

Clinical Depression and Risk of Out-of-Hospital Cardiac Arrest

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Background: The association of depression with coronary heart disease–related mortality has been widely recognized. This finding may partly reflect an association between depression and sudden death, in part because the imbalance between sympathetic and parasympathetic tone is altered in depressed subjects. We, thus, investigated whether the presence and severity of clinical depression was associated with a higher risk of sudden cardiac death.

Methods: We used data from a population-based case-control study of risk factors for incident out-of-hospital cardiac arrest (CA) conducted among enrollees of a health maintenance organization in western Washington State. Cases (n=2228) were aged 40 to 79 years and experienced CA between January 1, 1980, and December 31, 1994. Controls (n=4164) were a stratified random sample of enrollees defined by calendar year, age, sex, and prior heart disease. Clinical depression was defined as physician diagnosis of depression or use of antidepressant treatment within the year before the event. Referral to mental health

clinics or hospitalization for depression defined severe depression.

Results: Clinically depressed patients had a higher odds ratio (OR) of CA (1.88; 95% confidence interval [CI], 1.59-2.23), which persisted after adjustment for confounders (OR, 1.43; 95% CI, 1.18-1.73). The association was observed in both sexes, in various age groups, and in subjects with prior physician-diagnosed heart disease (OR, 1.27; 95% CI, 1.01-1.60) and without prior physician-diagnosed heart disease (OR, 1.71; 95% CI, 1.22-2.41) ($P=.13$ for the interaction). Compared with nondepressed subjects, the risk of CA was increased in less severely depressed subjects (OR, 1.30; 95% CI, 1.04-1.63) and further increased in severely depressed subjects (OR, 1.77; 95% CI, 1.28-2.45) ($P<.001$ for trend).

Conclusion: Clinical depression may be associated with a higher risk of CA independently of established coronary heart disease risk factors.

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IDENTIFYING INDIVIDUALS WHO ARE at increased risk of sudden cardiac death is a major challenge.¹ Observational studies suggest that depressive symptoms and major depression are associated with an increased risk of coronary heart disease (CHD)–related mortality in patients with²⁻⁷ and without⁸⁻¹⁵ prior clinical CHD. Alteration of the imbalance between sympathetic and parasympathetic tone has been described in depressed subjects, yielding the possibility that this population may be at particular increased risk of sudden cardiac death.^{16,17} However, the relationship between depressive disorders and sudden cardiac death has received limited attention.^{4,18,19} Prior studies suggested an association between depressive disorders (depression or depressive symptoms) and sudden death or arrhythmic death, but have been limited by few cardiac arrest (CA)–related events. These studies^{4,18,19} have been conducted in select populations, including individuals with CHD or elderly subjects. To our knowledge, the association of

out-of-hospital CA in the general population and the possibility of a graded relationship between more severe depression and increased risk of sudden cardiac death has not previously been explored.

We investigated whether the presence and the severity of physician-diagnosed clinical depression was associated with sudden cardiac death overall and in various demographic (age group and sex) and clinical (subjects with and without cardiac disease) subgroups. To address these questions, we used data from a large population-based case-control study of risk factors for out-of-hospital CA.

METHODS

STUDY DESIGN AND SUBJECTS

The setting of the study was the Group Health Cooperative of Puget Sound, a health maintenance organization (HMO) with more than 400 000 enrollees based in western Washington State. The design of the study has been previously described.²⁰

Cases

Cases (n=2228) were Group Health Cooperative enrollees aged 40 to 79 years who experienced incident out-of-hospital CA from presumed ventricular fibrillation due to heart disease between January 1, 1980, and December 31, 1994. Out-of-hospital CA was defined operationally as the occurrence of a sudden pulseless condition without a known noncardiac condition. Out-of-hospital CA events were initially identified from the emergency medical service incident reports of Seattle and King County, Washington, or the HMO's death records. For all possible CA events initially identified, the ambulatory medical record of the HMO was reviewed to determine whether a potentially life-threatening noncardiac condition existed before the CA. As part of the case definition, we excluded subjects who had had prior life-threatening noncardiac conditions, including metastatic cancer, brain tumor, end-stage renal disease, liver disease, or respiratory failure. We also excluded enrollees who had been enrolled in the HMO for less than 1 year or had fewer than 4 visits for ambulatory care before their event date. The κ value for the classification of CA based on the emergency medical service incident reports plus ambulatory care medical records compared with death certificates plus ambulatory care medical records was 0.9. The index date for cases was defined as the date of the CA.

