

Depression and Risk of Sudden Cardiac Death and Coronary Heart Disease in Women

Results From the Nurses' Health Study

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- Objectives** We assessed the association between depression and sudden cardiac death (SCD) and cardiac events among individuals without baseline coronary heart disease (CHD).
- Background** Depression is a risk factor for cardiac events and mortality among those with CHD, possibly from arrhythmia.
- Methods** We studied depressive symptoms and a proxy variable for clinical depression consisting of severe symptoms and/or antidepressant medication use and their relationship to cardiac events in the Nurses' Health Study. Questionnaires in 1992, 1996, and 2000 assessed symptoms with the Mental Health Index (MHI-5), and antidepressant use was assessed in 1996 and 2000. Primary end points included SCD, fatal CHD, and nonfatal myocardial infarction.
- Results** Among 63,469 women without prior CHD/stroke in 1992, 7.9% had MHI-5 scores <53, previously found to predict clinical depression. Depressive symptoms were associated with CHD events, and the relationship was strongest for fatal CHD, where the association remained significant even after controlling for CHD risk factors (hazard ratio [HR]: 1.49; 95% confidence interval [CI]: 1.11 to 2.00 for MHI-5 score <53). In models from 1996 onward, our proxy variable for clinical depression was most associated with SCD in multivariable models (HR: 2.33, 95% CI: 1.47 to 3.70), and this risk was primarily due to a specific relationship between antidepressant use and SCD (HR: 3.34, 95% CI: 2.03 to 5.50).
- Conclusions** In this cohort of women without baseline CHD, depressive symptoms were associated with fatal CHD, and a measure of clinical depression including antidepressant use was specifically associated with SCD. Although antidepressant use might be a marker of worse depression, its specific association with SCD merits further study. (J Am Coll Cardiol 2009;53:950–8) © 2009 by the American College of Cardiology Foundation

Depression has been identified as a possible risk factor for an adverse prognosis and reduced survival after myocardial infarction (MI) (1), and several studies have suggested that this poor prognosis might be due to an arrhythmic mechanism (2–4). Abnormalities in heart rate variability, levels of inflammatory biomarkers, platelet activation, omega-3 fatty acid levels, and plasma norepinephrine have been identified as potential mediators of this adverse prognosis (5–10).

Although depression seems to be a marker of increased risk after MI, it is currently unclear whether depression can be considered an independent risk factor (11) or whether treatment lowers this risk. The largest randomized trial thus far, the ENRICH (Enhancing Recovery in Coronary Heart Disease Patients) trial, did not show improvement in death or recurrent MI among post-MI patients treated with a strategy of cognitive behavior therapy and selective serotonin reuptake inhibitors (SSRIs) (12).

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Manuscript received June 16, 2008; revised manuscript received September 24, 2008, accepted October 26, 2008.

The relationship between depression and coronary heart disease (CHD) incidence is even less certain, with fewer observational studies reporting positive associations (1) and no randomized treatment trials. Also, there has been no large prospective assessment of depression and sudden

cardiac death (SCD) risk among individuals without pre-existing CHD. The Nurses' Health Study presented a unique opportunity to analyze the prospective relationship between depression and risk of SCD and other cardiac events, while controlling for updated traditional and nontraditional CHD risk factors, in a large cohort of women without baseline CHD.

Methods

The Nurses' Health Study cohort. The Nurses' Health Study began in 1976 when 121,701 female registered nurses, ages 30 to 55 years, completed a questionnaire about their medical history, CHD risk factors, and lifestyle factors. The cohort has been followed every 2 years with mailed questionnaires that update exposure information and inquire about newly diagnosed medical illnesses. Deaths are reported by next-of-kin or postal authorities or identified through the National Death Index. Family members are asked for permission to obtain further information from medical records and are interviewed about the circumstances surrounding the death if not adequately documented in the medical record. Subjects or family members provided written informed consent, and the study was approved by the institutional review board of Partners HealthCare System, Boston, Massachusetts. For this analysis, we excluded participants with a prior history of CHD, stroke, or cancer at baseline.

Depression measure. Self-reported symptoms of depression and use of antidepressant medication were used as measures of depression. Depressive symptoms were assessed in 1992, 1996, and 2000 with the Mental Health Index (MHI-5), a 5-item subscale of the Short-Form 36 health status survey (13,14) designed to capture psychological distress versus well-being (15,16). The MHI-5 asks respondents how much of the time over the past month (all, most, good bit, some, little, or none) they felt nervous, felt so down that nothing could cheer them up, felt calm and peaceful, felt down and blue, or felt happy. The scale is scored from 0 to 100, with lower scores indicating more depressive symptoms. The MHI-5 has been shown to have high sensitivity and specificity for major depression, with an area under the receiver-operating characteristic curve of 0.88 to 0.91 for the detection of mood disorders or major depression. In accordance with a prior study using this scale (17), we divided the participants into 4 categories of depressive symptoms according to their MHI-5 score (77 to 100, 76 to 85, 53 to 75, 0 to 52).

For our clinical depression analyses, we created a proxy measure for clinical depression consisting of a low MHI-5 score or reported regular antidepressant medication use. Participants were first asked to report regular antidepressant medication use in 1996, the baseline year for these analyses. This information was updated in 2000, when participants were asked to specifically report their regular use during the

past 2 years of fluoxetine, sertraline, paroxetine, citalopram, or other antidepressants, of which the tricyclic antidepressants amitriptyline, imipramine, and nortriptyline were provided as examples. Because an MHI-5 score of 52 or lower has been found to be predictive of major depression (18), this cutoff was used to define the group with "clinically significant depressive symptoms" and was combined with antidepressant use for the clinical depression analyses. Our proxy variable was found to highly correlate with a report of being previously diagnosed with clinical depression on the 2000 questionnaire (correlation coefficient 0.49, $p < 0.001$).

