

Depressive Symptoms and Mortality in Men

Results From the Multiple Risk Factor Intervention Trial

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Background and Purpose—Depression may be a risk factor for cardiovascular disease (CVD) mortality. We evaluated long-term mortality risk associated with depressive symptoms measured at middle age among men at high risk for coronary heart disease (CHD).

Methods—12 866 men without definite evidence of CHD at study entry but who had above average risk of CHD based on blood pressure, blood cholesterol levels, and/or cigarette smoking were recruited into the Multiple Risk Factor Intervention Trial (MRFIT). Survivors at the end of the trial were followed-up for mortality for an additional 18 years. Men who had completed the Center for Epidemiologic Studies Depression (CES-D) scale near the end of the trial (n=11 216) were used in a prospective analysis of post-trial all-cause and cause-specific mortality during 18-year follow-up after CES-D assessment.

Results—Greater depressive symptoms measured at the end of the trial were associated with significantly higher risk of all-cause mortality and for cause-specific death, a higher risk of CVD, and, more specifically, stroke mortality (all *P* values <0.02) but not CHD mortality (*P*=0.48) in linear trend analyses. The significant associations were strongest for those reporting the greatest depression: hazard ratio (HR)=1.15 (95% CI, 1.03 to 1.28; *P*<0.01) for all-cause mortality for those in the highest depressive symptom quintile, HR=1.21 for CVD mortality (95% CI, 1.03 to 1.41; *P*<0.05), and HR=2.03 for stroke mortality (95% CI, 1.20 to 3.44; *P*<0.01) compared with those in the lowest quintile. These associations were adjusted for age, intervention group, race, educational attainment, smoking at baseline and visit 6, trial averaged systolic blood pressure, alcohol consumption, and fasting cholesterol, as well as the occurrence of nonfatal cardiovascular events during the trial.

Conclusions—Greater depressive symptoms are associated with an increase in the risk of all-cause and, more specifically, CVD mortality in men. Stroke but not CHD was the form of CVD with which depressive symptoms were associated. (*Stroke*. 2005;36:98-102.)

Key Words: cardiovascular diseases ■ depression ■ stroke

A review of research relating depressive symptoms and mortality¹ finds that a majority (51%) of studies show positive associations between depressive symptoms and mortality,^{2,3} but nearly one-quarter (23%) show a negative association, and the remainder (26%) shows a different depression–mortality association for men and women. A number of mediators have been suggested as potential pathways from depression to increased risk of cardiovascular disease (CVD).⁴ These pathways include sympathoadrenal hyperactivity,⁵ diminished heart rate variability,⁶ ventricular instability and myocardial ischemia reaction to mental stress,⁷ and alterations in platelet reactivity.⁸ The present study examines the association of depressive symptoms with all-cause and cause-specific mortality for men without a history of cardiac disease but who are at

high risk for cardiac disease in the Multiple Risk Factor Intervention Trial (MRFIT).

Although a number of studies have considered the association of depressive symptoms with all-cause and cause-specific mortality,⁹ there are benefits to testing these associations in the MRFIT. First, the MRFIT is the only depression–CVD study to date with a lengthy mortality follow-up of 18 years. Second, relative to previous studies, the MRFIT data can provide a more reliable assessment of risk factors (eg, smoking, cardiac disease) by considering 6 yearly assessments throughout the trial. Third, there is nearly 100% ascertainment of mortality in MRFIT. Finally, depressive symptoms were measured during the sixth year of this 7-year trial using a well-standardized measure, the Center for Epidemiologic Studies Depression Scale (CES-D¹⁰).

