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Depression and Cardiovascular Health Care Costs Among Women With Suspected Myocardial Ischemia

Prospective Results From the WISE (Women's Ischemia Syndrome Evaluation) Study

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Objectives This study evaluated 3 novel questions in a prospective clinical cohort of women undergoing evaluation for suspected myocardial ischemia: 1) What is the relationship between depression and cardiovascular costs? 2) Does the relationship vary by definition of depression? 3) Do depression-cost relationship patterns differ among women with versus without coronary artery disease (CAD)?

Background Comorbid depression has been linked to higher medical costs in previous studies of cardiovascular patients.

Methods A total of 868 women presenting with suspected myocardial ischemia completed an extensive baseline examination including cardiovascular risk factor assessment and coronary angiogram. Depression was defined by: 1) current use of antidepressants; 2) a reported history of depression treatment; and 3) Beck Depression Inventory scores. Direct (hospitalizations, office visits, procedures, and medications) and indirect (out-of-pocket, lost productivity, and travel) costs were collected through 5 years of follow-up to estimate cardiovascular costs.

Results Using the study criteria, 17% to 45% of the women studied met study depression criteria. Depressed women showed adjusted annual cardiovascular costs $1,550 to $3,300 higher than nondepressed groups ($r = 0.08$ to 0.12, $p < 0.05$). Depression-cost relationships also varied by CAD status, with stronger associations present among women without evidence of significant CAD.

Conclusions Depression was associated with 15% to 53% increases in 5-year cardiovascular costs, and cost differences were present using 3 definitions of depression. The results reinforce the importance of assessing depression in clinical populations and support the hypothesis that improved management of depression in women with suspected myocardial ischemia could reduce medical costs. (J Am Coll Cardiol 2009;53:176–83) © 2009 by the American College of Cardiology Foundation

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Depression is a common and debilitating condition in the U.S., with widespread effects on health, quality of life, and the economy (1–5). Health risks associated with depression include premature mortality, cardiovascular disease (CVD), immune system suppression, sleep impairment, and higher rates of drug abuse, among many others (6–10). Estimates of the economic impact of depression in the U.S. range from $20 to $45 billion annually (11–13), rivaling those of chronic diseases such as hypertension and osteoarthritis (14). Depression may also combine with chronic diseases to increase health care costs. Among medical cohorts, for example, patients with conditions such as congestive heart failure, diabetes, and coronary artery disease (CAD) who also suffered from depression were shown to have larger health expenses compared with those without depression (15–19). Even minor depression increases economic burden (20).

Women are diagnosed with depression at more than twice the rate of men (21), suggesting that investigations of depression and health care costs should include a strong focus on women. The aim of the current study is to describe the relationship between depression and health care costs in a 5-year prospective investigation of women with suspected myocardial ischemia. Specifically, this report addresses the following questions:

1. What is the relationship between depression and cardiovascular costs?
2. Does the relationship vary by definition of depression?
3. Are depression-cost relationships similar across women with and without evidence of CAD?

Methods

Participant recruitment and entrance criteria. Women were eligible for participation in the WISE (Women's Ischemia Syndrome Evaluation) study if they were older than age 18 years and were referred for a coronary angiogram to evaluate suspected myocardial ischemia (22). The WISE study was designed to improve the understanding and diagnosis of ischemic heart disease in women. Exclusion criteria included current pregnancy, cardiomyopathy, recent myocardial infarction or revascularization procedure (percutaneous coronary intervention, coronary artery bypass graft), history of congenital heart disease, and a language barrier preventing questionnaire completion. This report includes data on 868 women with complete information on antidepressant use, depression treatment history, and indicators used to calculate cardiovascular cost estimates. A smaller number (654 women) were available for analyses with the Beck Depression Inventory (BDI) due to a lagged implementation of the questionnaire measures into the WISE study protocol. All participants provided written informed consent, and institutional review board approval was obtained for all participating sites.

Abbreviations and Acronyms

BDI = Beck Depression Inventory

CAD = coronary artery disease

CVD = cardiovascular disease

Measurement of CAD and clinical outcome events. Quantitative analysis of coronary angiograms was performed offline at the WISE Angiographic Core Laboratory (Rhode Island Hospital, Providence, Rhode Island) by investigators blinded to all other subject data (23). Luminal diameter was measured at all stenoses and at nearby reference segments using an electronic cine projector-based "cross-hair" technique (Vanguard Instrument Corporation, Melville, New York). Using the angiogram results, each participant was assigned a continuous CAD severity score based on a modified Gensini index (23). Significant CAD was defined as a maximum stenosis value ≥50% (22).