End point definition. The study end points included incident cases of SCD, fatal CHD, and nonfatal MI that occurred after return of the 1992 questionnaire and before June 1, 2004. The specific details regarding the classification of SCD in this cohort are described in detail elsewhere (19). Briefly, a cardiac death was considered sudden if the death or cardiac arrest that precipitated death occurred within 1 h of symptom onset as documented by medical records or next-of-kin reports. Unwitnessed deaths that could have occurred within 1 h of symptom onset with autopsy findings consistent with SCD were considered probable SCDs and were also included in the analysis. Secondary analyses were performed with SCD or death during sleep in the absence of prior known symptoms.

Fatal CHD was defined as International Classification of Diseases-9 codes 410 to 412 if confirmed by hospital records or autopsy or if CHD was the most likely cause and was listed as the cause of death on the death certificate, along with evidence of prior CHD. We designated as probable CHD those cases in which CHD was the underlying cause on the death certificate but for which no medical records concerning the death were available and included these cases in the analysis.

All women who reported having a nonfatal MI were asked for permission to review their medical records. The MIs were confirmed according to World Health Organization criteria by physicians blinded to exposure status. The MIs that required hospital admission and for which confirmatory information was obtained by interview or letter but for which no medical records were available were designated as probable and included in the analysis.

Statistical analyses. We computed age-adjusted means or proportions of cardiovascular risk factors across categories of MHI-5 score reported in 1992. Baseline measurements of cardiac risk factors were compared across MHI-5 category with Mantel-Haenszel chi-square tests for categorical variables and linear regression for continuous variables.

Abbreviations and Acronyms

CABG = coronary artery bypass graft
CHD = coronary heart disease
CI = confidence interval
HR = hazard ratio
MHI = Mental Health Index
MI = myocardial infarction
SCD = sudden cardiac death
SSRI = selective serotonin reuptake inhibitor

For the depressive symptom analysis, women who responded to the MHI-5 items on any of the 1992, 1996, or 2000 questionnaires were included in the analysis from the time of their earliest questionnaire response. Participants with a prior history of CHD, stroke, or cancer in the baseline year were excluded from both analyses. For each woman we calculated person-months of follow-up from the date of return of the earliest questionnaire to date of first end point, death, or to June 1, 2004, whichever came first. We used Cox proportional hazards models to estimate age- and multivariable-adjusted hazard ratios (HRs). The MHI-5 score was treated as a time-dependent variable using the most recent exposure to predict outcome, and the last observation was carried forward for those with missing values at a particular time point. Tests for linear trend were performed by including MHI-5 score as a continuous variable in separate proportional hazards models.

Two multivariable models were performed; the first model (multivariable model I) simultaneously adjusted for updated coronary risk factors except for reported nonfatal CHD during follow-up, hypertension, and diabetes, 3 possible biologic intermediates in the relationship between depression and heart disease outcome. The first model included variables for age, beginning year of follow-up, smoking status (never, past, current 1 to 14, 15 to 24, ≥ 25 cigarettes/day), body mass index (<25, 25 to 29.9, ≥ 30 kg/m²), alcohol intake (0, <5, 5 to 14, ≥ 15 g/day), menopausal status and postmenopausal hormone use, usual aspirin use (<1, 1 to 6, and 7+/week), multivitamin use, vitamin E supplement use, hypercholesterolemia, family history of MI (no, before age 60 years, after age 60 years), history of stroke, n-3 fatty acid intake (quintiles), alpha linolenic acid intake (quintiles), and moderate/vigorous physical activity (0, 1 to 1.9, 2 to 3.9, ≥ 4 h/week). The second multivariable model (multivariable model II) included the variables in model I, with the addition of nonfatal CHD during follow-up, hypertension, and diabetes.

For the clinical depression analysis, unadjusted Kaplan-Meier curves of time to cardiac event were estimated with 1996 baseline measurements of our proxy variable for clinical depression. Cox proportional hazards analyses included women who responded to the MHI-5 items and antidepressant medication questions on the 1996 or 2000 questionnaire, from the time of their earliest questionnaire response. Depression exposure was treated as a time-dependent variable, and multivariable models I and II included the same updated time-dependent covariates as described in the preceding text. All reported p values are 2-sided. Statistical analysis was performed with SAS statistical software version 8.2 (SAS Institute Inc., Cary, North Carolina).

Sensitivity analyses. To evaluate the possibility of reverse causality associated with the development of nonfatal CHD, we performed analyses excluding individuals who reported being diagnosed with another nonfatal CHD (angina, coronary artery bypass graft [CABG], or MI) end point

before the study outcome in question. We also evaluated for an interaction between MHI-5 score and prior diagnosis of CHD in the entire population, through the inclusion of cross-product terms in our proportional hazards models. In addition, we performed sensitivity analyses of our results for nonfatal MI by excluding cases not confirmed by medical record review.

