

Depression and Cardiac Function in Patients With Stable Coronary Heart Disease: Findings From the Heart and Soul Study

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Objective: To determine whether depression is associated with worse cardiac disease severity in patients with stable coronary heart disease (CHD). There is considerable evidence that depression is a risk factor for adverse cardiovascular events in patients with CHD. However, a frequent criticism of this literature is that the association between depression and adverse cardiovascular outcomes may be confounded by worse baseline cardiac disease severity in depressed patients. **Method:** In a sample of 1020 outpatients with stable CHD, we examined the association between major depression (assessed using the Computerized National Institute of Mental Health Diagnostic Interview Schedule) with measures of cardiac disease severity, including systolic dysfunction, diastolic dysfunction, exercise-induced ischemia, and cardiac wall motion abnormalities. Cross-sectional univariate and multivariate models controlling for demographic and clinical variables were computed. **Results:** Of the 1020 participants, 224 (22%) had current (past month) major depression. After adjustment for age, major depression was not associated with systolic dysfunction, diastolic dysfunction, inducible ischemia, or cardiac wall motion abnormalities. Similarly, multivariate models revealed no significant relationship between major depression and cardiac disease severity. **Conclusions:** Overall, we found little evidence that depression is associated with worse cardiac disease severity. This suggests that greater baseline cardiac disease severity is unlikely to be responsible for the increased risk of CHD events in depressed patients. **Key words:** depression, cardiac function, coronary heart disease.

AMI = acute myocardial infarction; **BMI** = body mass index; **CABG** = coronary artery bypass graft; **CDIS-IV** = Computerized National Institute of Mental Health Diagnostic Interview Schedule; **CHD** = coronary heart disease; **LVEF** = left ventricular ejection fraction; **PHQ-9** = Patient Health Questionnaire.

INTRODUCTION

A large body of evidence suggests that depression is a risk factor for morbidity and mortality in patients with existing coronary heart disease (CHD) (1). Recent meta-analyses and systematic reviews have concluded that the presence of depression is associated with an approximately two-fold increase in cardiac morbidity and mortality for various CHD populations, including patients with recent acute myocardial infarction (AMI), patients awaiting coronary artery bypass graft (CABG) surgery, and patients post revascularization (2–7).

The possibility that the relationship between depression and cardiac prognosis is confounded by cardiac disease severity is a continual source of controversy. There may be a direct physiological link between the severity of cardiac disease and depression, and/or the severity of cardiac disease may be related to depression via patient illness perceptions (e.g., due to worsening symptoms or diagnostic feedback). If patients with depression have greater baseline cardiac disease severity,

then the relationship between depression and future cardiovascular events may be due to underlying disease severity rather than depression (8–12).

In recent meta-analyses, Barth et al. (2), van Melle et al. (7), and Nicholson et al. (13) noted that studies in this area have varied considerably with respect to statistical control for potential confounders like cardiac disease severity. For example, although some studies have controlled for disease severity by including measures like left ventricular ejection fraction (LVEF) and/or Killip Class in statistical models (14–21), a sizable number have not. An additional concern is the possibility that measures of cardiac disease severity have been incomplete. Thus, even if studies have utilized measure(s) of disease severity for statistical control, some degree of residual confounding may remain (22).

We are not aware of prior studies that specifically have aimed to examine the multivariate association of depression with measures of cardiac disease severity such as systolic dysfunction, diastolic dysfunction, exercise-induced ischemia, and cardiac wall motion abnormalities. However, many prospective studies with the specific aim of investigating the association between depression and outcomes for patients with CHD have reported univariate associations between depression and disease severity measures at baseline. Some of these studies have reported an association between depression and lower LVEF and/or higher Killip Class (21,23), but many others have found no relationship between depression and various measures of cardiac disease severity (15–19,22,24–28). In addition, prior studies that have found a relationship between depression and outcome have sampled patients after acute CHD events such as AMI (14,17,27,29) or CABG surgery (16,19). Because rates of elevated depressive symptoms are particularly high at the time of hospitalization and tend to decrease within the subsequent months (16,30–32), increased scores at the time of hospitalization may be more likely to indicate transient distress rather than true clinical depression. Thus, studies are needed to investigate the relationship between depression and cardiac disease severity, utilizing a stable CHD sample, mul-

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Received for publication May 14, 2007; revision received December 3, 2007.