Cardiovascular-related events and cost estimates. Information concerning CVD events, hospitalizations, and medication use was collected at 6 weeks after baseline and annually thereafter by means of a scripted interview (24). During the interview, information regarding the occurrence of outpatient procedures, hospitalizations, and clinic visits to physician extenders, generalists, and specialists was collected. This data collection tool was previously validated against verified events (24). The CVD events included stroke, congestive heart failure, and myocardial infarction. Source documentation was not obtained for office visits. In the event of death, a death certificate was obtained.

Cost accounting methods. Details of the cost methods were previously published (25). In brief, we used a hybrid cost model (including hospital-specific and published costs as inputs) for cases in which patient bills were not available. In this model, we used extensive prior published reports on procedural and hospital costs as well as cost estimates from national and regional average procedural and hospital charges (adjusted by state-specific cost-charge ratios) (24,25). Hospitalization (for chest pain, myocardial infarction, heart failure) and procedural (for coronary angiography, revascularization, stress cardiac imaging) costs were obtained from published reports (24–30). Cardiovascular drug costs were derived from the 2003 Red Book (31). We performed numerous sensitivity analyses using a range of costs for procedures and hospitalizations. We totaled 5-year and annual costs for cardiovascular hospitalizations, coronary revascularization and angiography, outpatient testing, and visits to generalists, specialists, nurse practitioners/physician's assistants, or community clinics. Summed 5-year costs were considered a measure of direct cardiovascular care costs and did not include costs for mental health care. Costs were discounted with the use of a 5% annual rate, corrected for inflation by the U.S. medical service sector estimate (city average) of the consumer price index (for urban wage earners and clerical workers) (32). Each patient's out-of-pocket expenses (i.e., indirect costs) were

also collected by self-report (26,27). Indirect cost data were estimated for hours lost from work for health care, estimated reduced productivity hours, transportation costs, and out-of-pocket costs for drugs, medical devices (e.g., glucose meter), and alternative therapies (e.g., vitamins). Patient self-reported income was used to estimate indirect costs for lost productivity.

Depression, socioeconomic status, and functional capacity. Depression was quantified in 3 ways: 1) use of antidepressants within the week prior to study entry; 2) a self-reported history of depression requiring treatment; and 3) completion of the BDI (33). The BDI is a validated 21-item questionnaire that has been linked to poor CVD outcomes (34). Scores ≥10 on the BDI questionnaire are often used to indicate the presence of at least mild depression symptoms (34).

Education history served as an estimate of socioeconomic status. Lower socioeconomic status was defined as a reported education history of less than high school graduation. We used the Duke Activity Status Index questionnaire to estimate functional capacity based on self-reported ability to perform various activities that correlate with exercise treadmill results (35).

Traditional CVD risk factors. Major CVD risk factors in the WISE protocol included smoking (defined as current vs. former or never smokers), history of dyslipidemia (yes/no), history of diabetes (yes/no), history of hypertension (yes/no), elevated waist-hip ratio (yes/no), and physical activity (dichotomously coded per protocol). An elevated waist-hip ratio was defined using a value ≥0.85 consistent with the definition used for women in INTERHEART (A Study of Risk Factors for First Myocardial Infarction in 52 Countries and Over 27,000 Subjects) study (36). Physical activity was evaluated with the PEPI (Postmenopausal Estrogen-Progestin Intervention) study questionnaire (37), a self-reported estimate of average physical activity level at home, work, and leisure on a 4-point scale, ranging from inactive to heavy activity. Women who marked none of the PEPI questionnaire items as either moderate or heavy were considered physically inactive.