Controls

Controls (n=4164) were a stratified random sample of Group Health Cooperative enrollees, in whom the strata were defined by calendar year, age (decade), sex, and treatment with digoxin or nitroglycerin. The ratio of controls-cases was approximately 2:1.

Stratification by the use of digoxin or nitroglycerin served as a proxy for heart disease in the sampling of controls, because this information was available through automated pharmacy records for all enrollees. However, as stated later, we used ambulatory medical record data for the final classification of each case and control with regard to the presence or absence of prior physician-diagnosed heart disease.

Control subjects had the same exclusion criteria as cases, and they did not experience CA. An index date was assigned randomly to controls from the distribution of case index dates.

DATA COLLECTION

Ambulatory medical records of the HMO were reviewed to identify comorbid conditions and to collect clinical characteristics before the index or event date. The record includes not only notes from the ambulatory care visits but also results (and dates) of discharge summaries of hospitalization, consultant reports, and responses to annual HMO questionnaires and updated medical problem lists. The HMO computerized pharmacy database was used to assess medications. This database includes nearly all prescriptions filled for enrollees since 1976. Previous surveys suggest that 98% of all prescriptions for enrollees were filled at pharmacies included in the database.²¹

ASSESSMENT OF CLINICAL DEPRESSION

A subject was classified as having clinical physician-diagnosed depression (referred to as clinical depression) if a physician reported the diagnosis of depression in the medical record within the year of the index date or if the enrollee was being treated with antidepressant medication at the index date based on the automated pharmacy data. We also used information on referral to a mental health clinic and hospitalization for depression in the year

before the index date and defined 4 mutually exclusive categories of severity of clinical depression: (1) no clinical depression, (2) clinical depression without referral to a mental health clinic or hospitalization for depression in the prior year, (3) clinical depression with referral to a mental health clinic but without hospitalization for depression in the prior year, and (4) clinical depression with referral to a mental health clinic and hospitalization for depression in the prior year. Because only 13 subjects met the criteria for category 4, they were grouped together with subjects from category 3.

DATA DEFINITIONS

Physician-diagnosed heart disease was defined through review of the HMO medical record up to the index date, and included physician-recorded myocardial infarction, angina pectoris, congestive heart failure, valvular heart disease, arrhythmias, syncope, cardiomyopathy, arteriosclerotic heart disease, coronary artery bypass, or coronary angioplasty. Body mass index was defined as the weight in kilograms divided by the square of height in meters. Hypertension was defined as physician diagnosis of high blood pressure and treatment with antihypertensive medications. Diabetes mellitus was defined as physician-diagnosed diabetes mellitus treatment with insulin or oral hypoglycemic agents. Heavy alcohol consumption was defined as consumption of 4 or more drinks per day.

STATISTICAL ANALYSIS

Analyses were conducted overall and separately in subjects with and without physician-diagnosed heart disease. We used conditional logistic regression to estimate the odds ratio (OR) of out-of-hospital CA associated with the presence of clinical depression in the year before the index date, compared with subjects without clinical depression. Analyses were systematically adjusted for cigarette smoking, heavy alcohol consumption, physician-diagnosed hypertension and diabetes mellitus, and history of myocardial infarction and congestive heart failure, because these variables were available for nearly all subjects. We assessed potential interactions of clinical depression with heart disease, age (≥ 70 or < 70 years), and sex by the addition of interaction terms into the multivariate models. To investigate whether the OR of out-of-hospital CA increased with increasing severity of clinical depression, we estimated the multivariate-adjusted OR of the last 2 categories of severity as defined previously, and calculated the *P* value for linear trend across these 2 indicator variables, taking subjects without clinical depression as the reference. All analyses were performed using SAS statistical software, version 8.2 (SAS Institute Inc, Cary, NC).

