-15 suggest that the increased risk for incident or recurrent CHD outcomes caused by depression is limited to either clinical depression or high symptom levels, results of other studies6,7,11,13 are more consistent with a gradient association between depression and CHD.

Data from the New Haven, Conn, cohort of the Established Populations for the
PARTICIPANTS AND METHODS

STUDY POPULATION

Participants came from the New Haven sample of the EPESE project, 1 of 4 sites funded by the National Institute on Aging, Bethesda, Md, and the only EPESE site that has undertaken a review of medical charts of all patients hospitalized for suspected MI. The cohort was assembled by obtaining a stratified probability sample of the noninstitutionalized New Haven population aged 65 years and older living in 3 housing strata: public housing for the elderly (age and income restricted), private housing for the elderly (age restricted), and general community housing. The sampling strategies varied by housing stratum and included an oversampling of men. The response rate for the combined strata was 82%, yielding a sample at baseline of 2812 participants, including 1169 men and 1643 women. Of these, 324 participants (11.5%) with a physician-diagnosed history of MI at baseline were excluded because depression has been shown to affect post-MI survival. Of the remaining 2488 participants, 97 (3.9%) had missing data concerning depression, leaving 2391 participants for the analysis.

DATA COLLECTION AND MEASURES

Baseline data collection took place during in-home, face-to-face interviews in 1982 by trained EPESE interviewers. Contact with the cohort during follow-up was maintained by annual telephone interviews and in-home, face-to-face interviews every 3 years. Although these interviews served to update information on many variables that were assessed at baseline, we will rely on baseline information only in the present analysis to allow for a longer follow-up. Information on the end points of incident MI and CHD mortality was collected by evaluation of medical records and review of death certificates, respectively (see below).

Depressive Symptoms

The Center for Epidemiologic Studies Depression (CESD) Scale is a 20-item self-report scale designed to measure depressive symptoms in the general population. The items are scored on a 4-point (range, 0-3) scale, and individual item scores are totaled to yield a summary score, with higher scores indicating more symptoms. Participants having 4 or more items missing were excluded from the analyses, otherwise a total score was computed by imputing scores for missing items using the mean of the nonmissing items. In the analysis, we will use both the continuous CESD score and a dichotomous classification to identify participants with a “high” level of depressive symptoms. Although a cutoff score of 16 is usually used for this purpose, recent data indicate that a CESD score of 21 or higher is the optimum cutoff point among elderly participants. For convenience, we will use the term “high depression” to indicate a CESD score of 21 or higher, although these scores do not represent a clinical diagnosis of depression. For graphical presentation of the gradient effect of depressive symptoms, we also divided the CESD score into 5 categories representing scores from 0 to 1, 2 to 4, 5 to 9, 10 to 20, and 21 or higher. The highest category corresponds to the “depressed” category of the dichotomous classification, and the remainder of the scores were divided into 4 roughly equal subgroups.

CHD Risk Factors

Self-report information was obtained on smoking status (current, past, or never) and physician-diagnosed history of diabetes. We used exertional chest pain, as derived from a subset of the questions from the London School of Hygiene Chest Pain Questionnaire, to classify angina, rather than the Rose scale, because a previous analysis of the EPESE data had shown that exertional chest pain was a slightly better predictor of CHD mortality than the total Rose scale. As in a previous analysis, we used a 4-level variable for blood pressure based on actual blood pressure readings according to the Hypertension Detection and Follow-up Program. After averaging the systolic (SBP) and diastolic (DBP) blood pressures of the second and third readings, the following risk groups were created sequentially starting from the highest risk group: (1) SBP of less than 140 mm Hg and DBP of less than 90 mm Hg; (2) SBP of 140 to 159 mm Hg or DBP of 90 to 94 mm Hg; (3) SBP of 160 to 200 mm Hg or DBP of 95 to 99 mm Hg; and (4) SBP of 200 mm Hg or greater or DBP of 100 mm Hg or greater.

Physical Functioning

Physical functioning was measured by 4 questions about mobility-related functions of various intensities derived from commonly used instruments of physical function in the elderly. The items assessed the ability to walk up and down stairs, to walk a half mile, to walk across a small room, and to transfer from a bed to a chair. Responses to individual

Epidemiologic Studies of the Elderly (EPESE) project provided an opportunity to prospectively test the relationship between depression and CHD risk in a large, community-based sample of the elderly. Because it has been suggested that depression plays a larger role in CHD risk in women than in men, we also specifically tested for sex differences in the relationship between depression and CHD outcomes.