Statistical analyses. Descriptive statistics were compared using chi-square (proportions) and independent *t* tests (means). For descriptive purposes, women were divided into groups based upon: 1) use/no use of antidepressants at baseline; 2) history/no history of reported treatment for depression; and 3) BDI scores ≥10/<10. These groups were not exclusive; rather, each woman was evaluated for each depression definition and could fit more than 1 criterion. We also assessed BDI-cost relationships keeping the BDI scores in raw (noncategorized) format to examine BDI effects without the loss of power known to result from artificially dichotomizing continuous variables. Cumulative cardiovascular costs served as the primary outcome measure, tracked to either death or the 5-year follow-up point (25). In the event of death, costs were accumulated to the date of incidence, which served as the participant's final cost figure. We also included medication costs as a secondary outcome, expecting that this category would be more heavily confounded with psychotropic use. Due to significant variable skewing, we logarithmically transformed the cost and CAD severity variables before the analyses.

Multivariate linear regression models were completed to test associations between depression and CVD costs. Final models were adjusted for demographic factors, CVD risk factors, anxiolytic and cardiovascular medications, Duke Activity Status Index scores, insurance, marital, and disability status, and CAD severity scores (Table 1). Regression results were converted into r coefficients as a standardized effect size metric using the formula $r = \sqrt{(t^2/[t^2 + df])}$, where df = degrees of freedom available for the analysis (866 for antidepressant and depression treatment history results, 652 for BDI analyses). An alpha level of 0.05 was used as the criterion for significance in all tests, and statistics were completed using SPSS version 15.0 (SPSS Inc., Chicago, Illinois).

Results

Among 936 women participating in the WISE study, 868 had valid depression treatment history, antidepressant use, and cardiovascular cost data (654 with BDI data). Table 1 describes the WISE sample, including a breakdown of demographic variables and CVD risk factors by depression status. Depression was common in the WISE study, with 17.3% reporting use of antidepressants at baseline, 24.4% endorsing a history of treatment for depression, and 45.3% of women scoring ≥10 on the BDI. Status on the BDI correlated modestly with the antidepressant ($r = 0.18$, $p < 0.001$) and depression treatment history ($r = 0.21$, $p < 0.001$), whereas antidepressant use and depression treatment history overlapped more strongly ($r = 0.57$, $p < 0.001$). A total of 89 deaths occurred in the group over a median 5.9 years of follow-up.

Although significance patterns varied somewhat by depression marker, depressed women tended to be older, had poorer CVD risk factor profiles, reported lower functional capacity on the Duke Activity Status Index, and indicated lower rates of marriage and full-time employment and higher rates of disability. Depressed women also had lower rates of prescription drug coverage and spent a larger percentage of their income on health care expenses. Based upon the CAD severity score, depressed women had statistically less severe CAD but were more prone to cardiovascular events over follow-up. Depression was strongly related to combined death and CVD event risk, with elevated BDI scores (relative risk [RR]: 1.7, 95% confidence interval [CI]: 1.2 to 2.4), antidepressant use (RR: 2.2, 95% CI: 1.5 to 3.0), and depression treatment history (RR: 2.0, 95% CI: 1.5 to 2.8), each reliable predictors after age and CAD severity score adjustment. Women missing BDI, depression treatment history, or antidepressant data did not differ from those with valid depression information on factors listed in Table 1.

Table 1 Demographic and CVD Risk Factors Among Participants With/Without Depression Marker (N = 868)