This study was supported by grants to Dr. Whooley from the Department of Veterans Affairs Epidemiology Merit Review Program, Grant R01 HL079235 from the National Heart Lung and Blood Institute, the American Federation for Aging Research (Paul Beeson Scholars Program), the Robert Wood Johnson Foundation (Generalist Physician Faculty Scholars Program), the Ischemia Research and Education Foundation, and the Nancy Kirwan Heart Research Fund.

DOI: 10.1097/PSY.0b013e31816c3c5c

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tivariate models, and comprehensive measures of cardiac disease severity and depression.

In a sample of 1020 patients with stable CHD, we sought to examine the relationship between major depression and cardiac disease severity, including systolic dysfunction, diastolic dysfunction, exercise-induced ischemia, and cardiac wall motion abnormalities, as measured by stress echocardiography.

METHODS

Participants

Study participants were enrolled in the Heart and Soul Study, a longitudinal study of psychosocial risk factors and clinical outcomes in patients with CHD (33). We used administrative databases to identify patients with stable CHD at two Veterans Affairs medical centers, one university medical center, and nine public health clinics in the San Francisco Bay Area. Patients were eligible to participate in the study if they had a history of myocardial infarction or coronary revascularization, angiographic documentation of $\geq 50\%$ stenosis in at least one coronary artery, or evidence of exercise-induced ischemia by treadmill or cardiac perfusion testing. Patients were excluded if they were unable to walk one block, had experienced an acute coronary syndrome within the prior 6 months, or were planning to move out of the local area within 3 years. Between September 2000 and December 2002, a total of 1024 participants were enrolled in the study, and 1020 completed the diagnostic interview for depression. Participants underwent a baseline study examination that included a comprehensive health interview, blood samples, medical history questionnaire, psychosocial questionnaire, and exercise treadmill test with stress echocardiography. The Institutional Review Board at each of the sites approved the protocol, and all participants provided their written informed consent.

Measures

Depression Measures

To assess for the presence of major depression within the past month, a trained research assistant administered the Computerized National Institute of Mental Health Diagnostic Interview Schedule (CDIS-IV). The CDIS-IV is a computerized version of the Diagnostic Interview Schedule, a structured measure designed to assess for DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition) psychiatric diagnoses (34). Participants who met the criteria for major depression within the past month were informed of the results of the depression assessment, encouraged to discuss their symptoms with their primary care provider, and provided a list of additional local resources for treatment.

Prior research has suggested that both major depression and elevated depressive symptoms are associated with adverse cardiovascular outcomes (16,23,27,35). Therefore, we also assessed the presence of depressive symptoms, using the Patient Health Questionnaire (PHQ-9). The PHQ-9 is a nine-item, self-report measure designed to assess for the severity of depressive symptoms within the past 2 weeks. It has good validity for use in primary care, is based on DSM-IV criteria for major depression, and with only nine items, offers a low burden for study participants (36). We evaluated the PHQ-9 both as a continuous variable and as a dichotomous variable, using the standard cut-point of ≥ 10 (37).

Cardiac Function Measures

We performed a comprehensive assessment of cardiac disease severity, including systolic function, diastolic function, exercise-induced ischemia, and cardiac wall motion abnormalities. A complete resting two-dimensional echocardiogram, using an Acuson Sequoia Ultrasound System (Mountain View, California) with a 3.5-MHz transducer and Doppler ultrasound examination, including all standard views and subcostal imaging of the inferior vena cava, was performed just before and immediately after exercise. We obtained standard two-dimensional parasternal short-axis and apical two- and four-chamber views during held inspiration; these were planimeted, using a computerized digitization system to determine end-diastolic and end-systolic left ventricular volume (38).

