Depression as an Antecedent to Heart Disease Among Women and Men in the NHANES I Study

Amy K. Ferketich, MA; Judith A. Schwartzbaum, PhD; David J. Frid, MD; Melvin L. Moeschberger, PhD

Background: Depression predicts morbidity and mortality among individuals who have coronary heart disease (CHD), and there is increasing evidence that depression may also act as an antecedent to CHD. The studies that have reported a relationship between depression and CHD incidence or mortality either were restricted to men only or analyzed women and men together. The present investigation was conducted to evaluate the differential effect depression may have on CHD incidence and mortality in women and men.

Research Methods: We analyzed data from 5007 women and 2886 men enrolled in the first National Health and Nutrition Examination Survey (NHANES I) who were free of CHD at the 1982-1984 interview and who had completed the Center for Epidemiologic Studies Depression Scale (CES-D). Participants were evaluated from the 1982 interview date either until the end of the study (1992 interview date) or until the occurrence of a CHD event. Using CHD incidence and CHD mortality (International Classification of Disease, Ninth Revision, codes 410-414) as the outcome variables, Cox proportional hazards regression models were developed to evaluate the relative risk (RR) of CHD incidence and mortality in the depressed women and men separately, controlling for standard CHD risk factors.

Results: The women experienced 187 nonfatal and 137 fatal events, compared with 187 nonfatal and 129 fatal events among the men. The adjusted RR of CHD incidence among depressed women was 1.73 (95% confidence interval [CI], 1.11-2.68) compared with nondepressed women. Depression had no effect on CHD mortality in the women (RR, 0.74; 95% CI, 0.40-1.48). The adjusted RR of CHD incidence among depressed men was 1.71 (95% CI, 1.14-2.56) compared with nondepressed men. Depressed men also had an increased risk of CHD mortality compared with their nondepressed counterparts, with an adjusted RR of 2.34 (95% CI, 1.54-3.56).

Conclusions: In this sample, while controlling for possible confounding factors, depression was associated with an increased risk of CHD incidence in both men and women, as well as CHD mortality in men. Depression had no effect on CHD mortality in women.

Arch Intern Med. 2000;160:1261-1268

Depression is not unusual among individuals with coronary heart disease (CHD), with studies indicating that between 15% and 22% of patients suffer from depression after a cardiac event. In patients who have CHD, depression is associated with a reduction in both short- and long-term survival. Barefoot and coauthors evaluated patients with CHD for up to 19.4 years and found that depressed individuals experienced a greater risk of mortality than did nondepressed individuals. The authors speculate that long-term risk may be caused by factors that advance atherosclerosis, such as altered neuroendocrine function and failure to adhere to lifestyle behaviors that are recommended for the patient with CHD.

The question of whether depression promotes CHD in individuals who are free of disease has also been examined. The results from the Precursors Study indicate that depression predicts CHD and myocardial infarction (MI) in men, even after adjusting for possible confounding variables. Barefoot and Schroll evaluated a Danish cohort for 27 years and found that depression was associated with an elevated risk of MI. The authors also reported that a sex-depression interaction was not statistically significant. However, there may have been too few events to detect an interaction, since there were only 30 events among the 366 women during the follow-up. Pratt et al reported the results from a follow-up study conducted on the Baltimore cohort of the Epidemiologic Catchment Area Study, a

From the Division of Epidemiology and Biometrics (Ms Ferketich and Drs Schwartzbaum and Moeschberger) and Department of Internal Medicine (Dr Frid), The Ohio State University College of Medicine and Public Health, Columbus.
METHODS