	Depression Treatment History (n = 868)		Beck Depression Inventory ≥10 (n = 654)		Antidepressant Use (n = 868)	
	Yes (n = 228)	No (n = 640)	Yes (n = 292)	No (n = 362)	Yes (n = 166)	No (n = 702)
Age, mean (SD), yrs	55.3 (10.9)	59.2 (11.7)*	56.1 (11.3)	59.3 (11.3)*	55.8 (11.3)	58.8 (11.6)*
High school education	79.6	80.4	77.4	85.4*	82.7	79.8
Caucasian	84.6	80.1	80.5	86.7*	81.9	81.2
Using antidepressants	55.3	5.3*	25.8	11.6*	100.0	0.0
Using anxiolytics	36.5	14.3*	25.3	16.3	37.9	15.4*
Depression treatment history	100.0	0.0	33.6	15.3*	76.7	13.3*
Beck Depression Inventory ≥10	64.1	39.3*	100.0	0.0	64.1	40.3*
Diabetic	23.8	25.2	24.9	20.8	29.7	24.0
Dyslipidemia	61.0	52.5*	56.8	49.0	67.9	52.1*
Hypertensive	62.3	57.9	59.7	54.3	66.3	57.8*
Physically inactive	37.2	30.6	37.1	22.8*	43.9	30.3*
Current smoker	31.1	16.7*	27.4	12.7*	28.3	18.2*
Waist-hip ratio ≥0.85	51.6	46.2	49.6	39.4*	51.8	47.2
Using antihypertensive medications	50.2	57.8	49.0	45.0	58.4	46.2*
Using lipid lowering medications	25.2	30.6	30.5	32.0	32.5	28.6
Duke Activity Status Index (mean)	16.0 (13.6)	21.5 (14.5)*	17.2 (13.8)	25.4 (14.8)*	15.7 (13.1)	21.0 (14.6)*
CAD severity score (mean)	12.5 (12.2)	15.4 (15.4)*	12.8 (11.9)	13.9 (13.6)	13.1 (12.1)	15.2 (15.2)*
Married	58.3	64.0	57.2	67.9*	58.0	63.8
Daily chest pain	42.3	36.8	44.8	33.4*	44.2	36.6*
Employed	21.9	26.5	20.9	28.7*	19.4	26.4*
Disabled	31.6	13.7*	27.0	11.0*	34.0	15.0*
Medical insurance	39.0	30.0*	40.0	50.0*	34.0	37.0
Indirect costs†	9.3	12.2*	8.3	12.9*	9.2	13.9*
CABG	5.9	9.1	6.3	5.1	8.1	8.5
PTCA	18.6	15.4	14.0	14.5	18.6	15.6
Angiogram	30.4	27.7	29.1	27.3	34.8	26.9*
Congestive heart failure	8.2	6.7	8.1	4.2*	8.1	6.7
Myocardial infarction	6.4	2.8*	6.0	1.7*	6.8	2.9*
Stroke	5.0	4.8	6.3	3.6	6.8	4.2
Death	14.1	9.5*	9.8	7.5	14.3	9.9

Values are percentages unless otherwise indicated. Tests of proportions completed using chi-square tests. *t* tests used to compare differences in means. *$p < 0.05$ between depression groups; †percent of household income spent on health care.

CABG = coronary artery bypass graft; CAD = coronary artery disease; CVD = cardiovascular disease; PTCA = percutaneous transluminal coronary angioplasty.

Depression and health care costs. Figure 1 shows that trends in depression-related cardiovascular cost differences were apparent as soon as year 1, with significant differences emerging by year 2 for the antidepressant ($r = 0.10$, $p = 0.002$) and depression treatment history ($r = 0.10$, $p = 0.003$) groups and by year 3 for those with higher BDI scores ($r = 0.08$, $p = 0.03$). Translated into dollar figures, annual differences in cardiovascular costs were $3,200 (95% CI: $678 to $6,060), $3,300 (95% CI: $574 to $5,210), and $1,550 (95% CI: $143 to $4,056), for the antidepressant, depression treatment history, and BDI groups, respectively, versus their nondepressed counterparts. Table 2 presents age and CAD severity score-adjusted cost differences. Costs for depressed versus nondepressed women were significantly higher for cardiovascular and medication cost categories. The BDI grouping produced smaller cost differences, which were partly a result of the loss of power from dichotomizing the raw questionnaire scores. Using the continuous BDI scores as a measure of depression symptom severity, each age and CAD severity-adjusted point increase on the questionnaire was associated with a $670 increase in cardiovascular costs ($r = 0.11$, $p = 0.005$). Lastly, we also compared women based on their number of depression markers (range: 0 to 3), however, cost differences between those with 1 versus 2 or 3 depression criteria were not significant.

Subsequent multivariate analyses included all factors listed in Table 1 (with the exception of the cardiovascular events and procedures variables). Baseline antidepressant use and a history of depression treatment predicted adjusted CVD costs ($r = 0.08$, $r = 0.09$, respectively, $p = 0.02$, $p = 0.006$), however, BDI scores did not ($r = 0.02$, $p = 0.50$). Among the measured covariates older age, higher CAD severity scores, and nonmarried relationship status predicted CVD costs at the $p < 0.05$ level.