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Methods

Design of the MRFIT

Screening for the MRFIT in 1973 to 1975 involved 361 662 men 35 to 57 years of age at 22 clinical centers in 18 US cities. Based on this initial screening, 12 866 men were enrolled who were without definite evidence of clinical coronary heart disease (CHD) but who had above average risk of CHD because of high blood pressure, elevated blood cholesterol levels, and/or cigarette smoking.¹¹ Men were then randomized into the special intervention (SI; $n=6428$) or usual care ($n=6438$) group. SI involved intervention visits, designed to alter eating patterns, reduce weight, achieve smoking cessation, and a stepped-care approach for hypertension medication. Details of the multifactor intervention are described elsewhere.¹² All MRFIT participants had annual clinic visits for 6 years; follow-up was excellent, with >90% attendance each year.

Assessment of Depressive Symptoms

Depressive symptoms were assessed with the CES-D scale administered during the sixth annual examination. Because of death and attrition, the CES-D was administered to 11 263 of the original 12 866 participants. The CES-D consists of 20 questions about the frequency of experiencing certain feelings or symptoms during the last week on a 4-point scale ranging from 0 (rarely or none of the time [<1 day]) to 3 (most or all of the time [5 to 7 days]). Higher scores indicate more depressive symptoms, with a maximum score of 60. The CES-D has excellent internal consistency (average, 0.87) and reasonable test-retest reliability (average 0.57¹⁰). In the current sample, CES-D scores ($M=7.23$, $SD=6.84$) were positively skewed (ie, more high scores than expected around the sample mean). We chose to analyze depressive symptom quintiles rather than treat CES-D as a continuous measure for a number of reasons. First, the interpretation of individual CES-D scores is not advisable.¹⁰ Second, CES-D scores are positively skewed in the general population and in the MRFIT. Finally, quintiles provide enough groups to detect any important nonlinearity but not so many that group Ns become too small.

Risk Factor Assessment

The following risk factors were considered: age at study entry, MRFIT group assignment (SI versus usual care), race (white versus nonwhite), educational attainment (on a 7-point scale), occurrence of a nonfatal CVD event during the preceding year, cigarette smoking (cigarettes per day at baseline and smoking status as yes/no at year 6), and, from each annual examination before CES-D assessment, trial averages of systolic blood pressure, fasting cholesterol concentration, and alcohol use (drinks/week). A nonfatal CVD event during the trial was defined as angina, intermittent claudication,¹³ congestive heart failure, peripheral arterial occlusive disease, left ventricular hypertrophy by electrocardiogram, impaired renal function, accelerated hypertension, coronary artery bypass surgery, stroke, or definite clinical myocardial infarction (MI); nonfatal CVD events were not assessed after the end of the trial. Further details regarding these assessments are published elsewhere.¹⁴

Mortality Ascertainment

Before the end of the trial on February 28, 1982, deaths were ascertained using next-of-kin interviews, follow-up of missed clinic visits, responses to postcards sent to usual care participants, and searches of publicly accessible files of deceased persons. For deaths through December 1990, vital status was ascertained by matching participants' identifying information with the National Death Index or Social Security Administration files. To determine cause of death, death certificates were coded independently by 2 nosologists using the ICD-9,¹⁵ with disagreements adjudicated by a third nosologist. The latest search of the National Death Index was for all deaths January 1991 through December 1999 using National Death Index-Plus to obtain death dates and primary cause. Mortality follow-up is considered to be essentially 100% complete.¹⁶

Statistical Analyses

Participant characteristics were analyzed across CES-D quintiles. Mortality after the CES-D assessment was analyzed using Cox proportional hazard regression models (stratified by clinical center) with 95% confidence intervals (CIs) for the hazard ratios (HRs) associated with each depressive symptom quintile. To control for possible confounding variables, multivariate adjusted analyses included the risk factors described. Additional covariate control for use of beta-blockers, body mass index, fasting glucose, use of medications for diabetes, dietary cholesterol, sodium, saturated fatty acids, and polyunsaturated fatty acids neither appreciably nor significantly altered results, and those results are not discussed further.