We calculated LVEF as follows: (end-diastolic volume – end-systolic volume)/end-diastolic volume. Systolic dysfunction was defined as LVEF $\leq 50\%$. We defined diastolic dysfunction as the presence of at least one of the following: 1) impaired relaxation = E/A ratio ≤ 0.75 and systolic dominant pulmonary vein flow; 2) pseudonormal = $0.75 < E/A < 1.5$ and diastolic dominant pulmonary vein flow; and 3) restrictive filling = E/A ratio ≥ 1.5 and diastolic dominant pulmonary vein flow (39–41). All individuals underwent echocardiography, although the echocardiographic parameters necessary for ventricular dysfunction classifications were missing for some ($n = 2$ missing LVEF and $n = 212$ missing diastolic dysfunction classification because of a rhythm other than sinus, moderate-to-severe mitral regurgitation, or difficulty determining velocity time integral in the pulmonary vein).

We then performed a symptom-limited, graded exercise treadmill test according to a standard Bruce protocol. To achieve maximal heart rate, participants who were unable to continue the standard Bruce protocol were switched to lower settings on the treadmill and encouraged to exercise for as long as possible. Immediately after exercise, participants underwent a repeat echocardiogram. Apical two-chamber, four-chamber, and precordial long-axis and short-axis views were obtained to detect the development of wall motion abnormalities during exercise. The presence of inducible ischemia was defined as the presence of new echocardiographic wall motion abnormalities at peak exercise that were not present at rest.

To account for both fixed and exercise-induced wall motion defects, we also calculated the wall motion score index at peak exercise (38). Each of 16 wall segments in the left ventricle was scored based on the contractility visualized at peak exercise (1 = normal, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic, 5 = aneurysm). The wall motion score index was defined as the sum of wall motion scores divided by the number of segments visualized, with a normally contracting left ventricle receiving a wall motion score index of 1 (16/16=1), and higher wall motion scores indicating worse contractility.

Demographic and Clinical Characteristics

Demographic data and medical history were obtained by self-report questionnaire. Height and weight were measured at the study appointment to calculate body mass index (BMI). Resting blood pressure was measured, using a standard sphygmomanometer. High-density lipoprotein cholesterol, low-density lipoprotein cholesterol, total cholesterol, C-reactive protein, and NT-pro-B-type natriuretic peptide were measured from venous blood samples after a 12-hour fast. Creatinine clearance was calculated from a 24-hour urine collection sample. Participants brought their medications to their study appointments and current medications were recorded.

Statistical Analysis

For descriptive purposes, participants were grouped based on the presence or absence of current major depression (by CDIS-IV) and compared on clinical and demographic variables, using the general linear model for continuous variables and χ^2 tests for categorical variables. Similarly, the association of depression with each measure of cardiac function was evaluated, using the general linear model for continuous variables and logistic regression for dichotomous outcome variables. Separate models were computed for each measure of cardiac function. For the primary analyses, we compared cardiac function in patients with and without current major depression according to the CDIS-IV. To address the possibility that some patients met the study inclusion criteria on the basis of false-positive treadmill test results, we repeated the primary analysis excluding these 328 participants.

For the secondary analysis, we evaluated the association between depressive symptoms (entered both as continuous and dichotomous variables) and all measures of cardiac function. Both univariate and multivariate models were computed. The following clinical and demographic variables were selected a priori for inclusion in the multivariate models, and were retained regardless of statistical significance: age, sex, marital status, diabetes, revascularization, smoking, BMI, physical activity, antidepressant use, statin use, and creatinine clearance. Because depression was associated with younger age, we also computed a model controlling for age only to highlight the effect of age in the unadjusted models. Because few women were included in the analyses, we tested for an interaction between CDIS-IV major depression and

sex to explore the possibility that any relationship between depression and cardiac function would vary by sex.

RESULTS

Of the 1020 participants, 224 (22%) had current (past month) major depression. Compared with nondepressed participants, those with current depression were younger, less likely to be male, married or physically active, and more likely to smoke. Participants with major depression were less likely to have been revascularized, less likely to use statins, more likely to use antidepressants, and had better creatinine clearance (Table 1).

Major depression was associated with better cardiac functioning in the univariate analyses (Table 2). However, after controlling for younger age and other covariates, major depression was no longer associated with better cardiac function. Overall, we found no evidence that major depression was associated with systolic dysfunction, diastolic dysfunction, inducible ischemia, or wall motion abnormalities. The results including the entire sample were similar to results excluding the 328 participants with positive treadmill tests (multivariate models: systolic dysfunction, $p = .14$; diastolic dysfunction, $p = .94$; wall motion score index, $p = .41$; LVEF, $p = .13$).