The NHANES I was conducted from 1971 through 1975 by the National Center for Health Statistics as a probability sample of the noninstitutionalized population of the United States. The design involved oversampling of certain subgroups, including women of childbearing age, the elderly, and persons living in poverty areas. The survey included questions on sociodemographics, medical history, diet, and biochemical and anthropometric measures. Of the original cohort, 14,407 adults were included in the National Health and Nutrition Examination Follow-up Study (NHANES). Follow-up interviews were conducted in 1982, 1986, 1987, and 1992. The 1982 follow-up interview included an assessment of depression based on the Center for Epidemiologic Studies Depression scale (CES-D). In the present investigation, we analyzed the follow-up data for the cohort of participants who completed the CES-D from the 1982 interview date until the 1992 interview date. Of the 8111 individuals who participated in the 1982 follow-up interview and reported having no history of heart disease, 7928 (97.7%) completed the self-administered depression questionnaire. Compared with participants who completed the CES-D, the participants who did not complete the CES-D were older (58.2 vs 54.5 years) and of lower socioeconomic status (243% vs 277% of the federal poverty level). Furthermore, participants who did not complete the CES-D were less likely to be married than participants who completed the CES-D. However, the outcomes were not associated with whether the CES-D was completed. Participants who did not complete the CES-D were not at greater risk for nonfatal CHD (relative risk [RR], 1.11; 95% confidence interval [CI], 0.53-2.23) or fatal CHD (RR, 0.92; 95% CI, 0.47-1.79) compared with the completers.

DEFINITION OF DEPRESSION

The CES-D is a self-report scale designed to measure the current prevalence of depressive symptoms in the general population. The scale consists of a series of 20 questions, and each question is rated from 0 to 3, with 0 indicating that the symptom was experienced rarely or not at all during the past week and 3 indicating that the symptom was experienced most or all of the time during the past week. A rating of 1 or 2, or at least 6 symptoms were assigned a score implies that many of the symptoms were assigned a score. Between depressed and nondepressed patients because such scores other than the traditional cutpoint of 16 have been suggested to classify depression.

DEFINING THE STUDY COHORT

The participants who had complete data for the CES-D were considered in the analysis (5946 women and 3560 men). Next, individuals who reported a history of a physician-diagnosed heart condition, heart attack, or angina were excluded (920 women and 658 men). An additional 20 women and 14 men were excluded because of missing information on covariates. Thus, the analysis is based on 5006 women and 2888 men.

As stated above, the cohort interviewed in 1982 was evaluated until 1992, the year of the final follow-up interview. At that time, all participants not experiencing the event of interest were censored. That is, all follow-up information was used on those participants even though the event did not occur. Individuals lost to follow-up were censored at their last interview date (either the 1986 or 1987 date). If an individual did not participate in a follow-up interview after the 1982 interview, he or she was censored at 0.25 year. The model used to analyze the data, a Cox proportional hazards model, allows for censored data. Therefore, rather than eliminate the information on the participants who were not interviewed after 1982 (n = 179), we made the decision to use their information for 3 months. Seven percent of those in the sample were lost to follow-up. Participants lost to follow-up had higher depression scores than those who were evaluated until the 1992 interview (10.17 vs 7.91). Because depression scores were higher among participants who did not complete the study, the RR estimates for CHD incidence and mortality associated with depression may be conservative.

DEFINING THE FATAL EVENTS

Deaths among NHANES I cohort members were identified using the National Death Index and through tracing of vital status via proxy interview. The underlying causes of death on the death certificates are classified according to the International Classification of Diseases, Ninth Revision (ICD-9). For this study, the codes 410 to 414 were used to classify CHD-related deaths. We also looked at all-cause mortality to determine if depression was related to other fatal outcomes.
DEFINING THE NONFATAL EVENTS

To determine the incidence of nonfatal CHD events, data from hospital discharge records were used. Medical records were obtained from the hospitals where individuals had reported being hospitalized between 1982 and 1992. Discharge diagnoses were recorded by medical coders using ICD-9 codes. Each record included room for up to 10 diagnoses. Individuals who had a record with at least one ICD-9 code in the 410-414 range were defined as having a CHD event. We also looked at the subgroup of patients who had an ICD-9 code of either 410 (acute MI) or 411 (other acute and subacute ischemic diseases), as these codes represent acute events. Only first events were considered; therefore, individuals ceased to contribute time after the first diagnosis.

It is possible that the number of CHD events obtained by reviewing the health care facility stay records is lower than the number that actually occurred in the sample. Between 1982 and 1992, 23,301 health care facility stays were recorded.14-16 Fifty-six percent of these records were matched to a participant self-report; that is, a participant reported the stay and complete information from the facility was available. Twenty-four percent of the records were not matched. In these cases, a participant reported a stay but no information from the health care facility was available. Finally, 20% of the records corresponded to additional stays found. Thus, a facility reported an additional stay that was not reported by the participant. Because 24% of the self-reports had no associated information from the health care facility, it is possible that a greater number of CHD events occurred during the follow-up period. It is also possible that more events occurred but were not reported by the participant, and therefore no attempt was made to contact the facility. No information is available for specific diagnoses; however, if CHD event rates follow the same pattern, this would be a problem of nondifferential misclassification. This type of misclassification would result in an underestimation of the effect of depression in the analyses.