Results

Depressive symptoms. In 1992, 63,469 women of 102,482 (61.9%) total participants without prior CHD, stroke, or cancer responded to the items of the MHI-5. The median MHI-5 score was 80 (IQR 68 to 88), and 4,994 women (7.9% of the total) had an MHI-5 score <53, which has been shown to be predictive of clinical depression (Fig. 1) (18). Compared with women with an MHI-5 score 86 to 100, women with worse symptoms of depression—as represented by lower MHI-5 score—were younger and more likely to report a history of hypertension, diabetes, and high cholesterol (Table 1). Women with more depressive symptoms were also more likely to be smokers, obese, and less physically active. The n-3 fatty acid intake was lower among participants with worse symptoms of depression, and regular aspirin and multivitamin use was higher.

Table 2 displays the association between depressive symptoms, as measured by the MHI-5 score, and risk of SCD, fatal CHD, and nonfatal MI. Hazard ratios are shown for each MHI-5 category, compared with the reference category (MHI-5 score 86 to 100). In age-adjusted proportional hazards analyses, a lower MHI-5 score (i.e., more severe depressive symptoms) was associated with an increased risk of all 3 CHD outcomes. However, these associations were attenuated in multivariable analyses that included CHD risk factors, except for possible biological mediators (multivariable model I), and relationships for SCD and nonfatal MI became nonsignificant in the fully adjusted model (multivariable model II). The relationship between MHI-5 score and CHD mortality was attenuated but remained statistically sig-

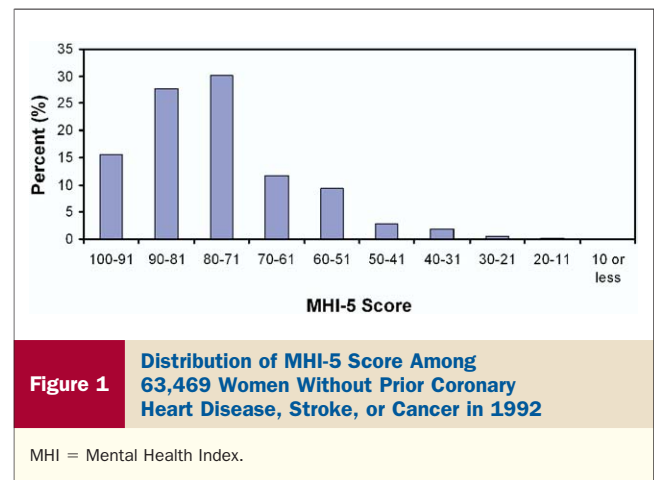


Table 1 CHD Risk Factors* Among 63,469 Women Without Prior CHD, Stroke, or Cancer According to Depression Symptom Category in 1992

	Depression Symptom Score			
	86–100 (Referent)	76–85	53–75	0–52 (Depressive)
No. of women (% total)	18,631 (29.4)	22,814 (36.0)	17,030 (26.8)	4,994 (7.9)
Mean age, yrs (SD)*	59.6 (7.1)	58.3 (7.2)	57.6 (7.2)	56.7 (7.4)
Smoking*				
Past	7,453 (39.9)	9,521 (41.7)	7,199 (42.5)	2,068 (41.8)
Current 1–14 cigarettes/day	952 (5.1)	1,305 (5.7)	1,120 (6.6)	320 (6.4)
Current 15–24 cigarettes/day	865 (4.8)	1,187 (5.2)	1,167 (6.8)	384 (7.4)
Current 25+ cigarettes/day	366 (2.0)	478 (2.1)	503 (2.9)	241 (4.8)
Reported diagnosis of				
Diabetes*	809 (4.1)	973 (4.3)	865 (5.3)	294 (6.3)
High cholesterol*	7,692 (39.7)	9,951 (43.7)	7,813 (46.9)	2,417 (50.4)
Hypertension*	5,562 (28.3)	7,165 (31.5)	5,768 (34.9)	1,774 (38.0)
Body mass index ≥ 30 kg/m ² *	3,001 (16.2)	3,773 (16.5)	2,968 (17.3)	1,038 (20.7)
Parental history of MI before age 60 yrs	2,399 (13.1)	3,007 (13.2)	2,282 (13.3)	686 (13.2)
Alcohol intake, g/day*				
0.1–4.9	5,357 (29.0)	6,592 (28.9)	4,946 (28.9)	1,347 (26.6)
5.0–14.9	3,018 (16.1)	3,793 (16.6)	2,705 (15.9)	682 (13.6)
15.0+	1,510 (7.9)	1,874 (8.2)	1,314 (7.8)	386 (7.8)
Aspirin use, 7+/week*	2,177 (11.5)	2,797 (12.3)	2,505 (14.8)	859 (17.2)
Post-menopausal*	14,945 (75.6)	17,177 (75.5)	12,347 (75.5)	3,467 (76.0)
n-3 fatty acid intake as % total calories (SD)*	0.145 (0.152)	0.143 (0.143)	0.139 (0.133)	0.136 (0.146)
Alpha linolenic acid intake as % total calories (SD)	0.530 (0.152)	0.527 (0.149)	0.526 (0.150)	0.528 (0.156)
Vitamin supplement use				
Vitamin E	3,262 (17.2)	3,939 (17.3)	2,981 (17.8)	868 (17.8)
Multivitamin*	7,661 (40.7)	9,759 (42.8)	7,421 (43.8)	2,206 (44.7)
Moderate/vigorous physical activity, h/week*				
0–1.9	5,637 (30.3)	7,493 (32.8)	5,840 (34.2)	1,699 (33.9)
2–3.9	3,236 (17.6)	4,011 (17.6)	2,640 (15.4)	671 (13.1)
≥ 4	4,109 (22.1)	4,352 (19.1)	2,663 (15.6)	612 (12.1)

Values are n (%) unless otherwise indicated. Age-adjusted. *p < 0.01.
 CHD = coronary heart disease; MI = myocardial infarction.

nificant (HR: 1.49 for MHI-5 score <53; 95% CI: 1.11 to 2.00; p trend = 0.007) in the fully adjusted multivariable model. When deaths that occurred during sleep without prior symptoms were included in the SCD end point (number of end points increased from 138 to 176), the association between symptoms of depression and SCD also remained significant but attenuated in the full multivariable model (HR: 1.51 for MHI-5 score <53; 95% CI: 0.89 to 2.56; p trend = 0.01).