When the PHQ score was entered as a continuous variable (or as the natural log of this variable) in age-adjusted models, depressive symptoms were not associated with systolic dysfunction, diastolic dysfunction, inducible ischemia, wall motion score index, or LVEF (all $p > .20$). Similarly, when entered as a dichotomous variable (PHQ ≥ 10), depressive symptoms were not associated with measures of cardiac disease severity, with the possible exception of worse systolic function (Table 3). There were no significant interactions between sex and major depression (multivariate models: systolic dysfunction, $p = .41$; inducible ischemia, $p = .41$; wall motion score index, $p = .95$; LVEF, $p = .82$), with the exception of the unexpected finding that major depression was associated with better diastolic function in women only (multivariate model, $p = .002$).

DISCUSSION

There is considerable debate about whether the association of depression with adverse cardiovascular outcomes is confounded by worse baseline cardiac disease severity in depressed patients. In a sample of 1020 patients with stable CHD, we found no evidence that major depression is associated with systolic dysfunction, diastolic dysfunction, inducible ischemia, or cardiac wall motion abnormalities. Similarly, we found little evidence of an association between depressive symptoms and CHD severity, with the exception of worse systolic function in patients with PHQ-9 scores of ≥ 10 . Overall, however, the lack of association we observed between major depression and cardiac disease severity suggests that greater underlying cardiac disease severity is unlikely to explain the increased risk of CHD events associated with depression.

As shown in the analyses controlling for age only, the univariate associations we observed between depression and better cardiac function were due, in large part, to the inverse

TABLE 1. Characteristics of 1020 Study Participants With Stable Coronary Heart Disease

Variable	Depressed ($n = 223$)	Not Depressed ($n = 797$)	p
Age (years), mean \pm SD	62 \pm 11	68 \pm 11	<.001
Male sex	156 (70)	680 (85)	<.001
White race	135 (61)	478 (60)	.90
Married	70 (32)	364 (46)	.001
Medical history			
Diabetes	68 (30)	197 (25)	.09
Myocardial infarction	110 (50)	435 (55)	.18
Congestive heart failure	40 (18)	137 (17)	.80
Hypertension	158 (71)	563 (71)	.99
Stroke	33 (15)	114 (14)	.84
Revascularization	111 (50)	489 (62)	.002
COPD or asthma	44 (20)	119 (15)	.08
Current smoker	64 (29)	137 (17)	<.001
Regular alcohol use	67 (30)	226 (29)	.64
BMI (kg/m^2), mean \pm SD	29 \pm 5.6	28 \pm 5	.02
Physically active	119 (54)	529 (67)	<.001
Medication use			
β blocker	124 (56)	466 (58)	.44
Statin	130 (58)	524 (66)	.04
Aspirin	174 (78)	616 (77)	.82
Renin-angiotensin system inhibitor	110 (49)	411 (52)	.55
Antidepressant			
SSRI	63 (28)	34 (4)	<.001
Tricyclic	18 (8)	26 (3)	.002
Other antidepressant	46 (21)	33 (4)	<.001
Laboratory tests			
HDL cholesterol	45 \pm 15	46 \pm 14	.58
LDL cholesterol	107 \pm 36	104 \pm 33	.23
Log C-reactive protein	0.75 \pm 1.3	0.70 \pm 1.3	.65
Log NT pro-B-type natriuretic peptide	5 \pm 1.2	5.3 \pm 1.4	<.001
Creatinine clearance	87.2 \pm 30.3	79.5 \pm 27.8	<.001
Cardiac function			
Resting heart rate, mean \pm SD	68 \pm 12	68 \pm 12	.41
Systolic blood pressure, mean \pm SD	133 \pm 22	133 \pm 21	.89
Diastolic blood pressure, mean \pm SD	76 \pm 12	74 \pm 11	.14

Data are presented as number (%) or mean \pm SD.