Depression-cardiovascular costs relationships by CAD status. Of 868 women, 338 (38.9%) met criteria for significant CAD (stenosis ≥50%). Assessing the relationship between depression and cardiovascular costs according to

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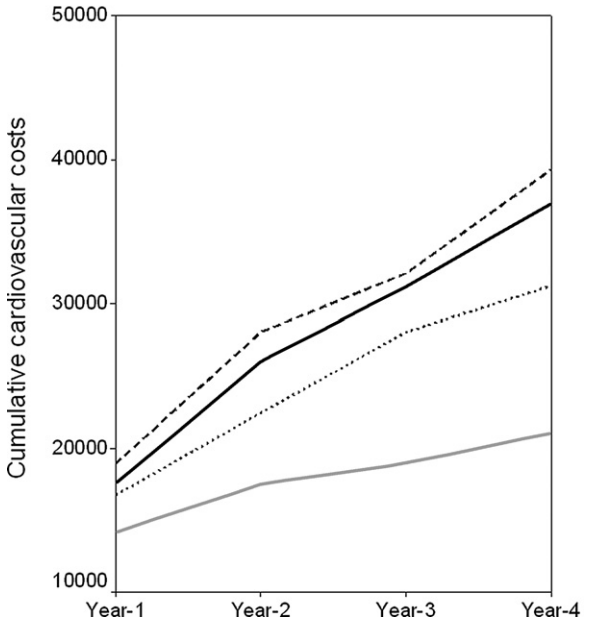

Figure 1 **Cardiovascular Costs Categorized by Depression Status**

All depression groups differed from nondepressed women in univariate analysis ($p < 0.05$). **Dashed line** = antidepressants; **solid line** = depression history; **dotted line** = Beck Depression Inventory >9; **gray line** = no depression.

CAD status revealed an uneven pattern of associations. As shown in Table 3, depressed status on any of the 3 depression markers was associated with significantly higher cardiovascular costs among women without significant CAD, but not among women with significant CAD.

Discussion

In a sample of women with suspected myocardial ischemia, participants meeting criteria for depression showed substantially higher cardiovascular costs. These higher costs were present whether measured in the form of antidepressant use, a history of depression treatment, or—to a slightly lesser degree—questionnaire-derived depression symptom severity. Cardiovascular cost increases were present despite evidence of less severe CAD among the depressed cohorts. The separate cost categories reinforce the stability of the findings, as cardiovascular cost outcomes are less likely to include costs for mental health treatment that may have artificially inflated the medication cost differences. Secondary analyses further indicated that depression-cost relationships were strongest among women without evidence of significant CAD. Collectively, these findings suggest that depression is an important factor in understanding overall and cardiovascular-related costs in symptomatic women. The results also support the efforts of recent interventional studies (38,39) showing that programs for identifying and managing depression can produce substantial savings.

Table 2 **Depression-Related Differences in Age and Coronary Artery Disease Severity Score Adjusted Health Care Costs by Cost Category**

Cost Category	Depression Treatment History (n = 868)		Beck Depression Inventory ≥10 (n = 654)		Antidepressant Use (n = 868)	
	Yes (n = 228)	No (n = 640)	Yes (n = 292)	No (n = 362)	Yes (n = 166)	No (n = 702)
Cardiovascular costs	$37,027.3 ($30,564.4–$43,490.2)	$24,945.7 ($21,296.0–$28,595.3)*	$30,147.7 ($27,736.5–$35,558.9)	$22,713.7 ($17,837.9–$27,589.4)*	$37,740.2 ($30,197.6–$45,282.9)	$25,788.9 ($22,316.9–$29,260.8)*
Medication costs	$14,076.7 ($13,305.2–$14,848.2)	$10,987.8 ($10,552.1–$11,423.5)*	$12,763.2 ($12,072.3–$13,454.1)	$10,535.6 ($9,913.0–$11,158.1)*	$16,008.2 ($15,135.4–$16,881.0)	$10,804.9 ($10,403.2–$11,206.7)*

Costs are given as mean (95% confidence intervals). *Depression groups differ on cost factor, $p < 0.05$.