Different analytic approaches addressed specific hypotheses. First, we considered the HR associated with each CES-D quintile (relative to the lowest quintile) and corresponding linear trends across quintiles. A linear trend analysis specifically tests the hypothesis that increasing depressive symptoms across quintile groups are associated with a consistent and linear increase in the risk of mortality. This approach addresses associations of mortality with depressive symptoms but not clinical depression. The relatively low incidence of CES-D scores at 16 or >16 in the MRFIT ($n=1103$; 9.78%), indicative of moderate symptoms,¹⁰ led to using this clinical cutoff (≥ 16 versus <16 on the CES-D) in secondary analyses. Additional analyses tested the interaction between CES-D quintiles and occurrence of a nonfatal CVD event to address whether the depression-mortality association varied in magnitude according to CVD events during the trial. Finally, we analyzed separately those who did not have a nonfatal CVD event during the trial.

Results

Characteristics of Participants With More Depressive Symptoms

Of the 11 263 men with valid CES-D scores, 47 had incomplete risk factor information and were excluded. For the remaining 11 216, quintiles were approximately equal in size and corresponded to the following CES-D scores: 0 to 1 (first quintile; $n=2226$); 2 to 4 (second quintile; $n=2441$); 5 to 7 (third quintile; $n=2200$); 8 to 12 (fourth quintile; $n=2515$); and 13 to 60 (fifth quintile; $n=1834$). Participants reporting more depressive symptoms were significantly younger, less likely to be in the SI group, less likely to be white, drank more alcohol, smoked more, were less educated, had lower serum cholesterol levels, and were more likely to experience a nonfatal CVD event relative to those reporting fewer depressive symptoms (Table 1). Some of these differences, although significant, were quite small and possibly of no clinical significance.

Post-Trial Mortality

The median length of follow-up for the 11 216 men from CES-D assessment through December 31, 1999 was 18.43 years. During this time, 1788 cardiovascular and 1909 non-cardiovascular deaths occurred. Using the linear trend results shown in Table 2, the unadjusted HR associated with more depressive symptoms was significant for all-cause mortality (HR, 1.05 for each higher quintile; 95% CI, 1.03 to 1.07; $P<0.001$). When considering cause-specific mortality, CVD (HR, 1.06; 95% CI, 1.02 to 1.10; $P=0.001$) and, specifically, stroke (HR, 1.17; 95% CI, 1.05 to 1.31; $P=0.005$) were associated with significantly higher risks for men with higher CES-D scores. Finally, men with higher CES-D scores had a significantly greater risk of non-CVD mortality in the unadjusted model (HR, 1.04; 95% CI, 1.01 to 1.07; $P=0.025$).

TABLE 1. Mean Characteristics of Those Administered CES-D as a Function of the Degree of Depressive Symptoms as Measured by the CES-D

Participant Characteristics	CES-D Quintile (Range of CES-D Scores)					P Value for Quintile Differences
	1 (0–1)	2 (2–4)	3 (5–7)	4 (8–12)	5 (13–60)	
No. of men	2226	2441	2200	2515	1834	
CES-D score, 6th visit	0.3	3.0	6.0	9.9	19.1	
Age, y, baseline	46.6	46.4	46.7	46.4	46.0	0.001
Study group, % in SI	54	51	50	49	48	0.003
Race, % white	92	90	90	88	89	<0.001
Alcohol, drinks/wk, trial average	10.5	10.3	10.3	10.6	11.2	0.034
Smoking, % yes, baseline	60	61	60	63	67	<0.001
Smoking, % yes, 6th visit	36	38	36	39	44	<0.001
Systolic BP, mm Hg, trial average	126.3	126.5	126.4	126.6	125.4	0.006
Diastolic BP, mm Hg, trial average	84.8	85.0	84.8	85.1	84.9	0.352
Serum cholesterol, mg/dL, trial average	233.1	232.8	234.2	233.3	229.9	<0.001
Education, y, baseline	14.1	14.1	13.8	13.7	13.8	<0.001
Nonfatal CVD event during trial, %	16	19	21	20	30	<0.001