Table 1 shows the baseline characteristics of the 2391 men and women included in this analysis and their association with depressive symptom levels. Overall, participant ages ranged from 65 to 99 years, with 43.3% aged 75 years and older; 60.5% of the participants were women. Depressive symptom levels were higher among older participants (P = .001), among women (P < .001), and among participants with fewer years of education (P < .001). Also, participants with diabetes, exertional chest pain, and 1 or more mobility impairments reported significantly higher symptom levels. Smoking status and blood pressure group were unrelated to depressive symptoms. A total of 201 participants (8.4%) had a CESD score of 21 or higher.

Among participants without a history of MI at baseline, there were 208 nonfatal MIs, 255 CHD deaths,
items were totaled (range, 0-4), with higher scores indicating higher physical function. These mobility-related functions were selected from a larger pool of physical function items because they were thought to be the most closely related to cardiovascular disease.

**Sociodemographic Variables**

Of all sociodemographic information available in the data set, the variables used in the analyses included age (coded in single years), sex, and education (years of schooling completed). Other variables, such as ethnicity, marital status, and income, did not contribute significantly to the prediction of outcomes and did not have a confounding effect over and above the selected control variables.

**Incident CHD Events**

Incident CHD events were defined as CHD mortality and total incident CHD events (nonfatal MI and CHD death). Participants hospitalized for MI during follow-up were identified by a surveillance system that conducted weekly reviews of all hospitalizations in the 2 local hospitals. All admissions for CHD were reviewed to identify New Haven EPESE study participants. Additional information on hospital admissions was obtained from the Medicare Part A Beneficiary Bill History data from the Health Care Financing Administration. Matching data on hospitalization from these 2 sources indicated that the surveillance system identified 99% of all CHD-related admissions. All participants with a discharge diagnosis of acute MI (International Classification of Diseases, Ninth Revision, Clinical Modification32 code 410.0-410.9) were identified, and the medical records were reviewed to verify the diagnosis of MI, requiring 2 of the following 3 criteria: (1) central anterior chest pain lasting at least 15 minutes or other symptoms consistent with MI (acute pulmonary edema, cardiogenic shock, or cardiac arrest); (2) characteristic electrocardiographic abnormalities, ie, new Q waves (>0.04 seconds) or ST-segment elevations or depressions in at least 2 leads; and (3) a typical rise and fall of the serum creatine kinase level with an increase of the MB fraction to 4% or greater. If there were no Q waves, then serum enzyme level elevations were required for the diagnosis of MI. To capture MIs potentially misclassified as unstable angina, medical records of participants with a discharge diagnosis of unstable angina (unless previously hospitalized for an MI) were reviewed. Patients who had more than 1 MI during follow-up were analyzed only in relation to their first event.

Mortality during follow-up was ascertained by monitoring local newspapers' obituary notices, by receiving information from relatives, and by eventually obtaining the death certificates of all deceased participants. Information on vital status was virtually complete (>99% of all cohort members). All death certificates were coded by a certified nosologist. Coronary heart disease mortality was defined as an underlying cause of death on the death certificate coded 410 through 414 according to the International Classification of Diseases, Ninth Revision, Clinical Modification.32

**ANALYSIS**

The risk associated with depressive symptoms for CHD events was analyzed using Cox (proportional hazards) regression models, with time to event as the dependent variable. The proportionality assumption was examined separately for each outcome (CHD mortality and total CHD events) for the dichotomous CESD variable and the 5-level CESD variable using the Grambsch and Therneau test in S-Plus.33 Time plots of the scaled Schoenfeld residuals were inspected to confirm the Grambsch and Therneau test results. These test results revealed no significant departures from proportionality in hazards over time.

The primary analysis was aimed at examining the association of depressive symptoms as a continuous variable (“gradient” effect) with CHD outcomes. In additional analyses, we tested for a possible “threshold” effect of depressive symptoms on CHD risk. This was done in 2 ways: we first modeled CESD scores as a dichotomous variable (high depression), and next we computed a separate model with the continuous CESD score as well as a CESD squared term (centered around the median CESD value of 8) as predictor variables.

The main analysis consisted of a series of proportional hazards models. The first step included adjustment for age only, the second step included additional adjustment for covariates representing other CHD risk factors that were available (education, smoking status, blood pressure group, diabetes, and exertional angina), and the final step consisted of adding physical functioning to the model. Sex differences in the effect of depressive symptoms were explored graphically (Figure 1) and were tested by adding an interaction term for sex by CESD scores to the age-adjusted proportional hazards models. Deaths by other causes were censored at the time of the event. We used SUDAAN statistical software34 to account for the complex sampling design of the New Haven EPESE cohort. All results are based on weighted analysis unless otherwise indicated.