SD = standard deviation; COPD = chronic obstructive pulmonary disease; BMI = body mass index; SSRI = selective serotonin reuptake inhibitor; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

relationship between depression and age, such that depressed participants were significantly younger than the nondepressed participants in our sample. This inverse association between depression and age is a common finding in both population (42) and CHD samples (43). The association between depression and cardiac function was no longer significant in the multivariate models controlling for age and other demographic and clinical risk factors.

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TABLE 2. Cardiac Disease Severity in 1020 Participants With Stable Coronary Heart Disease, Stratified by Presence or Absence of Past Month Major Depression by Computerized Diagnostic Interview Schedule

Variable	Unadjusted Mean (Standard Error) or Number (Proportion)			Age-Adjusted Mean (Standard Error) for Continuous Variables or Odds Ratio (95% CI) for Dichotomous Variables ^a			Multivariable-Adjusted Mean (Standard Error) for Continuous Variables or Odds Ratio (95% CI) for Dichotomous Variables ^a		
	Major Depression (n = 223)	No Major Depression (n = 797)	p	Major Depression (n = 223)	No Major Depression (n = 797)	p	Major Depression (n = 223)	No Major Depression (n = 797)	P
Systolic dysfunction	17 (8%)	100 (13%)	.04	0.57 (0.33–0.98)		.04	0.57 (0.31–1)		.07
Diastolic dysfunction	48 (25%)	244 (39%)	<.001	0.73 (0.49–1.1)		.10	0.63 (0.40–0.99)		.05
Inducible ischemia	36 (18%)	191 (26%)	.03	0.84 (0.55–1.3)		.39	0.73 (0.45–1.2)		.19
Wall motion score index	1.1 ± 0.03	1.2 ± 0.01	.02	1.1 ± 0.03	1.2 ± 0.01	.07	1.1 ± 0.03	1.2 ± 0.03	.21
Left ventricular ejection fraction	0.63 ± 0.006	0.61 ± 0.003	.02	0.63 ± 0.007	0.61 ± 0.003	.02	0.64 ± 0.008	0.62 ± 0.007	.05

^a Models evaluate association of current CDIS (Computerized National Institute of Mental Health Diagnostic Interview Schedule) major depression as predictor (independent) variable with cardiac function as outcome (dependent) variable. Age-adjusted mean adjusted for age only. Multivariable-adjusted mean adjusted for age, sex, marital status, diabetes, revascularization, smoking, body mass index, physical activity, antidepressant use, statin use, and creatinine clearance. CI = confidence interval.

Table 3. Cardiac Disease Severity in Patients With and Without Substantial Depressive Symptoms (PHQ Score ≥10 Versus <10)

Variable	Unadjusted Mean (Standard Error) or Number (Proportion)			Age-Adjusted Mean (Standard Error) for Continuous Variables or Odds Ratio (95% CI) for Dichotomous Variables ^a			Multivariable-Adjusted Mean (Standard Error) for Continuous Variables or Odds Ratio (95% CI) for Dichotomous Variables ^a		
	PHQ ≥10 (n = 198)	PHQ <10 (n = 822)	p	PHQ ≥10 (n = 198)	PHQ <10 (n = 822)	p	PHQ ≥10 (n = 198)	PHQ <10 (n = 822)	p
Systolic dysfunction	32 (16%)	85 (10%)	.02	1.7 (1.1–2.7)		.02	1.7 (1.01–2.8)		.04
Diastolic dysfunction	41 (29%)	251 (38%)	.05	0.87 (0.57–1.3)		.50	0.81 (0.51–1.3)		.38
Inducible ischemia	41 (24%)	186 (24%)	.93	1.2 (0.82–1.8)		.33	1.1 (0.74–1.8)		.55
Wall motion score index	1.2 ± 0.03	1.2 ± 0.01	.15	1.2 ± 0.03	1.2 ± 0.01	.06	1.2 ± 0.03	1.1 ± 0.02	.08
Left ventricular ejection fraction	0.61 ± 0.007	0.62 ± 0.003	.07	0.60 ± 0.007	0.62 ± 0.003	.05	0.62 ± 0.008	0.63 ± 0.007	.18

^a Models evaluate association of PHQ symptoms of depression as predictor (independent) variable with cardiac function as outcome (dependent) variable. Age-adjusted mean adjusted for age only. Multivariable-adjusted mean adjusted for age, sex, marital status, diabetes, revascularization, smoking, body mass index, physical activity, antidepressant use, statin use, and creatinine clearance. PHQ = Patient Health Questionnaire; CI = confidence interval.