DATA ANALYSIS

The percentage distributions for possible confounders were first evaluated among depressed and nondepressed participants separately in men and women. Race was categorized as white and black/other. Hypertension and diabetes were defined as a positive response to the questions asking whether a physician had ever diagnosed the participant with hypertension or diabetes. Smoking was dichotomized into never/former and current smoker. Alcohol use was ordered according to the total number of drinks of beer, wine, and spirits: nondrinker, 1 drink or less per day, and more than 1 drink per day. A self-report assessment of the participant’s usual recreational activity was used to classify individuals as sedentary, engaging in light exercise, or engaging in regular exercise. Marital status was assessed with 3 categories: single, married, and divorced/widowed/separated. Finally, the mean poverty index (percentage of the US poverty level) and body mass index (BMI) were compared between the depressed and nondepressed participants.

The relationships between depression and CHD incidence and between depression and CHD mortality were evaluated separately in men and women using Cox proportional hazards regression models. The data are left truncated, since individuals entered the study free of disease at different ages. Therefore, the analysis was conditional on the age at which the participant entered and left the study (because of either experiencing the event or being censored), because it is assumed that the hazard changes more as a function of age than of time in the study. For a description of the method, see Klein and Moeschberger17 and Korn et al.18

Four models were then developed to determine the effect that depression had on CHD incidence and mortality in men and women, adjusting for confounding variables. A combination of backward elimination and forward selection techniques was used to select variables. A variable was included in the model either if $P < .20$ or if its removal affected the parameter estimate for depression by at least 20%.19 In all of the models, continuous variables were entered as continuous variables and quadratic functions. The likelihood ratio test was used to determine if the quadratic terms added significantly to the model. The final model was then checked for proportional hazards by comparing a model that included log(time) interactions with each independent variable with the model that included only the independent variables. The likelihood ratio test was used to compare these 2 models. In the male incidence model, smoking did not meet the proportional hazards assumption. A term that accounted for the interaction between smoking and log(time), which was the function of time used to check the proportional hazards assumption, was included in the final model.

In the mortality analyses we had to address the fact that some patients had nonfatal CHD events prior to the fatal CHD event. Nonfatal events predict depression and they increase risk of CHD mortality. Thus, if caused by a mechanism other than depression, nonfatal events should be treated as a confounding variable in the relationship between depression and fatal CHD. On the other hand, nonfatal CHD events are intermediate steps between depression and fatal CHD; that is, depression may lead to a nonfatal event, which then results in fatal CHD. Although there are methods for doing so, we did not have enough information to treat depression as both a confounding variable and an intermediate step in the fatal CHD analyses. Such an assessment would have required repeated measurements of depression over time. We decided to treat nonfatal events as time-dependent covariates in the mortality analyses. This resulted in conservative RR estimates; however, the conclusions did not differ from those in the models that did not include nonfatal events as covariates (results not shown).

Interactions between depression and smoking and between depression and poverty (135% of the poverty level was selected as the cutpoint for defining poverty) were then examined. The interactions between depression and smoking and between depression and poverty were chosen based on their relationship to depression and CHD. Previous studies have shown that the prevalence of depression has a negative relationship to household income.4,10 Furthermore, living close to the poverty level may be associated with an increased risk of CHD. Smoking

Continued on next page
is an established risk factor for CHD, and Anda et al\textsuperscript{21} reported that depression plays a role in individual’s current smoking status and the probability of quitting smoking. It is therefore possible that an interaction exists between depression and either poverty level or smoking status.

To eliminate the possibility that subclinical disease biased the relationship between depression and CHD, the analysis was performed a second time after excluding the first 2 years of follow-up. We also wanted to eliminate the possibility that antidepressant or tranquilizer use confounded the effect of depression on CHD incidence and mortality, since these medications may be related to mortality. We tested for an effect of self-reported use of antidepressants and tranquilizers at baseline (1982 interview) in the final models.