RESULTS

GENERAL CHARACTERISTICS

Table 1 compares the characteristics of cases and controls overall and according to physician-diagnosed heart disease status. The total sample consisted of 6392 subjects, 3641 with and 2751 without prior heart disease; 92.9% of the subjects were white. Given the stratified random sampling of controls, the sex distribution and mean age were similar in cases and controls. As expected, cases had a less favorable pattern of cardiovascular risk factors than did controls, in subjects with and without heart disease. While case and control sampling was stratified by treatment with digoxin and nitroglycerin, the presence of prior clinically diagnosed heart disease from re-

Table 1. Characteristics of Cases and Controls in the Overall Sample and by Heart Disease Status*

Characteristic	Total Sample (N = 6392)		Those With Heart Disease (n = 3641)		Those Without Heart Disease (n = 2751)	
	Cases (n = 2228)	Controls (n = 4164)	Cases (n = 1402)	Controls (n = 2239)	Cases (n = 826)	Controls (n = 1925)
Age, y†	66.3 (10.2)	66.2 (9.9)	68.2 (8.6)	68.3 (8.1)	63.1 (11.9)	63.8 (11.1)
Male sex	71.1	69.5	73.0	73.0	67.7	65.4
White race	92.7	93.1	93.1	93.5	91.9	92.7
Occupation‡						
Manual	53.6	49.3	55.8	52.1	49.8	46.0
Clerical or technician	9.0	8.4	8.2	7.8	10.5	9.1
Tertiary	37.4	42.3	36.0	40.1	39.8	44.9
Currently working	25.4	30.3	18.5	23.2	37.4	38.7
Current smoker	29.3	16.6	25.8	15.7	35.2	17.7
Heavy drinker	11.4	6.5	10.4	6.7	13.0	6.4
Diabetes mellitus	18.4	8.0	22.5	11.3	11.5	4.1
Hypertension	46.5	34.0	50.7	43.6	39.2	22.8
Prior myocardial infarction	31.4	16.6	49.9	30.8	NA	NA
Congestive heart failure	29.4	9.1	46.7	17.0	NA	NA
BMI†	26.7 (5.3)	26.6 (4.5)	26.5 (5.2)	26.9 (4.6)	27.1 (5.4)	26.4 (4.4)
Pulse rate at rest, beats/min†	77.6 (14.1)	74.6 (12.6)	77.1 (14.2)	73.8 (13.2)	78.7 (13.8)	75.7 (11.6)
Total cholesterol, mg/dL†	238.3 (49.2)	228.7 (42.2)	236.1 (48.9)	230.1 (42.9)	242.7 (49.4)	226.7 (41.3)
Clinical depression	13.5	7.8	16.0	10.4	9.2	4.9
Referral to a mental health clinic in the prior year	4.2	2.3	5.0	2.9	2.9	1.6
Hospitalization for clinical depression in the prior year	0.4	0.1	0.4	0.2	0.4	0.1

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); NA, data not applicable.

SI conversion factor: To convert cholesterol to millimoles per liter, multiply by 0.0259.

*Data are given as percentage of each group unless otherwise indicated.

†Data are given as mean (SD).

‡Percentages may not total 100 because of rounding.

view of ambulatory medical records was more frequent among cases than controls (62.9% vs 53.8%; $P < .001$). Overall, clinical depression was more common in cases than in controls, and in subjects with and without prior heart disease ($P < .001$ for all). More severe clinical depression, as defined by referral to a mental health clinic or hospitalization for depression within the prior year, was also more frequent in cases than in controls.

CHARACTERISTICS OF CLINICALLY DEPRESSED AND NONDEPRESSED SUBJECTS

Table 2 compares the characteristics of controls with and without clinical depression. Subjects with clinical depression were older on average; had higher rates of unemployment; were more likely to be involved in a clerical occupation; were more likely to be current smokers, diabetics, hypertensive, and have congestive heart failure; and had a higher mean pulse rate at rest. In contrast, heavy alcohol consumption, body mass index, and total cholesterol level did not differ between the 2 groups. Similar results were observed in analyses stratified by physician-diagnosed heart disease (data not shown).

ESTIMATED OR OF OUT-OF-HOSPITAL CA FOR CLINICAL DEPRESSION

Table 3 shows that the estimated risk of out-of-hospital CA for patients with clinical depression was nearly 2-fold higher than among subjects without

clinical depression. After adjustment for current cigarette smoking, heavy alcohol consumption, physician-diagnosed diabetes mellitus, hypertension, prior myocardial infarction, and prior congestive heart failure, the estimated OR remained elevated. Results were similar after additional adjustment for body mass index, total cholesterol level, or pulse rate. The exclusion of patients who used antidepressant medications (134 cases and 143 controls, 82.2% of whom used tricyclic antidepressant medications) minimally altered the risk associated with clinical depression (OR, 1.37; 95% confidence interval [CI], 1.07-1.75). Consistent results were also observed even after adjustment for antiarrhythmic agents (type IA, 102 cases and 124 controls) (OR, 1.43; 95% CI, 1.19-1.73).