The association between PHQ-9 depressive symptoms and worse systolic function raises the possibility that currently elevated depressive symptoms and past month clinical depression may be differentially related to cardiac function. It is possible that the frequency and recency of depressive symptoms captured by the continuous PHQ score may be more strongly associated with cardiac function than the number of criteria required for a clinical diagnosis of major depression within the past month. Nonetheless, these results should be interpreted with caution. Not only was there no association between systolic function and depression in the primary analysis using the CDIS-IV but the primary analysis actually suggested a nonsignificant trend in the opposite direction. Thus, any differences in the association of cardiac function with depressive symptoms versus a clinical diagnosis of depression would need confirmation in other studies.

Consistent with our present results, previous longitudinal studies have reported no significant association between depres-

sion and baseline measures of cardiac disease severity, such as LVEF and Killip Class (15–19,24–28), although some have reported a significant association (21,23). Our study adds to this literature by evaluating the association of depression with comprehensive measures of systolic function, diastolic function, inducible ischemia, and wall motion abnormalities. It should be noted, however, that although our study suggests there is no relationship between major depression and objective measures of disease severity, these findings do not necessarily reflect patients' perceptions of the severity of their illness. Depression may be related to cardiac function via patient perceptions unrelated to objective physiological measures. For example, Knol et al. (44) found that patients with Type 2 diabetes who were aware of their illness had increased rates of depression, whereas those unaware of their illness did not, highlighting the importance of patient perceptions over objective disease severity.

Our study is unique in utilizing multivariate models and comprehensive measures of both depression and cardiac dis-

ease severity to examine the relationship between depression and cardiac disease severity. In addition, our study included only patients with stable CHD, whereas prospective studies generally have included patients hospitalized with acute CHD events, such as patients pre CABG, post AMI, or post revascularization. Depression detected in our sample of patients with stable CHD may be more likely to reflect true clinical depression, rather than transient distress in response to an acute event.

An important limitation of the present study is that only 184 women were included in the primary analysis. This calls into question the generalizability of these results to women. However, we found no consistent evidence for a sex by depression interaction. The significant interaction between sex and diastolic dysfunction, such that major depression was associated with better diastolic function for women, should be interpreted with caution due to the small number of women ($n = 184$) in the analyses and the large number of tests in our secondary analyses. However, the large sample size, complete statistical control, and use of comprehensive measures of both depression and cardiac disease severity are notable strengths of this study.

If depression does not serve as a marker for cardiac disease severity, then it is important to identify the mechanisms that link depression with subsequent CHD events. There are several plausible biobehavioral mechanisms for which there is initial empirical support, including lifestyle factors like diet, exercise, tobacco use, heavy use of alcohol, and nonadherence to treatment; traditional risk factors like hypertension, diabetes, obesity, and insulin resistance; other physiological factors associated with depression, such as platelet activation, autonomic nervous system dysregulation, endothelial dysfunction, and inflammation; and genetic factors associated with both depression and CHD (6,45,46). It is also possible that depression increases the risk of acute cardiac events, but not chronic atherosclerosis (47). These are important areas for additional study, as identifying mechanisms may help to guide interventions for patients with CHD who are at increased risk due to depression.

In sum, the results of the present study found little evidence for an association between depression and cardiac disease severity in patients with stable CHD. This suggests that it is unlikely that depression is confounded with disease severity in prospective studies of depression and stable CHD outcomes.

REFERENCES

1. Whooley MA. Depression and cardiovascular disease: healing the broken-hearted. *JAMA* 2006;295:2874–81.
2. Barth J, Schumacher M, Herrmann-Linger C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. *Psychosom Med* 2004;66:802–13.
3. Hemingway H, Marmot M. Evidence based cardiology: psychosocial factors in the aetiology and prognosis of coronary heart disease. Systematic review of prospective cohort studies. *BMJ* 1999;318:1460–7.
4. Kuper H, Marmot M, Hemingway H. Systematic review of prospective cohort studies of psychosocial factors in the etiology and prognosis of coronary heart disease. *Semin Vasc Med* 2002;2:267–314.
5. Lett H, Blumenthal J, Babyak M, Sherwood A, Strauman T, Robins C.