To evaluate the sensitivity of these results to possible reverse causality associated with the development of nonfatal CHD, we performed analyses excluding all women who reported being diagnosed with another nonfatal CHD event (angina, CABG, or MI) before each study outcome. The HR for each MHI-5 score category (data not shown) as well as the overall association between depression score and SCD (p for trend = 0.079), fatal CHD (p for trend = 0.008), and nonfatal MI (p for trend = 0.28) were not materially different from our primary analyses. There was also no evidence for an interaction between MHI-5 score and CHD during follow-up for any of the CHD outcomes. In addition, for analyses of nonfatal MI, exclusion of cases not

confirmed by medical record review (24.6% of cases) did not materially change the results compared with our primary analyses.

Clinical depression and antidepressant use. In 1996, 4,280 women (6.0% of the cohort in that year) had an MHI-5 score <53, and in 2000, 3,399 women (4.8%) had an MHI-5 score <53. In 1996, 4,769 women (6.7%) and in 2000, 6,869 women (9.7%) reported use of medications that are commonly used as antidepressants. In 2000, among those reporting antidepressant use, 61% reported using an SSRI (sertraline, fluoxetine, paroxetine, or citalopram), and 39% reported “other antidepressant use.” An MHI-5 score <53 and antidepressant use both significantly correlated with a report of a diagnosis of clinical depression on the 2000 questionnaire (correlation coefficient 0.21 and 0.54, respectively).

Using this information on antidepressant use, we evaluated the association between a proxy variable for clinical depression, which consisted of either MHI-5 score <53 or use of antidepressant medication, and cardiac events. Unadjusted Kaplan-Meier curves with 1996 baseline data for our proxy measure are shown in Figure 2, and multivariable

Table 2 Long-Term Relative Risks (95% CI) of Mortality/MI Among 81,875 Women Without Prior CHD, Stroke, or Cancer at Baseline Followed From 1992 to 2004

Outcome	Depression Symptom Score				p for Trend* (Continuous)
	86-100 (Referent)	76-85	53-75	0-52 (Depressive)	
Person-yrs	311,391	293,969	201,794	54,932	
SCD					
No. of cases	46	37	43	12	
Age-adjusted	1.0	0.98 (0.64-1.51)	1.72 (1.13-2.61)	1.96 (1.03-3.71)	<0.001
Multivariable I	1.0	0.91 (0.59-1.41)	1.36 (0.89-2.08)	1.36 (0.71-2.61)	0.050
Multivariable II	1.0	0.87 (0.56-1.34)	1.27 (0.83-1.94)	1.21 (0.63-2.33)	0.13
Fatal CHD					
No. of cases	171	147	159	64	
Age-adjusted	1.0	1.01 (0.81-1.25)	1.67 (1.35-2.08)	2.81 (2.11-3.75)	<0.001
Multivariable I	1.0	0.93 (0.74-1.15)	1.30 (1.04-1.62)	1.79 (1.33-2.40)	<0.001
Multivariable II	1.0	0.86 (0.69-1.07)	1.14 (0.91-1.42)	1.49 (1.11-2.00)	0.007
MI					
No. of cases	406	392	298	87	
Age-adjusted	1.0	1.10 (0.95-1.26)	1.27 (1.09-1.47)	1.49 (1.18-1.87)	<0.001
Multivariable I	1.0	1.05 (0.92-1.21)	1.14 (0.98-1.33)	1.24 (0.98-1.57)	0.02
Multivariable II	1.0	1.03 (0.89-1.18)	1.08 (0.93-1.25)	1.13 (0.90-1.43)	0.19

According to categories of depression symptom score. Hazard ratios from proportional hazards models with time-dependent variables. Women who responded to the Mental Health Index (MHI-5) items on any of the 1992, 1996, or 2000 questionnaires and were free of prior coronary heart disease, stroke, or cancer at the time of their earliest questionnaire response were included in the analysis from this time point on. Please see Methods section for description of variables for multivariable models I and II. *The p value reflects test for linear trend with MHI-5 score as continuous variable.

CI = confidence interval; SCD = sudden cardiac death; other abbreviations as in Table 1.

proportional hazards analyses using time-varying measurements are shown in Table 3. The proxy variable for clinical depression was associated with increased risk of all 3 CHD outcomes in age-adjusted and multivariable models excluding biological intermediates, similar to the results for MHI-5 score. However, the elevation in risk was greatest for SCD, where a 2.33-fold association (95% CI: 1.47 to 3.70, $p < 0.001$) persisted in the full multivariable model (multivariable model II). In comparison, the associations for fatal CHD (HR: 1.37, 95% CI: 1.04 to 1.81; $p = 0.03$) and nonfatal MI (HR: 1.20, 95% CI: 0.99 to 1.46; $p = 0.06$) were markedly attenuated and only marginally significant after full multivariable adjustment. Similar to the results for depressive symptoms, these results for the proxy measure of clinical depression were not materially altered when women who developed an intervening nonfatal CHD event (angina, CABG, or MI) were excluded from the analysis (for SCD, HR: 2.20, 95% CI: 1.35 to 3.57, $p = 0.002$; for fatal CHD, HR: 1.31, 95% CI: 0.96 to 1.78, $p = 0.09$; for nonfatal MI, HR: 1.25, 95% CI: 1.03 to 1.53, $p = 0.027$).