The association of clinical depression with out-of-hospital CA was observed in both sexes (men: OR, 1.47 [95% CI, 1.08-1.98]; and women: OR, 1.40 [95% CI, 1.09-1.79]) ($P = .66$ for the interaction) and in subjects younger than 70 years (OR, 1.21; 95% CI, 0.93-1.58) and 70 years and older (OR, 1.70; 95% CI, 1.29-2.23) ($P = .12$ for the interaction).

The presence of clinical depression was associated with a higher risk of out-of-hospital CA in the absence and presence of prior physician-diagnosed heart disease (Table 3), although the magnitude of the association was somewhat greater in subjects without than with heart disease ($P = .13$ for the interaction). Similar trends for those with and without clinical heart disease were observed in both sexes and both age categories (data not shown).

Table 2. Characteristics in Control Patients With and Without Clinical Depression*

Characteristic	Those With Clinical Depression (n = 327)	Those Without Clinical Depression (n = 3837)	P Value†
Age, y‡	67.0 (9.5)	66.2 (9.9)	.13
Male sex	52.3	71.0	<.001
White race	95.7	92.9	.13
Occupation			
Manual	49.2	49.2	<.001
Clerical or technician	14.2	8.0	
Tertiary	36.6	42.8	
Currently working	20.1	31.2	<.001
Current smoker	20.8	16.3	.04
Heavy drinker	7.0	6.5	.70
Diabetes mellitus	12.8	7.6	.001
Hypertension	39.8	33.5	.02
Prior myocardial infarction	20.2	16.2	.07
Congestive heart failure	21.7	8.1	<.001
BMI‡	26.5 (4.9)	26.7 (4.5)	.55
Pulse rate at rest, beats/min‡	77.9 (13.6)	74.2 (12.4)	<.001
Total cholesterol, mg/dL‡	228.3 (39.5)	228.7 (42.5)	.89

Abbreviations: See Table 1.

SI conversion factor: See Table 1.

*Data are given as percentage of each group unless otherwise indicated.

†Conditional logistic regression was used for statistical analyses.

‡Data are given as mean (SD).

Table 3. Crude and Multivariate-Adjusted OR for Out-of-Hospital CA Associated With Clinical Depression in the Total Sample and by Heart Disease Status

Group	Case-Control Ratio	OR (95% CI)	
		Crude	Multivariate Adjusted*
Total sample			
Depression absent	1928:3837	1.00	1.00
Depression present	300:327	1.88 (1.59-2.23)	1.43 (1.18-1.73)
Those without heart disease			
Depression absent	750:1830	1.00	1.00
Depression present	76:95	2.04 (1.48-2.82)	1.71 (1.22-2.41)
Those with heart disease			
Depression absent	1178:2007	1.00	1.00
Depression present	224:232	1.74 (1.42-2.13)	1.27 (1.01-1.60)

Abbreviations: CA, cardiac arrest; CI, confidence interval; OR, odds ratio.

*The ORs were estimated by conditional logistic regression and adjusted for smoking status, heavy alcohol drinking, hypertension, diabetes mellitus, and history of myocardial infarction and congestive heart failure.

INCREASING SEVERITY OF CLINICAL DEPRESSION AND OR OF OUT-OF-HOSPITAL CA

The estimated risk of out-of-hospital CA increased in a graded manner with clinical markers of severity of clinical depression (**Figure**). Compared with subjects without clinical depression, the risk of CA was increased in subjects with less severe clinical depression (neither referral to a mental health clinic nor hospitalization for depression) (OR, 1.30; 95% CI, 1.04-1.63) and further increased in subjects with severe clinical depression, as defined by referral to a mental health clinic and/or hospitalization for depression in the prior year (OR, 1.77; 95% CI, 1.28-2.45) ($P < .001$ for trend). After the exclusion of nonclinically depressed subjects, severely clinically depressed patients with referral and/or hospitaliza-

tion for depression in the prior year had a tendency to have a higher risk of CA compared with less depressed subjects (OR, 1.36; 95% CI, 0.93-2.00). Overall, analysis of the severity of clinical depression yielded similar results in subjects with and without physician-diagnosed heart disease (data not shown).