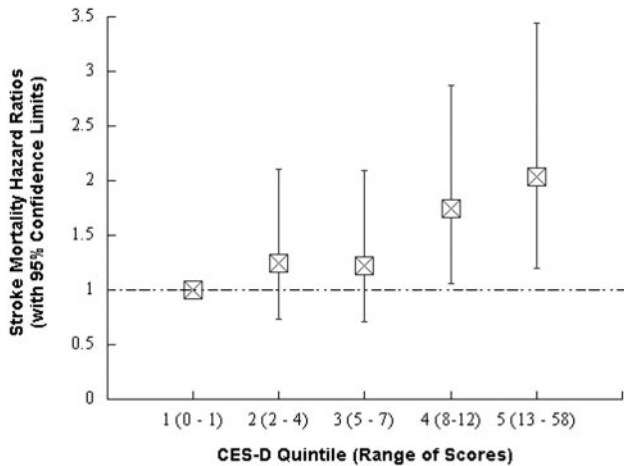
After the addition of covariates, more depressive symptoms were still associated with a significantly increased post-trial risk for all-cause (HR, 1.03 for each higher quintile; 95% CI, 1.01 to 1.06; $P=0.011$), CVD (HR, 1.05; 95% CI, 1.01 to 1.08; $P=0.013$), and stroke (HR, 1.20; 95% CI, 1.07 to 1.34; $P=0.002$) mortality. However, more depressive

symptoms were no longer significantly associated with non-CVD mortality (HR, 1.02; 95% CI, 0.98 to 1.05; $P=0.371$). The HRs for stroke mortality across depressive symptom quintiles are shown in Figure 1. The significant linear trend suggests that each quartile increase in depression symptoms is associated with an incremental increase in the risk of stroke

TABLE 2. Cause of Death and Hazard Ratio (With 95% Confidence Limits) During the 18-year Post-trial Period Associated With Degree of Depression

Cause of Death§ (No. of Deaths)	Depression Quintile					P Value for Linear Trend Across Quintiles
	1 (n=2226)	2 (n=2441)	3 (n=2200)	4 (n=2515)	5 (n=1834)	
Unadjusted models						
All-cause (3715)	1.00	1.04 (0.94–1.15)	0.99 (0.89–1.10)	1.12 (1.01–1.23)*	1.23 (1.11–1.37)‡	<0.001
Cardiovascular (1788)	1.00	1.09 (0.94–1.26)	1.01 (0.87–1.18)	1.19 (1.03–1.37)*	1.27 (1.09–1.49)‡	0.001
Coronary heart disease (1248)	1.00	1.02 (0.86–1.22)	0.95 (0.79–1.13)	1.03 (0.87–1.23)	1.18 (0.98–1.41)†	0.125
Acute MI (551)	1.00	1.09 (0.84–1.41)	0.91 (0.69–1.21)	1.12 (0.86–1.45)	1.26 (0.96–1.66)†	0.125
Other CHD (697)	1.00	0.98 (0.77–1.23)	0.97 (0.77–1.23)	0.97 (0.77–1.22)	1.12 (0.88–1.42)	0.493
Cerebrovascular (167)	1.00	1.23 (0.73–2.10)	1.26 (0.73–2.15)	1.74 (1.06–2.85)*	1.86 (1.11–3.14)*	0.005
Non-cardiovascular (1909)	1.00	0.98 (0.85–1.13)	0.97 (0.84–1.12)	1.04 (0.90–1.19)	1.19 (1.02–1.37)‡	0.025
Adjusted models¶						
All-cause (3715)	1.00	1.01 (0.91–1.12)	0.95 (0.85–1.05)	1.05 (0.95–1.16)	1.15 (1.03–1.28)‡	0.011
Cardiovascular (1788)	1.00	1.06 (0.92–1.23)	0.95 (0.81–1.11)	1.13 (0.98–1.31)†	1.21 (1.03–1.41)*	0.013
Coronary heart disease (1248)	1.00	1.00 (0.84–1.19)	0.88 (0.74–1.06)	0.98 (0.83–1.17)	1.10 (0.91–1.32)	0.476
Acute MI (551)	1.00	1.06 (0.81–1.38)	0.86 (0.65–1.13)	1.07 (0.83–1.39)	1.16 (0.88–1.52)	0.353
Other CHD (697)	1.00	0.96 (0.76–1.21)	0.90 (0.71–1.14)	0.92 (0.73–1.16)	1.05 (0.82–1.34)	0.906
Cerebrovascular (167)	1.00	1.24 (0.73–2.11)	1.22 (0.71–2.09)	1.75 (1.06–2.87)*	2.03 (1.20–3.44)‡	0.002
Non-cardiovascular (1909)	1.00	0.96 (0.84–1.11)	0.94 (0.81–1.08)	0.96 (0.84–1.11)	1.09 (0.94–1.27)	0.371