- Depression as a risk factor for coronary artery disease: evidence, mechanisms, and treatment. *Psychosom Med* 2004;66:305–15.
6. Smith TW, Ruiz JM. Psychosocial influences on the development and course of coronary heart disease: current status and implications for research and practice. *J Consult Clin Psychol* 2002;70:548–68.
7. van Melle J, de Jonge P, Spijkerman T, Tijssen J, Ormel J, van Veldhuisen D, van den Brink R, van den Berg M. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. *Psychosom Med* 2004;66:814–22.
8. Lane D, Carroll D, Lip GY. Anxiety, depression, and prognosis after myocardial infarction: is there a causal association? *J Am Coll Cardiol* 2003;42:1808–10.
9. Mendes de Leon CF. Depression and social support in recovery from myocardial infarction: confounding and confusion. *Psychosom Med* 1999;61:738–9.
10. Steptoe A, Whiteman MC. Depression, stress, and coronary heart disease: the need for more complex models. *Heart* 2005;91:419–20.
11. Stewart RA, North FM, West TM, Sharples KJ, Simes RJ, Colquhoun DM, White HD, Tonkin AM, Long-Term Intervention With Pravastatin in Ischaemic Disease (LIPID) Study Investigators. Depression and cardiovascular morbidity and mortality: cause or consequence? *Eur Heart J* 2003;24:2027–37.
12. Lane D, Carroll D, Ring C, Beevers DG, Lip GY. In-hospital symptoms of depression do not predict mortality 3 years after myocardial infarction. *Int J Epidemiol* 2002;31:1179–82.
13. 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.
14. Ahern DK, Gorkin L, Anderson JL, Tierney C, Hallstrom A, Ewart C, Capone RJ, Schron E, Kornfeld D, Herd JA. Biobehavioral variables and mortality or cardiac arrest in the Cardiac Arrhythmia Pilot Study (CAPS). *Am J Cardiol* 1990;66:59–62.
15. Barefoot JC, Helms MJ, Mark DB, Blumenthal JA, Califf RM, Haney TL, O'Connor CM, Siegler IC, Williams RB. Depression and long-term mortality risk in patients with coronary artery disease. *Am J Cardiol* 1996;78:613–7.
16. Blumenthal JA, Lett H, Babyak M, White W, Smith P, Mark D, Jones R, Mathew J, Newman M. Depression as a risk factor for mortality after coronary artery bypass surgery. *Lancet* 2003;362:604–9.
17. Bush DE, Ziegelstein RC, Tayback M, Richter D, Stevens S, Zahalsky H, Fauerbach JA. Even minimal symptoms of depression increase mortality risk after acute myocardial infarction. *Am J Cardiol* 2001;88:337–41.
18. Carney RM, Rich MW, Freedland KE, Saini J, Tevelde A, Simeone C, Clark K. Major depressive disorder predicts cardiac events in patients with coronary artery disease. *Psychosom Med* 1988;50:627–33.
19. Connerney I, Shapiro PA, McLaughlin JS, Bagiella E, Sloan RP. Relation between depression after coronary artery bypass surgery and 12-month outcome: a prospective study. *Lancet* 2001;358:1766–71.
20. Jiang W, Alexander J, Christopher E, Kuchibhatla M, Gaulden LH, Cuffe MS, Blazing MA, Davenport C, Califf RM, Krishnan RR, O'Connor CM. Relationship of depression to increased risk of mortality and rehospitalization in patients with congestive heart failure. *Arch Intern Med* 2001;161:1849–56.
21. Lesperance F, Frasure-Smith N, Juneau M, Theroux P. Depression and 1-year prognosis in unstable angina. *Arch Intern Med* 2000;160:1354–60.
22. Lane D, Ring C, Lip GYH, Carrol D. Depression, indirect clinical markers of cardiac disease severity, and mortality following myocardial infarction. *Heart* 2005;91:531–2.
23. Frasure-Smith N, Lesperance F, Juneau M, Talajic M, Bourassa MG. Gender, depression, and one-year prognosis after myocardial infarction. *Psychosom Med* 1999;61:26–37.
24. Strik JJ, Lousberg R, Cherix EC, Honig A. One year cumulative incidence of depression following myocardial infarction and impact on cardiac outcome. *J Psychosom Res* 2004;56:59–66.
25. Romanelli J, Fauerbach JA, Bush DE, Ziegelstein RC. The significance of depression in older patients after myocardial infarction. *J Am Geriatr Soc* 2002;50:817–22.
26. Lesperance F, Frasure-Smith N, Talajic M. Major depression before and after myocardial infarction: its nature and consequences. *Psychosom Med* 1996;58:99–110.
27. Frasure-Smith N, Lesperance F, Talajic M. Depression and 18-month prognosis after myocardial infarction. *Circulation* 1995;91:999–1005.