COMMENT

In this large, population-based, case-control study, the presence of clinical depression was associated with a higher risk of out-of-hospital CA due to heart disease. The association persisted after adjustment for other cardiovascular risk factors, and was evident across demographic subgroups and in subjects with and without phy-

sician-diagnosed heart disease. Severity of depression, as reflected by referral to a mental health clinic and hospitalization for depression, was associated with further increase in risk of out-of-hospital CA.

Our findings are in agreement with those of the few prior studies^{18,19} that suggest an association between depressive disorders and sudden cardiac death. In the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial,¹⁸ consisting of survivors of a recent myocardial infarction, depressive symptoms were associated with sudden death during a 2-year follow-up (relative risk, 2.45; 95% CI, 1.14-5.35) (34 events). In another study⁴ of patients after myocardial infarction, depression was associated with a higher risk of cardiac death (19 events, including 11 arrhythmic-related deaths) over 18 months of follow-up (OR, 6.64; 95% CI, 1.8-25.1). However, in these 2 studies, the presence of depressive disorders was evaluated after the onset of myocardial infarction, yielding the possibility that the association between depressive disorders and sudden cardiac death (or arrhythmic-related death) was secondary to myocardial infarction. In a prospective cohort of healthy Finnish elderly men and women, depressive symptoms at baseline were associated with sudden cardiac death but not with non-sudden cardiac death over 8 years of follow-up, with nearly a 3-fold increase in the risk after adjustment for CHD risk factors (38 events).¹⁹ However, this study was restricted to elderly individuals 70 years or older.

These previous studies examined selected populations (those after myocardial infarction or those >70 years) and had a limited number of sudden cardiac deaths (<40 events). The present study, with 2228 CA events, extends these previous observations by demonstrating the association of physician-diagnosed depression with out-of-hospital CA in a large population with a wide range of demographic and clinical characteristics. Higher risk was observed in elderly men and women and in middle-aged subjects (<70 years). In addition, an association was found in patients with and without prior heart disease. The result in this latter population (those free of prior heart disease) minimizes the possibility that diagnosed cardiac disease accounts for the association between clinical depression and out-of-hospital CA. Furthermore, our findings suggest a dose effect whereby the risk of out-of-hospital CA increases with increasing severity of clinical depression, which has not previously been investigated.

The findings are strengthened by the robustness of our results. The association between clinical depression and out-of-hospital CA remained highly significant after adjustment for major CHD risk factors. Additional adjustment for total cholesterol level and body mass index did not alter the results. Likewise, further adjustment for more specific risk markers of sudden death, including resting pulse rate, did not alter the results substantially.²²

A previous case-control study¹¹ suggested that the use of tricyclic antidepressant medication was associated with sudden cardiac death. However, the respective contribution of depression and tricyclic agents was not investigated in that study. In the present report, exclusion of persons actively taking antidepressant medication (277 subjects, 82.2% of whom were taking tricyclic agents) did

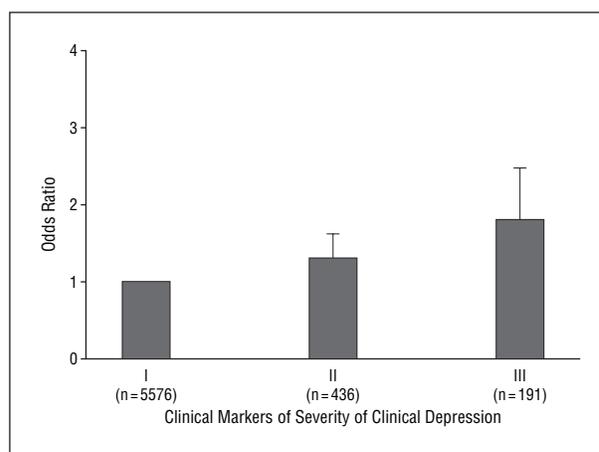


Figure. Clinical markers of the severity of clinical depression and multivariate-adjusted risk of out-of-hospital cardiac arrest. The odds ratios were estimated by conditional logistic regression and adjusted for smoking status, heavy alcohol consumption, hypertension, diabetes mellitus, and history of myocardial infarction and congestive heart failure. Bars represent the upper limit of the 95% confidence interval of the odds ratio. I indicates those subjects without clinical depression (reference category); II, those subjects with clinical depression without referral to a mental health clinic and without hospitalization for depression; and III, those subjects with clinical depression with referral to a mental health clinic and/or hospitalization for depression in the prior year.

not change the association between clinical depression and out-of-hospital CA, suggesting that depression is an independent risk factor for CA.