We then looked at the effect of varying the cutpoint on the 2 outcomes. We computed age-adjusted RR estimates for each outcome separately, using each score between 0 and 25 as a possible cutpoint. The data became sparse after a CES-D score of 25, and therefore the estimates may not be stable. We did this separately for men and women and then plotted the RR vs the CES-D score.

The prevalence of depression differs between men and women. Women in the Barefoot and Schroll\textsuperscript{4} study or tested for an interaction but observed none, likely owing to a differential effect of depression in men and women, or tested for an interaction but observed none, likely owing to low power.

The prevalence of depression differs between men and women. Women in the Barefoot and Schroll\textsuperscript{4} study had significantly higher scores on the depression scale than did the men. Similarly, Anda et al\textsuperscript{8} reported a higher percentage of women with depressed affect than men (13.5% vs 8.5%). In the Pratt et al\textsuperscript{5} investigation, 74% of the participants with a history of major depressive disorder were female. Thus, there is evidence that women tend to be more susceptible to depression than men. Whether this higher susceptibility affects the relationship between depression and CHD is not known. The present investigation was conducted to test the hypothesis that the effect of depression on CHD incidence and mortality differs in men and women. A large, nationally representative data set was used to examine this question.

The mean ± SD ages for the women and men were 53.7 ± 13.9 and 55.9 ± 14.4 years, respectively. The mean ± SD CES-D score for the women was 8.79 ± 8.60. Using 16 as the cutpoint for defining depression, 17.5% of the women were classified as depressed. The men had a lower mean ± SD CES-D score, 6.77 ± 7.13, and 9.7% were depressed. The prevalence of sociodemographic and cardiac risk factors among depressed men and women is presented in Table 1. Among both men and women, depressed individuals were more likely to be in the following categories: age 50-59 and 70+ years, black, smoker, nondrinker, diabietic, hypertensive, sedentary, and not married. Also, the mean poverty index was lower for depressed men and women. Depressed women had a higher BMI than women who were not depressed. The mean duration of follow-up was 8.3 years (range, 0.02-11.1 years). Women experienced 187 nonfatal and 137 fatal CHD events. Men experienced 187 nonfatal and 129 fatal CHD events.

### DEPRESSION AND CHD IN WOMEN

The crude RR of nonfatal CHD among women scoring 16 or higher on the CES-D was 1.32 (95% CI, 0.94-1.87). We then decided to use the cutpoint of 23 to define depression in the female sample because, as stated above, the higher score reduces the false-positive classification rate from 16.6% to 7%.\textsuperscript{12} Also, women generally have higher scores on the CES-D, and this may be because the CES-D scale is sex biased. Stommel et al\textsuperscript{22} found that the responses to 2 items on the CES-D (“talked less than usual” and “had crying spells”) depended on the sex of the respondent, even after controlling for the general level of depressive symptoms. It was thought that the higher cutpoint would reduce the misclassification of depression among the truly nondepressed women. All further results are based on the classification of depression using the cutpoint of 23. The crude RR of nonfatal CHD among women scoring 23 or higher on the CES-D was 2.09 (95% CI, 1.35-3.23). Table 2 contains the crude and adjusted RR estimates. The final model included the following variables: poverty index and (poverty index)\textsuperscript{2}, diabetes, hypertension, smoking, and BMI. The adjusted RR of nonfatal CHD among depressed women was 1.73 (95% CI, 1.11-2.68). After eliminating the first 2 years of follow-up, the risk decreased slightly, to 1.68 (95% CI, 1.01-2.79).

The crude and adjusted RR estimates of acute CHD events (corresponding to ICD-9 codes 410 and 411)
associated with depression among women are listed in Table 2. The adjusted RR estimate of an acute event among depressed women was 1.56 (95% CI, 0.80-3.03). There were only 88 such events; therefore, there may not have been enough power to detect a significant elevation in risk.

The crude RR for fatal CHD associated with depression among women was 1.02 (95% CI, 0.53-1.94). After adjusting for poverty index, smoking, diabetes, BMI, and nonfatal events during the follow-up period, the RR decreased to 0.74 (95% CI, 0.40-1.48). The adjusted RR of all-cause mortality associated with depression among women was 1.21 (95% CI, 0.90-1.62). Depression therefore had no effect on fatal CHD or on all-cause mortality among women. The RR estimates for fatal events are listed in Table 2.