Table 3 5-Year Cardiovascular Costs by Depression Status and Presence/Absence of Significant CAD

Cost Category	Depression Treatment History (n = 868)*		Beck Depression Inventory ≥10 (n = 654)*		Antidepressant Use (n = 868)*	
	Yes (n = 228)	No (n = 640)	Yes (n = 292)	No (n = 362)	Yes (n = 166)	No (n = 702)
No significant CAD†	$29,300 ($21,603–$36,996)	$16,179 ($11,421–$20,938)	$25,771 ($20,016–$31,525)	$16,528 ($11,454–$21,601)	$34,716 ($25,439–$44,000)	$16,357 ($11,901–$20,814)
Significant CAD	$51,227 ($39,585–$62,868)	$38,516 ($32,864–$44,168)	$41,862 ($32,616–$51,109)	$33,932 ($25,396–$42,468)	$43,567 ($30,977–$56,159)	$40,380 ($34,885–$45,875)

Costs are given as mean (95% confidence interval). *Differences between depressed and nondepressed participants were statistically reliable at $p < 0.05$ among those with no evidence of significant coronary artery disease (CAD). Statistical tests were completed using logarithmic transformations of the table data to adjust for variable skewing. †Significant CAD was defined as the presence of at least 1 coronary occlusion ≥50% from the participant's coronary angiogram results.

However, whether depression treatment can lower costs specifically in cardiac populations is untested at this time.

As an extension to previous research highlighting depression-related cost increases in cardiac samples, an important analytic aim in this study was to investigate explanatory mechanisms for increased costs among depressed women. Toward this objective, our regression models included a comprehensive set of demographic, CVD risk factors, CAD severity, and other covariates, and these factors offered some valuable insights into the cost relationships. Higher cardiovascular costs among women with elevated BDI scores, for example, were largely explained by differences in CVD risk factors such as smoking rates and obesity, as well as higher levels of functional disability in this population. In contrast, costs among women using antidepressants or with a history of depression treatment remained statistically higher after demographic and CVD risk factor adjustment. For all 3 depression definitions, the clearest pathway to increased health care costs was the higher rates of CVD events experienced by depressed women (Table 1) despite less severe angiographic CAD. It is also possible that the depression treatment history and antidepressant were more reliable predictors of costs and CVD outcomes because they represent more severe or enduring forms of depression. However, this difference may also be a result of power differences in the 2 models (roughly 30% fewer women had BDI scores and dichotomization of the BDI scores). To our knowledge, no study to date has been able to compare and contrast cost relationships with multiple measures of depression or has provided a statistical basis for understanding the pathways that contribute to higher costs.

The results presented in this report are consistent with those from a growing body of research demonstrating increased medical expenses in chronic disease populations for patients suffering from depression (17–19). For example, Sullivan et al. (18) reported relative cost increases of 26% to 29% among heart failure patients using antidepressants versus nondepressed patients, and Simon et al. (5) observed 50% to 75% higher costs in a diabetic sample among those who were also depressed based on questionnaire criteria. Many factors probably contribute to the added health care expenses among depressed patients. Depression is associated with poorer treatment adherence, poor health behavior patterns, social isolation, and biological factors such as elevations in proinflammatory markers such as C-reactive protein, and hypercortisolemia (40). Further, depression is an established predictor of cardiac event risk (6,40), a relationship that was also observed here. Finally, mental health conditions such as depression and anxiety are associated with higher rates of physical symptoms (41), and the Shaw et al. (25) earlier cost analyses from the WISE sample reinforced the need for understanding symptom-driven care patterns in the interpretation of cardiovascular costs. The WISE protocol was well designed for capturing the presence of a broad range of medical and psychiatric symptoms; however, symptom

characteristics that were generally not included in our measurement such as symptom duration or stability over time could be important to explicate in future research addressing depression-cost relationships.

Study limitations. Health care expenses were a secondary outcome in the WISE study. For this reason, a number of important limitations were present. All 3 definitions employed in this report to estimate rates of depression in the WISE study contain limitations to accuracy. The WISE protocol, for example did not include an assessment of the class, dose, or effectiveness of antidepressants (e.g., selective serotonin reuptake inhibitor vs. tricyclics) prescribed among those reporting use at baseline. Antidepressants can be prescribed for a variety of common medical conditions such as insomnia and chronic pain, and for parallel mental health conditions such as anxiety disorders.