¶In the adjusted Cox proportional hazard models, the following characteristics were included as covariates: age, intervention group, race, educational attainment, smoking at baseline and visit 6, trial averaged SBP, alcohol consumption, and fasting cholesterol, as well as the occurrence of nonfatal cardiovascular events during the trial. Significant HRs are highlighted: † $P<0.10$; * $P<0.05$; ‡ $P<0.01$. § ICD-9 and ICD-10 codes corresponding to the cause-specific mortality categories are as follows: CVD (390–459; I00–I99), CHD (410–414, 429.2; I20–I25), acute MI (410; I21–I22), other CHD (411–414, 429.2; I20, I23–I25), cerebrovascular (430–438; I60–I69), and non-cardiovascular (all non-CVD codes).



Hazard ratios for stroke mortality during the 18-year post-trial period as a function of depressive symptoms (adjusted for covariates).

mortality. A quadratic term was not significant ($P>0.50$) in this analysis and the pattern of HRs across quintiles in Figure 1 suggest there is no threshold above which the effect of depressive symptoms emerges. In the analysis of stroke mortality, the following covariates had significant HRs: serum cholesterol (HR, 1.05; 95% CI, 1.002 to 1.106; $P=0.04$), age at study entry (HR, 1.12; 95% CI, 1.08 to 1.15; $P<0.0001$), visit-6 cigarette smoking (HR, 1.54; 95% CI, 1.03 to 2.30; $P=0.03$), and systolic blood pressure (HR, 1.04; 95% CI, 1.03 to 1.06; $P<0.0001$).

In secondary analyses, clinical depression (CES-D >16) was associated with significantly greater risk of all-cause mortality (HR, 1.12; 95% CI, 1.01 to 1.24; $P=0.03$) and, more specifically, a marginally elevated risk of stroke (HR, 1.48; 95% CI, 0.93 to 2.36; $P=0.097$) and non-CVD mortality (HR, 1.14; 95% CI, 0.99 to 1.32; $P=0.070$) in fully adjusted models. These effects were comparable to the effects when considering depressive symptom quintiles, although significance was attenuated.

Because the proportion of men with a nonfatal CVD event differed by quintile of depressive symptoms, for each cause of death, an interaction term between CES-D and occurrence of a nonfatal CVD event was fit; none was significant (all P values >0.05 , not shown). Similarly, analyses excluding those with a during-trial nonfatal CVD event showed similar results but were less statistically significant (data not shown).

Discussion

In the MRFIT, more depressive symptoms were associated with a significantly higher risk of all-cause and CVD mortality, but not with non-CVD mortality. The results indicate that stroke is the specific CVD cause with which depressive symptoms are associated, whereas CHD and its components are not. In addition to statistical significance, the depression–stroke association is likely of clinical significance as well, with a risk of stroke in the group with the most depressive symptoms more than twice that of men reporting no depressive symptoms. This finding is consistent with a number of studies demonstrating the association of depression with stroke risk.^{17,18} However, a number of studies have suggested

that underlying CVD (eg, silent strokes¹⁹) may produce depressive symptoms, as well as place a person at a higher risk for future stroke mortality. Therefore, another advantage of the current study is covariate control for previous clinically detectable stroke, MI, or other nonfatal CVD events, and a number of other potential confounders, thus suggesting an association between depressive symptoms and stroke mortality may not be a spurious product of a comorbid condition. Finally, the significant linear trend demonstrating the depression–mortality association suggests that depressive symptoms need not reach a clinical threshold to be associated with mortality risk.