Neither tranquilizer use nor antidepressant use had an effect on CHD incidence and mortality among women, and use of these medications did not affect the RR estimates associated with depression (results not shown).

The RR estimates of nonfatal CHD for smokers who were not depressed and depressed participants who were not smokers, compared with those who did not smoke and were not depressed, were similar: 1.66 (95% CI, 1.00-2.78) and 1.75 (95% CI, 1.19-2.57), respectively. However, the RR estimate for smokers who were depressed compared with those who did not smoke and were not depressed was 3.38 (95% CI, 1.47-7.78). A statistical test for the interaction term was not significant (P = .77). No interaction between poverty and depression was apparent, and no interaction effects on the fatal event outcome were tested because of sparse data among depressed participants in some of the categories.

### DEPRESSION AND CHD IN MEN

The standard cutpoint of 16 on the CES-D was used to classify depression among men. The crude RR of nonfatal CHD associated with depression among men was 1.02 (95% CI, 0.53-1.94). After adjusting for poverty index, smoking, diabetes, BMI, and nonfatal events during the follow-up period, the RR decreased to 0.74 (95% CI, 0.40-1.48). The adjusted RR of all-cause mortality associated with depression among women was 1.21 (95% CI, 0.90-1.62). Depression therefore had no effect on fatal CHD or on all-cause mortality among women. The RR estimates for fatal events are listed in Table 2.

Neither tranquilizer use nor antidepressant use had an effect on CHD incidence and mortality among women, and use of these medications did not affect the RR estimates associated with depression (results not shown).

The RR estimates of nonfatal CHD for smokers who were not depressed and depressed participants who were not smokers, compared with those who did not smoke and were not depressed, were similar: 1.66 (95% CI, 1.00-2.78) and 1.75 (95% CI, 1.19-2.57), respectively. However, the RR estimate for smokers who were depressed compared with those who did not smoke and were not depressed was 3.38 (95% CI, 1.47-7.78). A statistical test for the interaction term was not significant (P = .77). No interaction between poverty and depression was apparent, and no interaction effects on the fatal event outcome were tested because of sparse data among depressed participants in some of the categories.

### DEPRESSION AND CHD IN MEN

The standard cutpoint of 16 on the CES-D was used to classify depression among men. The crude RR of nonfatal CHD associated with depression among men was 1.79 (95% CI, 1.19-2.67). After adjusting for poverty index, race, hypertension, BMI, smoking and smoking × time, the RR estimate decreased slightly, to 1.71 (95% CI, 1.47-2.56). Table 3 contains the crude and adjusted RR estimates. After eliminating the first 2 years of follow-up, the RR of CHD among the depressed men actually increased, to 2.03 (95% CI, 1.28-3.22).

There were 102 acute CHD events among the male cohort (ICD-9 codes 410 and 411). The crude and ad-