Figure 1 shows the rate per 1000 person-years for CHD mortality and total CHD incidence by level of depressive symptoms. For the total cohort, the association of incident CHD events with depressive symptom levels followed a roughly linear trend, although the highest symptom group showed the greatest absolute increase compared with the next highest level. The graph also illustrates that the relationship between depressive symptoms and CHD risk differed considerably between men and women. For men, there is no indication that higher symptom levels are associated with higher risk; in fact, the risk was lowest in the group with the highest CESD scores. For women, the plots suggest a high-risk group in the highest symptom group, although, especially for total CHD events, the risk also showed a gradient effect at the lower symptom levels.
The differential effect by sex in the association between depressive symptoms and CHD outcomes was confirmed in the proportional hazards models, which revealed a significant sex by CESD scores interaction term \((P<.05\) for all) for both CHD outcomes. We, therefore, calculated separate risk estimates for men and women \((Table 3\). There was no significant association of depressive symptoms with either CHD end point among men. Among women, however, depressive symptom levels showed a significant age-adjusted association with CHD mortality (relative risk [RR] = 1.03, 95% confidence interval [CI] = 1.01-1.05) and with total CHD incidence (RR = 1.03, 95% CI = 1.01-1.04). These associations were largely unaffected by standard CHD risk factors. Additional adjustment for impaired physical function attenuated the associations of depressive symptoms with incident CHD end points, and, although still positive, they were no longer statistically significant \((Table 3\).

To illustrate the magnitude of the effect of depressive symptoms on CHD risk, we calculated the RRs at the median values of each of the 5 CESD categories \((0-1, 2-4, 5-9, 10-20, \text{ and } \geq 21)\) using the results of the multivariate models shown in \(Table 3\). As shown in \(Figure 2\), the second highest symptom group (median CESD score = 14) had an increased RR of 1.52 \((95\% \text{ CI} = 1.09-2.12)\), and the highest symptom group (median CESD score = 27) had an increased RR of 2.25 \((95\% \text{ CI} = 1.19-4.24)\) compared with the lowest symptom group after adjustment for CHD risk factors. Additional adjustment for impaired physical function reduced the risks by approximately half, and these risks were no longer statistically different from the risk among women with no symptoms.

Other significant predictors of CHD mortality in the final proportional hazards models included age \((RR = 1.12, 95\% \text{ CI} = 1.08-1.16)\), current smoking \((RR = 2.22, 95\% \text{ CI}, 1.17-4.20)\), diabetes \((RR = 3.11, 95\% \text{ CI} = 1.88-5.15)\), and each additional level of impaired physical function \((RR = 1.36, 95\% \text{ CI} = 1.10-1.69)\). Similar associations were found in the models for total CHD incidence.

![Figure 1. Coronary heart disease death (left) and total event (right) rates during follow-up (1982-1991) by depressive symptoms. 1 indicates Center for Epidemiologic Studies Depression (CESD) category 0 to 1; 2, CESD category 2 to 4; 3, CESD category 5 to 9; 4, CESD category 10 to 20; and 5, CESD category 21 or higher.](image-url)
The role of depression in CHD has drawn increasing attention in recent years, not only with regard to its adverse impact on prognosis among patients with established CHD but also with regard to its potential contribution to the pathogenesis of CHD. Although several well-conducted, prospective studies have reported findings in support of an increased risk associated with depression for incident CHD events, our investigation focused specifically on the elderly, the age at which the preponderance of heart disease becomes clinically manifest. Moreover, our sample was ethnically and socioeconomically diverse and broadly representative of community-dwelling elderly participants in general. The only other study on depression and incident CHD end points in the elderly involved a secondary analysis of data from the Systolic Hypertension in the Elderly Program (SHEP) trial. The latter results, however, have more limited generalizability because the participants in the SHEP trial were considerably healthier than are community-dwelling elderly individuals in general.

Our findings suggest that among older women, but not older men, depressive symptoms are associated with an increased risk for incident CHD events independent of established CHD risk factors. However, additional adjustment for impaired physical function decreased the risk for incident CHD outcomes to non-significant levels, with a reduction in risk estimates of about 50%. We also examined whether the risk for inci-
dent CHD events might be mostly restricted to those with unusually high symptom levels. Among men, there was no consistent relationship between symptom levels and outcomes. The relationship among women seemed more consistent with a gradient effect for increasing symptom levels rather than a threshold effect at high symptom levels, although neither effect survived adjustment for physical function. Thus, our data are not consistent with the notion that the “clinically” depressed form a special risk category for incident CHD events, although we certainly cannot dismiss this possibility entirely because of the lack of a clinical diagnosis of depression.