To further evaluate the elevated risk of SCD associated with the composite clinical depression measure, we assessed the individual components (MHI-5 score <53 and antidepressant use) simultaneously in proportional hazard models (Table 4). In these models, antidepressant medication use was associated with a markedly elevated risk of SCD in the fully adjusted models (HR: 3.34, 95% CI: 2.03 to 5.50), whereas MHI-5 score <53 no longer conferred an elevated risk (HR: 1.04, 95% CI: 0.51 to 2.12). By contrast, there was no relationship between antidepressant use and fatal CHD (HR: 1.07, 95% CI: 0.75 to 1.53) or nonfatal MI

(HR: 1.21, 95% CI: 0.96 to 1.53) in these models. Unadjusted Kaplan-Meier curves of time to SCD stratified by antidepressant use and MHI-5 score <53 at baseline in 1996 are shown in Figure 3. In a secondary analysis of data from 2000 to 2004 with separate variables for SSRI use and "other antidepressant use" (31 total SCDs), we found similar HRs for the 2 categories of medications in age-adjusted analyses (for SSRI use, HR: 5.07, 95% CI: 1.73 to 14.8; for other antidepressant use, HR: 3.19, 95% CI: 0.92 to 11.00).

Discussion

In this prospective study among women without known cardiovascular disease at baseline, symptoms of depression were directly associated with the risk of CHD events in age-adjusted and multivariable models excluding potential biologic intermediates. Symptoms were most strongly related to fatal CHD events, where the association remained significant even after controlling for all CHD risk factors. However, depressive symptoms were also associated with multiple risk factors for CHD, and the relationships between depressive symptoms and all 3 end points, including fatal CHD, were attenuated in multivariable analyses that adjusted for updated CHD risk factor status. These CHD risk factors might act as biologic intermediates in the relationship between depressive symptoms and cardiac events, given their strong association with depression in this and prior studies (20). When we examined a proxy variable for clinical depression that consisted of either MHI-5 score <53 or use of antidepressant medication, a strong association with risk of SCD emerged that was not attenuated in

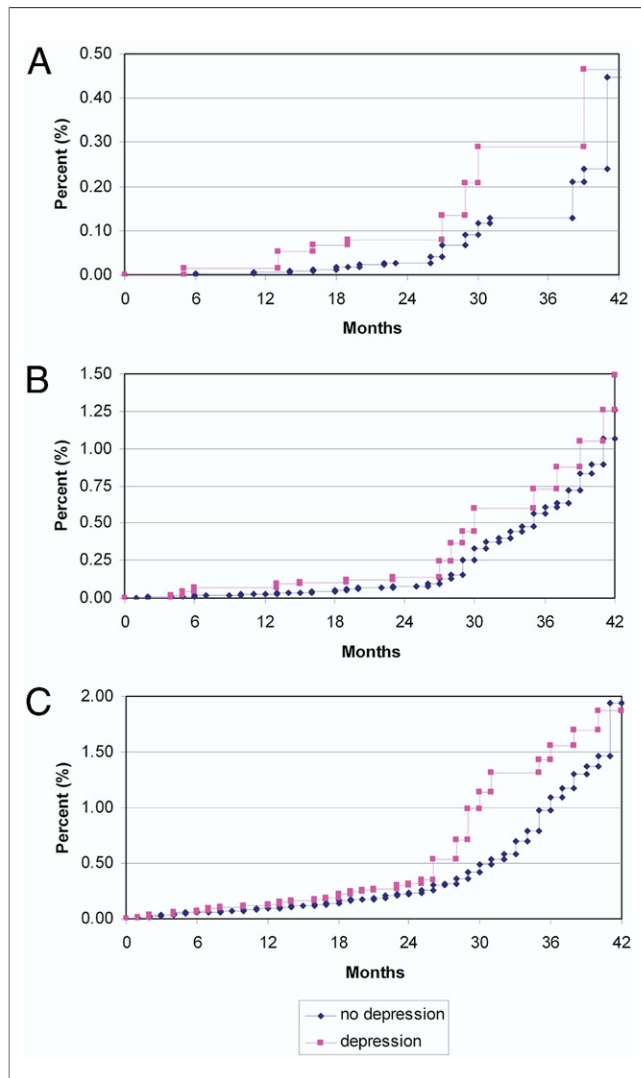


Figure 2 Unadjusted Kaplan-Meier Curves of Time to First Event

Unadjusted Kaplan-Meier curves of time to first event for sudden cardiac death (A), fatal coronary heart disease (B), and nonfatal myocardial infarction (C), according to depression status as defined by Mental Health Index-5 score <53 or reported use of antidepressant medication at baseline starting in 1996. Curves are truncated at 42 months. The p values for log-rank test were 0.02 for sudden cardiac death, 0.31 for fatal coronary heart disease, and 0.80 for nonfatal myocardial infarction.

multivariable models. When examined separately, this increased risk seemed to result primarily from a specific elevation in the risk of SCD among women who reported antidepressant use. Neither depression score nor antidepressant use was significantly associated with nonfatal events in multivariable models.