---

**Table 1. Distribution of Potential Confounders in Depressed and Nondepressed Subjects by Sex**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nondepressed (n = 2617)</th>
<th>Depressed (n = 280)</th>
<th>Nondepressed (n = 4132)</th>
<th>Depressed (n = 874)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-39</td>
<td>16.0</td>
<td>15.7</td>
<td>16.8</td>
<td>17.0</td>
</tr>
<tr>
<td>40-49</td>
<td>23.1</td>
<td>19.3</td>
<td>29.9</td>
<td>27.7</td>
</tr>
<tr>
<td>50-59</td>
<td>21.8</td>
<td>22.5</td>
<td>22.5</td>
<td>26.3</td>
</tr>
<tr>
<td>60-69</td>
<td>18.9</td>
<td>12.5</td>
<td>13.8</td>
<td>11.9</td>
</tr>
<tr>
<td>≥70</td>
<td>20.2</td>
<td>30.0</td>
<td>17.0</td>
<td>21.1</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>88.1</td>
<td>85.3</td>
<td>86.4</td>
<td>80.6</td>
</tr>
<tr>
<td>Black/other</td>
<td>11.9</td>
<td>14.7</td>
<td>13.6</td>
<td>19.4</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>23.8</td>
<td>28.6</td>
<td>26.5</td>
<td>34.5</td>
</tr>
<tr>
<td>No</td>
<td>76.2</td>
<td>71.4</td>
<td>73.5</td>
<td>65.5</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5.3</td>
<td>9.6</td>
<td>4.6</td>
<td>8.1</td>
</tr>
<tr>
<td>No</td>
<td>94.7</td>
<td>90.4</td>
<td>95.4</td>
<td>91.9</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never/former</td>
<td>69.5</td>
<td>64.6</td>
<td>73.8</td>
<td>67.3</td>
</tr>
<tr>
<td>Current</td>
<td>30.5</td>
<td>35.4</td>
<td>26.2</td>
<td>32.7</td>
</tr>
<tr>
<td>Alcohol use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nondrinker</td>
<td>26.6</td>
<td>35.8</td>
<td>48.0</td>
<td>58.1</td>
</tr>
<tr>
<td>≤1/d</td>
<td>48.0</td>
<td>41.4</td>
<td>43.7</td>
<td>33.5</td>
</tr>
<tr>
<td>&gt;1/d</td>
<td>25.4</td>
<td>22.8</td>
<td>8.3</td>
<td>8.4</td>
</tr>
<tr>
<td>Exercise</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedentary</td>
<td>25.2</td>
<td>38.7</td>
<td>32.5</td>
<td>48.4</td>
</tr>
<tr>
<td>Light exercise</td>
<td>52.7</td>
<td>41.2</td>
<td>52.5</td>
<td>40.4</td>
</tr>
<tr>
<td>Regular exercise</td>
<td>22.1</td>
<td>19.1</td>
<td>15.0</td>
<td>11.2</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>5.4</td>
<td>6.8</td>
<td>4.5</td>
<td>5.9</td>
</tr>
<tr>
<td>Married</td>
<td>82.0</td>
<td>65.6</td>
<td>66.2</td>
<td>53.2</td>
</tr>
<tr>
<td>Separated/divorced/widowed</td>
<td>12.6</td>
<td>27.6</td>
<td>29.3</td>
<td>40.9</td>
</tr>
<tr>
<td>Poverty index†</td>
<td>302.1 ± 149.8</td>
<td>270.8 ± 145.5</td>
<td>270.8 ± 146.3</td>
<td>234.8 ± 137.5</td>
</tr>
<tr>
<td>Body mass index†</td>
<td>25.9 ± 4.1</td>
<td>25.8 ± 4.2</td>
<td>25.1 ± 5.3</td>
<td>26.0 ± 5.9</td>
</tr>
</tbody>
</table>

*Values are percentages, unless otherwise indicated.
†Mean ± SD.
Table 2. Crude and Adjusted Relative Risk Estimates Associated With Depression (CES-D Score ≥23) in Women

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Crude Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All nonfatal CHD events†</td>
<td>187</td>
<td>1.79 (1.19-2.67) 1.71 (1.14-2.56)</td>
</tr>
<tr>
<td>Acute and subacute events‡</td>
<td>102</td>
<td>1.22 (0.65-2.28) 1.14 (0.61-2.14)</td>
</tr>
<tr>
<td>Fatal events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD events§</td>
<td>137</td>
<td>2.73 (1.81-4.12) 2.34 (1.54-3.56)</td>
</tr>
<tr>
<td>All fatal events†</td>
<td>572</td>
<td>1.85 (1.48-2.31) 1.69 (1.35-2.11)</td>
</tr>
</tbody>
</table>

*CES-D indicates Center for Epidemiologic Studies Depression scale; CI, confidence interval.
†Adjusted for poverty index and (poverty index)², smoking, hypertension, diabetes, and body mass index.
‡Adjusted for poverty index, smoking, hypertension, diabetes, and body mass index.
§Adjusted for poverty index, smoking, diabetes, body mass index, and nonfatal coronary heart disease events.