The findings suggest that depressive symptoms may be related to CHD risk in older women because of their correlation with impaired physical function. Impaired physical function is often considered a measure of general frail health, resulting from the cumulative burden of morbidities incurred throughout life. It is highly predictive of overall mortality in the elderly and has shown strong associations with CHD mortal-

ity, severity of MI, and post-MI survival. Impaired physical function also may be more specifically related to CHD end points as a potential marker of subclinical disease. Physical function represents mobility-related activities, such as walking a half mile or climbing stairs, and older persons may reduce these kinds of activities to prevent coronary ischemic episodes or because of other preexisting cardiovascular conditions, such as intermittent claudication or congestive heart failure. Impaired function might also result from silent ischemic events or asymptomatic MIs, the incidence of which is known to increase with age and predispose to cardiac death. Regardless of how impaired physical function affects CHD risk, it is strongly correlated with depressive symptoms and perhaps overwhelms any independent effect of these symptoms on CHD outcomes.

Although our findings seem to negate a truly independent contribution of depression to coronary risk in the elderly population in general, the results from our exploratory analysis are suggestive of an independent effect of these symptoms in a subgroup of elderly women, that is, women who are in relatively good physical health, defined in our analysis as those who survived at least 3 more years event-free or who had no mobility-related impairments. This would be consistent with the generally much stronger associations between depression and incident CHD outcomes in middle-aged populations, where the prevalence of impaired physical function, or overall frail health, is minimal. It is also consistent with the increased risk associated with depression for CHD outcomes among the relatively healthy women in the SHEP trial. In addition, there is some evidence that suggests that depression may actually precipitate a decline in physical functioning. This raises the possibility that impaired physical function is perhaps an intermediary step in the causal pathway between depression and CHD events, for example, by being a manifestation of early or subclinical disease. In this case, controlling for physical function might, in fact, have amounted to overadjustment. Thus, our findings do leave open the possibility that depressive

Figure 2. Adjusted relative risks for coronary heart disease (CHD) mortality among women by depressive symptoms. 1 indicates a Center for Epidemiologic Studies Depression (CESD) score of 0; 2, a CESD score of 3; 3, a CESD score of 7; 4, a CESD score of 14; and 5, a CESD score of 27.

Figure 3. Coronary heart disease mortality rate among women by physical function status (left) and follow-up period (right). 1 indicates Center for Epidemiologic Studies Depression (CESD) category 0 to 1; 2, CESD category 2 to 4; 3, CESD category 5 to 9; 4, CESD category 10 to 19; and 5, CESD category 20 or higher.
symptoms contribute independently to risk for acute CHD events in healthier older women.

Various mechanisms have been proposed to account for the increased risk for CHD outcomes associated with depression in middle-aged populations and that may also play a role in healthier older women. For example, depression has been linked to altered neuroendocrine function involving the adrenergic and corticosteroid systems, to poor adherence to medical treatment, and to co-occurrence with established risk factors. Depression is also thought to increase coronary risk by promoting arrhythmogenic events through its impact on autonomic tone, especially increased sympathetic tone and decreased vagal tone. Altered autonomic tone has been shown to increase risk for ventricular arrhythmias and sudden cardiac death by a number of mechanisms, including elevated catecholamine levels, prolongation of the electrocardiographic QT interval, and reduced heart rate variability.

The lack of an association between depressive symptoms and CHD risk among older men was unexpected. Most recent studies fail either to report or to find a differential effect by sex. However, data from the SHEP trial also showed no association between depression and CHD risk in older men but a positive association in older women, although the SHEP findings were limited to women who reported an increase in depressive symptoms. We also considered examining changes in depression status, but the power for this analysis was very limited, partly because of missing depression data during follow-up. A recent study using combined data from 3 EPES sites found some evidence for an association between changes in depression status and increased risk for incident cardiovascular disease. However, this effect was, in contrast to those of the SHEP trial, limited to men, and more studies are clearly needed to establish whether changes in depression reliably increase risk for incident CHD in elderly men or women. Our approach of classifying individuals according to initial depression status is consistent with most other studies on this subject and our findings raise doubt that a single assessment of depression is a useful predictor of incident CHD in the elderly.

In summary, similar to traditional CHD risk factors, depression does not predict CHD outcomes nearly as consistently in this older population as it does in middle-aged populations. Depression was not associated with an increased risk for incident CHD among older men, whereas among older women the increased risk is possibly limited to those who are relatively healthy or who do not have serious limitations in physical function. Except for perhaps in this latter group, our data suggest that these symptoms may not be useful for the identification of older persons at high risk for CHD, and, unlike for the secondary prevention of CHD, targeting these symptoms is unlikely to be an effective strategy for the purpose of primary prevention. However, our findings, together with those of the SHEP trial, lend some support to the notion, advocated by others, that depression is possibly a more important risk factor for CHD in women than it is in men.

REFERENCES