Prior studies have examined the association between depression and incident cardiac events, with varying results. Two meta-analyses of observational studies both estimated that depression conferred a 1.6-fold increased risk of CHD (21,22) and clinically relevant depression seemed to be a stronger predictor than depressive symptoms (22)—similar to the relationship observed here for SCD. With respect to

prior large-scale data among women, investigators from the Women’s Health Initiative also found that depressive symptoms were associated with a significantly higher risk of fatal cardiovascular events (adjusted risk ratio: 1.5, 95% CI: 1.10 to 2.03) among 73,098 women without a history of cardiovascular disease over 4 years of follow-up (23). As observed in our study, relationships seemed stronger for fatal versus nonfatal events; however, separate risks were not reported for antidepressant use, and SCD was not specifically examined.

Part of the association with fatal events observed in this and previous studies could be explained if part of the elevated mortality risk associated with depression were due to an increased risk of fatal ventricular arrhythmias. The strong association between our proxy measure of clinical depression and SCD supports this possibility. A large case control study also found a significant association between a diagnosis of clinical depression and out-of-hospital cardiac arrest independent of established CHD risk factors (2). Depressive symptoms have also been specifically associated with ventricular arrhythmias among individuals with implantable defibrillators (3). Possible mechanisms for the elevated risk of ventricular arrhythmias and SCD associated with depression include greater sympathetic nervous system activation (9), higher resting heart rates, increases in QT dispersion (24), and reduced heart rate variability (8) among individuals with depression. Another possibility is that treatments for depression might elevate the risk of ventricular arrhythmias. When examined separately, we found an elevated risk of SCD associated with antidepressant use and not with more severe depressive symptoms according to MHI-5 score <53. It is also noteworthy that, as opposed to the HR corresponding to MHI-5 score, the HR for SCD corresponding to antidepressant use was minimally attenuated despite adjustment for multiple coronary risk factors (HR in fully adjusted model: 3.34, 95% CI: 2.03 to 5.50).

Table 3 HRs (95% CI) for Mortality/MI Among 75,718 Women Without Prior CHD, Stroke, or Cancer Followed at Baseline 1996 to 2004

Outcome	HR (95% CI)	p Value
SCD (n = 99)		
Age-adjusted	2.91 (1.85–4.57)	<0.001
Multivariable I	2.49 (1.57–3.94)	<0.001
Multivariable II	2.33 (1.47–3.70)	<0.001
Fatal CHD (n = 342)		
Age-adjusted	1.87 (1.42–2.46)	<0.001
Multivariable I	1.54 (1.17–2.03)	0.002
Multivariable II	1.37 (1.04–1.81)	0.03
MI (n = 811)		
Age-adjusted	1.41 (1.17–1.71)	<0.001
Multivariable I	1.28 (1.05–1.56)	0.01
Multivariable II	1.20 (0.99–1.46)	0.06

According to depression score <53 or use of antidepressant medication (in 1996 or 2000). Please see Methods section for description of variables for multivariable models I and II. HR = hazard ratio; other abbreviations as in Tables 1 and 2.

Table 4 HRs (95% CI) for Mortality/MI Among 75,718 Women Without Prior CHD, Stroke, or Cancer Followed From 1996 to 2004

Outcome	Depression Score <53		Antidepressant Medication Use	
	HR (95% CI)	p Value	HR (95% CI)	p Value
SCD (n = 99)				
Age-adjusted	1.36 (0.67-2.77)	0.40	3.59 (2.20-5.86)	<0.001
Multivariable I	1.09 (0.53-2.24)	0.81	3.53 (2.15-5.81)	<0.001
Multivariable II	1.04 (0.51-2.12)	0.92	3.34 (2.03-5.50)	<0.001
Fatal CHD (n = 342)				
Age-adjusted	2.07 (1.43-2.99)	<0.001	1.30 (0.91-1.84)	0.15
Multivariable I	1.58 (1.09-2.29)	0.02	1.19 (0.83-1.70)	0.34
Multivariable II	1.41 (0.97-2.04)	0.07	1.07 (0.75-1.53)	0.71
MI (n = 814)				
Age-adjusted	1.14 (0.85-1.54)	0.38	1.38 (1.10-1.74)	0.006
Multivariable I	1.05 (0.78-1.41)	0.77	1.27 (1.01-1.60)	0.04
Multivariable II	0.98 (0.73-1.33)	0.91	1.21 (0.96-1.53)	0.10

From multivariable models that included depression score <53 and use of antidepressant medication (in 1996 or 2000). Please see Methods section for description of variables for multivariable models I and II.

HR = hazard ratio; other abbreviations as in Tables 1 and 2.

In addition to our own study, prior observational studies have noted a higher mortality risk associated with antidepressant use in patients with heart failure (25) and in patients undergoing CABG surgery (26). Fluoxetine, which has been shown to cause direct and indirect reductions in the human ether-a-go-go-related gene potassium current in a human embryonic kidney cell model (27), has been reported to result in QT prolongation and torsades de pointes (28,29). Tricyclic antidepressants are also known to cause QT prolongation and ventricular arrhythmias in

overdose and, in doses >100 mg, have been associated with SCD risk in a retrospective cohort study (30). In this same study, standard doses of SSRIs and tricyclic antidepressants were not associated with increased risk; however, the study was unable to control for other confounding factors.

Although proarrhythmic effects from antidepressant medications might have resulted in a higher risk of SCD in our study, it must be emphasized that observational studies cannot prove causality, and confounding by indication can never be completely ruled out. Because antidepressant use more significantly correlated with a diagnosis of clinical depression than the MHI-5 score, it is entirely possible that antidepressant use identified participants with more severe depression that was not fully captured by the MHI-5 questionnaire. In addition, these risks need to be put in perspective and balanced against known benefits of these medications on depression. Sudden cardiac death among healthy women is an uncommon event, and although elevated, the absolute risk among women who reported antidepressant use in this study was still very low (46 SCDs/100,000 person-years).