Several mechanisms have been suggested to explain the association between depression and CHD-related mortality, including sudden death. In the present study, adjustment for major CHD risk factors decreased the association under investigation (from 1.88 to 1.43; however, the association remained highly significant), suggesting that atherosclerosis may in part be implicated. Moreover, alteration of the cardiac autonomic response, including a decrease in heart rate variability, has been reported in patients with depression recovering from myocardial infarction.^{16,17} Low red blood cell membrane levels of ω -3 polyunsaturated fatty acids, which are associated with an increased risk of sudden cardiac death,²³ have also been reported in patients with major depressive disorders.²⁴ Poor adherence to treatment, especially in depressed patients recovering from myocardial infarction, might also be involved.²⁵ Finally, clinical depression may be associated with unhealthy lifestyle habits, such as smoking and physical inactivity, which in turn increase the risk of out-of-hospital CA. However, in the present study, the association between clinical depression and out-of-hospital CA persisted even after adjustment for smoking status.

The present study has several strengths. It includes many out-of-hospital CA events and was, thus, sufficiently powered to detect association. We identified all cases of out-of-hospital CA within a defined population and minimized potential misclassification of out-of-hospital CA due to noncardiac causes by reviewing ambulatory care medical records, emergency medical services' incident reports, death certificates, medical examiner reports, and autopsy reports. Cases and controls were selected from the same population of HMO enrollees and

had similar access to care. Furthermore, the use of a staff-model HMO as the source population and the point of medical and mental health care for cases and controls also minimizes potential sources of bias.

Several limitations to the interpretation of our findings deserve consideration. Depression frequently is unrecognized in primary care.²⁵ In this study, however, there is no reason to suspect that clinical depression had been systematically and more frequently underestimated among the controls than among cases. Unrecognized depression would be misclassified as not depressed, and this might introduce a conservative bias, reducing the strength of the association between clinical depression and out-of-hospital CA. Although we adjusted the association of clinical depression with out-of-hospital CA for a wide range of potential confounders, residual confounding may still have occurred. For example, we had no information on diet and exercise, factors that have been associated with out-of-hospital CA and may be related to depression. Furthermore, despite a detailed review of ambulatory medical records to identify the presence and extent of prior physician-diagnosed heart disease, we cannot exclude the possibility of residual bias due to the presence and extent of unrecognized heart disease in the group of enrollees classified as free of prior physician-diagnosed heart disease. While we controlled the association between clinical depression and out-of-hospital CA for a wide range of potentially proarrhythmic medications, we had no information on certain medications, including erythromycin or antifungal agents, that are known to prolong the QT interval. Last, the study population was predominantly white and enrolled in an HMO. Thus, extrapolation of the results to other populations should be done with caution.

In conclusion, these data suggest that the presence and severity of clinical depression was associated with higher odds of out-of-hospital CA. To the extent that similar results are observed in other settings, these results may have potential clinical implications with regard to risk stratification for out-of-hospital CA.