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28. Carney RM, Saunders RD, Freedland KE, Stein P, Rich MW, Jaffe AS. Association of depression with reduced heart rate variability in coronary artery disease. *Am J Cardiol* 1995;76:562–4.
29. Welin C, Lappas G, Wilhelmsen L. Independent importance of psychosocial factors for prognosis after myocardial infarction. *J Intern Med* 2000;247:629–39.
30. Parashar S, Rumsfeld JS, Spertus JA, Reid KJ, Wenger NK, Krumholz HM, Amin A, Weintraub WS, Lichtman J, Dawood N, Vaccarino V. Time course of depression and outcome of myocardial infarction. *Arch Intern Med* 2006;166:2035–43.
31. Lesperance F, Frasure-Smith N, Talajic M. Major depression before and after myocardial infarction: its nature and consequences. *Psychosom Med* 1996;58:99–110.
32. Schleifer SJ, Macari-Hinson MM, Coyle DA, Slater WR, Kahn M, Gorlin R, Zucker HD. The nature and course of depression following myocardial infarction. *Arch Intern Med* 1989;149:1785–9.
33. Ruo B, Rumsfeld JS, Hlatky MA, Liu H, Browner WS, Whooley MA. Depressive symptoms and health-related quality of life: the Heart and Soul Study. *JAMA* 2003;290:215–21.
34. Robins LN, Helzer JE, Croughan J, Ratcliff KS. National Institute of Mental Health Diagnostic Interview Schedule. Its history, characteristics, and validity. *Arch Gen Psychiatry* 1981;38:381–9.
35. 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.
36. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. *JAMA* 1999;282:1737–44.
37. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001;16:606–13.
38. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schnittger I. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 1989;2:358–67.
39. Ren X, Ristow B, Na B, Ali S, Schiller N, Whooley M. Prevalence and prognosis of isolated diastolic dysfunction in ambulatory patients with coronary heart disease: data from the Heart and Soul Study. *Am J Cardiol*, In Press.
40. Angeja B G, Grossman W. Evaluation and management of diastolic heart failure. *Circulation* 2003;107:659–63.
41. Redfield MM, Jacobsen SJ, Burnett JC Jr, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA* 2003;289:194–202.
42. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000.
43. Rudisch B, Nemeroff CB. Epidemiology of comorbid coronary artery disease and depression. *Biol Psychiatry* 2003;54:227–40.
44. Knol MJ, Heerdink ER, Egberts AC, Geerlings MI, Gorter KJ, Numans ME, Grobbee DE, Klungel OH, Burger H. Depressive symptoms in subjects with diagnosed and undiagnosed type 2 diabetes. *Psychosom Med* 2007;69:300–5.
45. Musselman DL, Evans DL, Nemeroff CB. The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment. *Arch Gen Psychiatry* 1998;55:580–92.
46. Lett H, Sherwood A, Watkins L, Blumenthal J. Depression and prognosis in cardiac patients. In: Steptoe A, editor. *Depression and Physical Illness*. New York: Cambridge University Press; 2007.
47. Whooley MA. Mind your heart. *Ann Intern Med* 2006;144:858–60.