Although the individual risk is low, the possible public health implications of an arrhythmic risk from these commonly prescribed medications at a societal level remain large. This potential risk coupled with recent data suggesting that the clinical benefit of newer antidepressant agents might be less than previously thought (31) highlights the need for large-scale randomized trials of antidepressant medications that are adequately designed and powered to detect important adverse cardiovascular outcomes such as proarrhythmia as well as efficacy. Although the SADHART (Sertraline Antidepressant Heart Attack Randomized Trial) trial was specifically designed to examine cardiovascular safety in patients with acute MI or unstable angina, the primary study end points were intermediate end points such as left ventricular ejection fraction and significant corrected QT interval prolongation (32). With only 369 patients

Figure 3 Unadjusted Kaplan-Meier Curves of Time to Sudden Cardiac Death

Unadjusted Kaplan-Meier curves of time to sudden cardiac death stratified by Mental Health Index-5 score <53 and reported use of antidepressant medication at baseline starting in 1996. The p value for log-rank test across strata was 0.01.

enrolled, the trial had minimal power to examine hard end points such as SCD or fatal CHD. The largest randomized trial thus far, the ENRICH trial, enrolled 2,481 post-MI patients and did not find an increase or decrease in the risk of death or recurrent MI associated with cognitive behavioral therapy supplemented with SSRI but raised the possibility of an interaction by sex, with higher risks of cardiovascular events among women treated with the intervention (12).

Strengths of our study include the relatively large sample size, the long follow-up period, rigorously documented CHD end points, and the updated measures of depression and cardiac risk factors over the course of follow-up. There are also additional limitations of the present study that warrant consideration. First, reverse causality might account for at least part of the association observed between depression and cardiovascular disease in this and other observational studies. Individuals who are diagnosed with CHD or with conditions that predispose them to coronary disease such as diabetes or hypertension might develop depression and therefore would also be at higher risk for fatal cardiac events. Our study excluded women with known CHD at baseline, and sensitivity analyses that excluded participants who reported CHD in follow-up did not significantly change our results, arguing that reverse causality by symptomatic CHD is less likely to be a significant source of bias. Although we attempted to adjust for as many potential confounding factors as possible in our multivariable analyses, there might still be residual confounding from CHD risk factors and prevalent CHD. Also, for the nonfatal MI analysis: women who are depressed might be more likely to self-report MI, and this could inflate the detection of MI, particularly with respect to the probable cases not confirmed by medical records. However, analyses excluding these probable cases revealed similar results.

Second, we did not have a measure of adherence to medications in our data. Because depression has previously been associated with reduced adherence to medications (33), adherence might be a confounder in our results. Also, we did not collect information on antidepressant dose, and therefore, it is not possible to analyze our data for a dose-response relationship between antidepressants and SCD. In addition, our analysis does not include other comorbid psychological factors, such as anxiety, which might be collinear with depression and which has been correlated with arrhythmia (34). Another limitation is the relatively small number of SCD events in our analyses (138 SCDs for analyses starting in 1992, 99 SCDs for analyses starting in 1996), compared with the fatal CHD and nonfatal MI end points. Finally, the Nurses' Health Study represents a relatively healthy group of mostly Caucasian females, and findings from this analysis might not be generalizable to other populations. However, the estimated 7.9% prevalence of depression as measured by an MHI-5 score <53 is comparable to the prevalence of major depression (4.8%) estimated among white women ages 45 to 54 years

with a structured interview in the National Comorbidity Survey (35).

Conclusions

In this prospective cohort of women without baseline cardiovascular disease, we found that symptoms of depression are associated with higher risks of cardiac events, and at least part of this association seems to be explained by differences in coronary risk factors, which might act as causal intermediates in the risk conferred by depression. When we used a proxy for clinical depression, which included antidepressant medication use, we observed a stronger association for SCD, suggesting a possible proarrhythmic mechanism. Although antidepressant medication use might be a marker of worse depression, its specific association with elevated risk of SCD merits further study.

Acknowledgments

The authors are indebted to the participants in the Nurses' Health Study for their outstanding commitment and cooperation and to Julie Pester, Lisa Dunn, and Barbara Egan for their expert assistance.