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REFERENCES

1. Zipes DP, Wellens HJ. Sudden cardiac death. *Circulation*. 1998;98:2334-2351.
2. Ahern DK, Gorkin L, Anderson JL, et al; CAPS Investigators. Biobehavioral variables and mortality or cardiac arrest in the Cardiac Arrhythmia Pilot Study (CAPS). *Am J Cardiol*. 1990;66:59-62.
3. Ladwig KH, Kieser M, König M, Breithardt G, Borggreffe M. Affective disorders and survival after acute myocardial infarction: results from the post-infarction late potential study. *Eur Heart J*. 1991;12:959-964.
4. Frasure-Smith N, Lespérance F, Talajic M. Depression and 18-months prognosis after myocardial infarction. *Circulation*. 1995;91:999-1005.
5. Barefoot JC, Helms MJ, Mark DB, et al. Depression and long-term mortality in patients with coronary artery disease. *Am J Cardiol*. 1996;78:613-617.
6. Bush DE, Ziegelstein RC, Tayback M, et al. Even minimal symptoms of depression increase mortality risk after acute myocardial infarction. *Am J Cardiol*. 2001;88:337-341.
7. Lespérance F, Frasure-Smith N, Talajic M, Bourassa MG. Five-year risk of cardiac mortality in relation to initial and one-year changes in depression symptoms after myocardial infarction. *Circulation*. 2002;105:1049-1053.
8. Anda R, Williamson D, Jones D, et al. Depressed affect, hopelessness, and the risk of ischemic heart disease in a cohort of US adults. *Epidemiology*. 1993;4:285-294.
9. Ford DE, Mead LA, Chang PP, Cooper-Patrick L, Wang NY, Klag MJ. Depression is a risk factor for coronary artery disease in men: the Precursors Study. *Arch Intern Med*. 1998;158:1422-1426.
10. Pratt LA, Ford DE, Crum RM, Armenian HK, Gallo JJ, Eaton WW. Depression, psychotropic medication, and risk of myocardial infarction: prospective data from the Baltimore ECA follow-up. *Circulation*. 1996;94:3123-3129.
11. Hippisley-Cox J, Fielding K, Pringle M. Depression as a risk factor for ischaemic heart disease in men: population based case-control study. *BMJ*. 1998;316:1714-1719.
12. Stansfeld SA, Fuhrer R, Shipley MJ, Marmot MG. Psychological distress as a risk factor for coronary heart disease in the Whitehall II Study. *Int J Epidemiol*. 2002;31:248-255.
13. Barefoot JC, Schroll M. Symptoms of depression, acute myocardial infarction, and total mortality in a community sample. *Circulation*. 1996;93:1976-1980.
14. Ferketich AK, Schwartzbaum JA, Frid DJ, Moeschberger ML. Depression as an antecedent to heart disease among women and men in the NHANES I study: National Health and Nutrition Examination Survey. *Arch Intern Med*. 2000;160:1261-1268.
15. Penninx BW, Beekman AT, Honig A, et al. Depression and cardiac mortality: results from a community-based longitudinal study. *Arch Gen Psychiatry*. 2001;58:221-227.
16. Carney RM, Blumenthal JA, Stein PK, et al. Depression, heart rate variability, and acute myocardial infarction. *Circulation*. 2001;104:2024-2028.
17. Carney RM, Freedland KE, Miller GE, Jaffe AS. Depression as a risk factor for cardiac mortality and morbidity: a review of potential mechanisms. *J Psychosom Res*. 2002;53:897-902.
18. Irvine J, Basinski A, Baker B, et al. Depression and risk of sudden cardiac death after acute myocardial infarction: testing the confounding effects of fatigue. *Psychosom Med*. 1999;61:729-737.
19. Luukinen H, Laippala P, Huikuri HV. Depressive symptoms and the risk of sudden cardiac death among the elderly. *Eur Heart J*. 2003;24:2021-2026.
20. Whitsel EA, Raghunathan TE, Pearce RM, et al. RR interval variation, the QT interval index and risk of primary cardiac arrest among patients without clinically recognized heart disease. *Eur Heart J*. 2001;22:165-173.
21. Saunders KW, Davis RL, Stergachis A. Group Health Cooperative of Puget Sound. In: Strom B, ed. *Pharmacoepidemiology*. 3rd ed. New York, NY: John Wiley & Sons Inc; 2000:247-262.
22. Jouven X, Zureik M, Desnos M, Guerot C, Ducimetiere P. Resting heart rate as a predictive risk factor for sudden death in middle-aged men. *Cardiovasc Res*. 2001;50:373-378.
23. Siscovick DS, Raghunathan TE, King I, et al. Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest. *JAMA*. 1995;274:1363-1367.
24. Tiemeier H, van Tuijl HR, Hofman A, Kiliaan AJ, Breteler MM. Plasma fatty acid composition and depression are associated in the elderly: the Rotterdam Study. *Am J Clin Nutr*. 2003;78:40-46.
25. Hirschfeld RM, Keller MB, Panico S, et al. The National Depressive and Manic-Depressive Association consensus statement on the undertreatment of depression. *JAMA*. 1997;277:333-340.