Although a number of studies show that greater depression is associated with a significantly higher risk of all-cause and CVD mortality,¹ the literature is less clear on the question of whether CHD or stroke are the specific CVD causes associated with depressive symptoms. For example, in a recent review⁹ of 13 studies that have addressed the association between depressive symptoms and heart disease in patients without existing heart disease, only 1 study²⁰ tested the association of depressive symptoms with stroke. Moreover, this study reported a significant relative risk (RR) for stroke mortality (RR, 1.21; $P=0.001$; from 204 deaths) but a nonsignificant RR for MI mortality (RR, 1.14; $P=0.11$; from 126 deaths). The difference in significance is partially a function of more stroke events relative to MIs and therefore greater power in the analysis of stroke. Studies evaluating specific types of CVD restrict their focus to either stroke¹⁷ or CHD,²¹ without ascertaining both CHD and stroke within a single study, making it difficult to evaluate the relative importance of CHD and stroke to the CVD–depression association. The exception is the recent report from the Women's Health Initiative Observational Study (WHI-OS)²² showing that among women with a history of CVD, depressive symptoms measured by a shortened version of the CES-D predicted stroke incidence but no other form of CVD. In contrast, among women with no history of CVD, depressive symptoms were not related to stroke, CHD, congestive heart failure, and coronary artery disease incidence but were related to CVD death. The current study suggests that stroke is the form of CVD most strongly associated with depressive symptoms, especially among persons at high risk. The fact that a significant CHD–depression association was observed in our unadjusted models suggests that perhaps insufficient control for confounding variables accounts for previous findings of a CHD–depression association.

This study has limitations. First, findings are restricted to men at high risk for CHD. The relative strength of the depression–stroke association may be unique to populations with a high prevalence of hypertension (eg, MRFIT men or WHI-OS women with no history of CVD) and thereby not generalize to other more normotensive populations. Second, the assessment of depressive symptoms occurred near the end of MRFIT and by this time, some participants were no longer free from CVD (22%); therefore, our current findings may not generalize to other prospective studies of depression in those initially free of CVD. This possibility is unlikely, however, because the depression–CVD association in the present study was not significantly qualified by whether the

participants had a history of CVD. Finally, although all analyses included a number of covariate measures with particular attention to CVD risk factors, unmeasured factors (eg, silent strokes) might have contributed to an increased risk of depressive symptoms and CVD mortality.

Clinical Implications and Conclusions

More depressive symptoms in men with above average risk of CHD mortality were associated with a significantly greater risk of CVD mortality during an 18-year post-trial period. The association was primarily with stroke mortality, and not with CHD mortality or its components. Finding this association in the context of controls for numerous potential confounders provides more evidence of a causal link between depressive symptoms and stroke mortality in particular. The clinical implications of a dose-dependent (eg, linear) association suggest that any reduction in depressive symptoms in those at above average risk for CHD may potentially result in a corresponding decline in future stroke mortality. Moreover, as measured by the χ^2 test statistic, the magnitude of the effect of depressive symptoms on stroke mortality is greater than smoking and cholesterol but not as large as age or blood pressure. As previously noted with cholesterol and blood pressure,²³ population-wide reductions in depressive symptoms might provide the greatest reductions in CVD. Physicians' ability and willingness to assess depression in patients at higher risk for CHD and implement the corresponding psychosocial interventions as part of the medical management might thereby affect the clinical course of stroke.²⁴

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