Table 3. Crude and Adjusted Relative Risk Estimates Associated With Depression (CES-D Score ≥16) in Men

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Crude Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All nonfatal CHD events†</td>
<td>187</td>
<td>1.79 (1.19-2.67) 1.71 (1.14-2.56)</td>
</tr>
<tr>
<td>Acute and subacute events‡</td>
<td>102</td>
<td>1.22 (0.65-2.28) 1.14 (0.61-2.14)</td>
</tr>
<tr>
<td>Fatal events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD events§</td>
<td>137</td>
<td>2.73 (1.81-4.12) 2.34 (1.54-3.56)</td>
</tr>
<tr>
<td>All fatal events†</td>
<td>572</td>
<td>1.85 (1.48-2.31) 1.69 (1.35-2.11)</td>
</tr>
</tbody>
</table>

*CES-D indicates Center for Epidemiologic Studies Depression scale; CI, confidence interval.
†Adjusted for poverty index, smoking, and smoking x natural log (age at coronary heart disease event), hypertension, race, and body mass index.
‡Adjusted for poverty index, smoking, race, hypertension, and body mass index.
§Adjusted for poverty index, smoking, race, hypertension, diabetes, body mass index, and nonfatal coronary heart disease events.
∥Adjusted for poverty index, smoking, race, hypertension, diabetes, and body mass index.

Neither self-reported tranquilizer use nor antidepressant use had an independent effect on CHD incidence and mortality, and use of these medications did not affect the RR estimates associated with depression among men. None of the interactions tested was significant.

VARYING THE CUTPOINT TO DEFINE DEPRESSION

Varying the cutpoint resulted in different patterns in men and women, and the patterns further differed according to the outcome. The results are presented in Figure 1. First, in women, there is only a slight increase in risk with each 1-point increase in the cutpoint until a CES-D score of 20, after which the risk increases more dramatically with each 1-point increase. In men, the risk increases slightly with each 1-point increase in the cutpoint until the CES-D score reaches 12, after which the RR estimates begin to increase more steeply. The RR estimates then decrease below 1.5 above a cutpoint of 20. It is important to note that there were only 10 events among the men who scored above 20. Therefore, these RR estimates may not be stable because of the sparse data. To assess which cutpoint is optimal, we looked at the −2 log likelihood from each model. The cutpoint that results in the model with the smallest −2 log likelihood (or largest log likelihood) is the optimal cutpoint.17 Among women, the model with the smallest −2 log likelihood was the one that used 24 as a cutpoint, and among men it was the model that used 15. We then evaluated the CES-D score as a continuous variable, adjusting for the potential confounders. Among women, a quadratic term for CES-D score was significant (P = .03). Among men, only the linear term was significant (P = .02). Therefore, 2 different continuous functions explained the relationship between CES-D score and nonfatal CHD events in men and women.

An entirely different pattern emerged when the fatal RR estimates were plotted against the CES-D score (Figure 2). Varying the cutpoint did nothing to alter the RR estimates in women. However, in men, beginning at a score of 10, the RR estimates increase rather sharply. As we did with CHD incidence, we determined...
which cutpoint was optimal for CHD mortality using the model −2 log likelihood values. For the men, 25 was the optimal cutpoint, and for the women, all models resulted in a similar −2 log likelihood value. We also analyzed the CES-D score as a continuous variable, and in the men a quadratic term was significant, even after adjusting for covariates (P<.001).

This study is the first to demonstrate that depression affects CHD risk in women. We have shown that the effect of depression on CHD risk differs in men and women. More severe levels of depression were related to nonfatal CHD events in women, but there was no relationship to fatal CHD. Among men, depression was related to both nonfatal and fatal CHD.

These findings are in agreement with previous investigations that analyzed the effect of depression on CHD incidence and mortality. As in the present investigation, Anda et al. evaluated data from NHANES I; however, they used the General Well-being Schedule to define depression, and their cohort consisted of the augmented sample interviewed at the baseline interview. They reported that the adjusted RRs of CHD incidence and mortality among depressed participants were 1.6 (95% CI, 1.1-2.4) and 1.5 (95% CI, 1.0-2.3), respectively. Similarly, Barefoot and Schroll reported an effect of depression on fatal and nonfatal myocardial infarction (adjusted RR, 1.7; 95% CI, 1.2-2.3). The recent data from the Precursors Study also suggest that depression acts as an antecedent to CHD. In their male cohort, the adjusted RR of CHD among depressed participants was 2.1 (95% CI, 1.2-3.6).