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REFERENCES

1. Frasure-Smith N, Lespérance F. Recent evidence linking coronary heart disease and depression. *Can J Psychiatry* 2006;51:730–7.
2. Empana JP, Jouven X, Lemaitre RN, et al. Clinical depression and risk of out-of-hospital cardiac arrest. *Arch Intern Med* 2006;166:195–200.
3. Whang W, Albert CM, Sears SF Jr., et al. Depression as a predictor for appropriate shocks among patients with implantable cardioverter-defibrillators: results from the Triggers of Ventricular Arrhythmias (TOVA) study. *J Am Coll Cardiol* 2005;45:1090–5.
4. Carney RM, Blumenthal JA, Stein PK, et al. Depression, heart rate variability, and acute myocardial infarction. *Circulation* 2001;104:2024–8.
5. Bush DE, Ziegelstein RC, Patel UV, et al. Post-myocardial Infarction Depression. Evidence Report/Technology Assessment No. 123. AHRQ Publication Number 05-E018-1. Rockville, Maryland: Agency for Healthcare Research and Quality, 2005.
6. Vaccarino V, Johnson BD, Sheps DS, et al., for the National Heart, Lung, and Blood Institute. Depression, inflammation, and incident cardiovascular disease in women with suspected coronary ischemia: the National Heart, Lung, and Blood Institute-sponsored WISE study. *J Am Coll Cardiol* 2007;50:2044–50.
7. Carney RM, Rich MW, Tevelde A, Saini J, Clark K, Jaffe AS. Major depressive disorder in coronary artery disease. *Am J Cardiol* 1987;60:1273–5.
8. Carney RM, Blumenthal JA, Stein PK, et al. Depression, heart rate variability, and acute myocardial infarction. *Circulation* 2001;104:2024–8.
9. Carney RM, Freedland KE, Veith RC. Depression, the autonomic nervous system, and coronary heart disease. *Psychosom Med* 2005;67 Suppl 1:S29–33.
10. Gold PW, Wong ML, Goldstein DS, et al. Cardiac implications of increased arterial entry and reversible 24-h central and peripheral norepinephrine levels in melancholia. *Proc Natl Acad Sci U S A* 2005;102:8303–8.

11. Nicholson A, Kuper H, Hemingway H. Depression as an aetiological and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies. *Eur Heart J* 2006;27:2763–74.
12. Berkman LF, Blumenthal J, Burg M, et al; Enhancing Recovery in Coronary Heart Disease Patients Investigators (ENRICHD). Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Randomized Trial. *JAMA* 2003;289:3106–16.
13. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473–83.
14. Ware JE, Snow KK, Kosinski M. SF-36 Health Survey: Manual & Interpretation Guide. Lincoln, RI: QualityMetric Incorporated, 2000.
15. McHorney CA, Ware JE Jr., Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36). II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care* 1993;31:247–63.
16. Ware J, Snow K, Kosinski M, et al. SF-36 Health Survey: Manual and Interpretation Guide. Boston, MA: The Health Institute, New England Medical Center, 1993.
17. Kroenke CH, Bennett GG, Fuchs C, et al. Depressive symptoms and prospective incidence of colorectal cancer in women. *Am J Epidemiol* 2005;162:839–48.
18. Berwick DM, Murphy JM, Goldman PA, et al. Performance of a five-item mental health screening test. *Med Care* 1991;29:169–76.
19. Albert CM, Chae CU, Grodstein F, et al. Prospective study of sudden cardiac death among women in the United States. *Circulation* 2003;107:2096–101.
20. Skala JA, Freedland KE, Carney RM. Coronary heart disease and depression: a review of recent mechanistic research. *Can J Psychiatry* 2006;51:738–45.
21. Wulsin LR, Singal BM. Do depressive symptoms increase the risk for the onset of coronary disease? A systematic quantitative review. *Psychosom Med* 2003;65:201–10.
22. Rugulies R. Depression as a predictor for coronary heart disease. A review and meta-analysis. *Am J Prev Med* 2002;23:51–61.
23. Wassertheil-Smoller S, Shumaker S, Ockene J, et al. Depression and cardiovascular sequelae in postmenopausal women. The Women's Health Initiative (WHI). *Arch Intern Med* 2004;164:289–98.
24. Carney RM, Freedland KE, Stein PK, et al. Effects of depression on QT interval variability after myocardial infarction. *Psychosom Med* 2003;65:177–80.
25. Sherwood A, Blumenthal JA, Trivedi R, et al. Relationship of depression to death or hospitalization in patients with heart failure. *Arch Intern Med* 2007;167:367–73.
26. Xiong GL, Jiang W, Clare R, et al. Prognosis of patients taking selective serotonin reuptake inhibitors before coronary artery bypass grafting. *Am J Cardiol* 2006;98:42–7.
27. Rajamani S, Eckhardt LL, Valdivia CR, et al. Drug-induced long QT syndrome: hERG K⁺ channel block and disruption of protein trafficking by fluoxetine and norfluoxetine. *Br J Pharmacol* 2006;149:481–9.
28. Appleby M, Mbewu A, Clarke B. Fluoxetine and ventricular torsade—is there a link? *Int J Cardiol* 1995;49:178–80.
29. Wilting I, Smals OM, Holwerda NJ, Meyboom RH, de Bruin ML, Egberts TC. QTc prolongation and torsades de pointes in an elderly woman taking fluoxetine. *Am J Psychiatry* 2006;163:325.
30. Ray WA, Meredith S, Thapa PB, Hall K, Murray KT. Cyclic antidepressants and the risk of sudden cardiac death. *Clin Pharmacol Ther* 2004;75:234–41.
31. Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. *N Engl J Med* 2008;358:252–60.
32. Glassman AH, O'Connor CM, Califf RM, et al., for the Sertraline Antidepressant Heart Attack Randomized Trial (SADHEART) Group. Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA* 2002;288:701–9.
33. Gehi A, Haas D, Pipkin S, Whooley MA. Depression and medication adherence in outpatients with coronary heart disease: findings from the Heart and Soul Study. *Arch Intern Med* 2005;165:2508–13.
34. Burg MM, Lampert R, Joska T, Batsford W, Jain D. Psychological traits and emotion-triggering of ICD shock-terminated arrhythmias. *Psychosom Med* 2004;66:898–902.
35. Blazer DG, Kessler RC, McGonagle KA, Swartz MS. The prevalence and distribution of major depression in a national community sample: the National Comorbidity Survey. *Am J Psychiatry* 1994;151:979–86.

Key Words: coronary disease ■ epidemiology ■ sudden cardiac death ■ women.