It is unclear why depression is related to CHD incidence but not mortality in women. In the Precursors Study, depressed men had an increased risk of total CHD events but not CHD mortality. However, Anda et al. found that depression had a similar relationship to fatal and nonfatal outcomes. In the present investigation, the effect of depression on CHD mortality was greater than its effect on CHD incidence in the male cohort.

Depression was only measured once, at the beginning of the study, which is the main limitation of this study. Serial measurements would have provided information on the dynamics of depression and how changes in depression affect CHD. Also, we could have evaluated chronicity and severity of depression and how these 2 indices relate to heart disease. Other investigators have faced a similar problem. In his original report on the properties of the CES-D, Radloff reported that the 1-year test-retest correlation (of total score) was 0.49 in a community sample. It is therefore possible that many of the individuals classified as depressed in 1982 remained in that classification throughout the follow-up period.

Another limitation of the study was the lack of information on serum cholesterol level in the 1982 interview. We cannot rule out the possibility that the results may be confounded because of unmeasured serum cholesterol levels. Other investigators had information on this risk factor, and controlling for cholesterol did not diminish the effect of depression on CHD. Thus, it is unlikely that unmeasured serum cholesterol levels acted as a strong confounding variable in the present study.

The strengths of this study include its prospective design, large sample, and relatively long follow-up period. Also, unlike previous studies of depression and CHD, we were able to analyze depression effects separately in women and men. Another strength of the present study and the NHANES I data set in general was the ability to control for many cardiac risk factors and demographic variables.

The present analyses controlled for baseline cardiac risk factors, socioeconomic status, and preexisting disease. Some of the participants may have had subclinical disease, which could have had an impact on both the CES-D score and the CHD event. After eliminating the first 2 years of follow-up, the relationships between depression and nonfatal CHD remained in both men and women, and the relationship between depression and fatal CHD remained in men; this indicates that subclinical disease did not affect the results.

There are several pathways by which depression may act to increase the risk of CHD. First, there is a general clustering of behavioral risk factors among depressed individuals that may affect the development of CHD. Depressed individuals are more likely to be current smokers and less likely to quit smoking than nondepressed individuals. In the present investigation, standard cardiac risk factors were controlled for in the analyses, making confounding by known risk factors an unlikely explanation. The second explanation for the relationship between depression and CHD is that altered autonomic tone affects heart rate variability, which then increases susceptibility to CHD. Carney et al. reported that depressed CHD patients had lower heart rate variability compared with nondepressed CHD patients, and this relationship was not caused by disease severity. The authors stated that lower heart rate variability was likely related to dysregulation of the autonomic nervous system, and it could place the individual at greater risk of ventricular fibrillation, leading to an increased risk of CHD death. Another possible mechanism linking depression to CHD is increased platelet aggregation. Fielding reviewed the literature and stated that elevated sympathetic activity may be present in depressed patients. Sympathetic catecholamines may

**Figure 2. Relative risk of fatal coronary heart disease event by Centers for Epidemiologic Studies Depression scale (CES-D) score.**
activate platelets and stimulate platelet-derived growth factor formation.\(^{23}\)

Future research should focus on defining the mechanism that links depression to elevated CHD risk in a non-coronary patient population. After specifying this relationship, interventions (behavioral and pharmacological) to reduce the risk of CHD in depressed individuals can be tested. Studies should also further examine the underlying relationship between depression and CHD. We found that continuous functions explained the relationship between depression score and nonfatal events in men and women and between depression score and fatal events in men. Analyzing the score as a continuous variable may be more desirable than classifying depression according to a cutpoint because misclassification of depression near the cutpoint could bias the results.

Accepted for publication October 14, 1999.

Presented at the 39th Annual Conference on Cardiovascular Disease Epidemiology and Prevention, American Heart Association Council on Epidemiology and Prevention, Orlando, Fla, March 26, 1999, and at the 127th annual meeting of the American Public Health Association, Chicago, Ill, November 10, 1999.

We thank Lynn Mitchell for her assistance in the programming. We also thank the National Center for Health Statistics for conducting the NHANES I survey and making it available for public use.

Reprints: Amy K. Ferketich, The Ohio State University School of Public Health, M-116 Starling-Loving Hall, 320 W 10th Ave, Columbus, OH 43210 (e-mail: ferketich.1@osu.edu).

REFERENCES