Likewise, our assessment of depression treatment history did not gather information concerning type of treatment, when the treatment occurred, or the outcome of the treatment. The WISE women were largely of middle to lower socioeconomic status, with limited access to insurance to cover medication prescriptions or mental health care (25). As a result, the primary source of depression recognition and treatment likely resulted from primary care physicians, who may underestimate rates of mental health conditions (42). On the other hand, because this was a patient group identified by the presence of angina and suspected myocardial ischemia, depression symptom questionnaires such as the BDI—which are heavily influenced by the presence of physical symptoms—probably overestimated the rates of actual depression in the WISE sample. Given the imprecision in depression assessment, the reliability of the depression-cost relationships we observed is surprising, and the true relationship between these variables may be even stronger than reported.

Conclusions

Depression was associated with 15% to 53% increases in 5-year cardiovascular costs in a symptomatic sample of women, and these cost differences were only partially explained by a comprehensive collection of covariate predictors. Relationships between depression and costs were particularly strong among women without evidence of significant CAD, suggesting that depression may play a larger cost role in women without traditional markers of heart disease. The substantial published data indicates that depression is common in cardiac populations. The current results corroborate rates from prior research—with depression estimates ranging from 17% to 45% using different definitions—and support future research testing of the hypothesis that improved attention to diagnosing and effectively treating depression could result in reduced medical expenses among women with suspected CAD.

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REFERENCES

1. Evans DL, Charney DS, Lewis L, et al. Mood disorders in the medically ill: scientific review and recommendations. Biol Psychiatry 2005;58:175–89.
2. Pincus HA, Pettit AR. The societal costs of chronic major depression. J Clin Psychiatry 2001;62 Suppl 6:5–9.
3. Whooley MA. Depression and cardiovascular disease: healing the broken-hearted. JAMA 2006;295:2874–81.
4. Creed F, Morgan R, Fiddler M, Marshall S, Guthrie E, House A. Depression and anxiety impair health-related quality of life and are associated with increased costs in general medical inpatients. Psychosomatics 2002;43:302–9.
5. Simon GE, Katon WJ, Lin EH, et al. Diabetes complications and depression as predictors of health service costs. Gen Hosp Psychiatry 2005;27:344–51.
6. Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. Psychosom Med 2004;66:802–13.
7. Brunello N, Armitage R, Feinberg I, et al. Depression and sleep disorders: clinical relevance, economic burden and pharmacological treatment. Neuropsychobiology 2000;42:107–19.
8. Garcia-Cebrian A, Gandhi P, Demyttenaere K, Peveler R. The association of depression and painful physical symptoms—a review of the European literature. Eur Psychiatry 2006;21:379–88.
9. Kop WJ, Gottdiener JS. The role of immune system parameters in the relationship between depression and coronary artery disease. Psychosom Med 2005;67 Suppl 1:S37–41.
10. Volkow ND. The reality of comorbidity: depression and drug abuse. Biol Psychiatry 2004;56:714–7.
11. Berto P, D'Ilario D, Ruffo P, Di Virgilio R, Rizzo F. Depression: cost-of-illness studies in the international literature, a review. J Ment Health Policy Econ 2000;3:3–10.
12. Stewart WF, Ricci JA, Chee E, Hahn SR, Morganstein D. Cost of lost productive work time among US workers with depression. JAMA 2003;289:3135–44.
13. Burton WN, Chen CY, Conti DJ, Schultz AB, Edington DW. The association of antidepressant medication adherence with employee disability absences. Am J Manag Care 2007;13:105–12.
14. Garis RI, Farmer KC. Examining costs of chronic conditions in a Medicaid population. Manag Care 2002;11:43–50.
15. Le TK, Able SL, Lage MJ. Resource use among patients with diabetes, diabetic neuropathy, or diabetes with depression. Cost Eff Resour Alloc 2006;4:18.
16. Simon GE, Katon WJ, Lin EH, et al. Cost-effectiveness of systematic depression treatment among people with diabetes mellitus. Arch Gen Psychiatry 2007;64:65–72.
17. Luppa M, Heinrich S, Angermeyer MC, Konig HH, Riedel-Heller SG. Cost-of-illness studies of depression: a systematic review. J Affect Disord 2007;98:29–43.
18. Sullivan M, Simon G, Spertus J, Russo J. Depression-related costs in heart failure care. Arch Intern Med 2002;162:1860–6.
19. Katon WJ, Lin E, Russo J, Unutzer J. Increased medical costs of a population-based sample of depressed elderly patients. Arch Gen Psychiatry 2003;60:897–903.
20. Cuijpers P, Smit F, Oostenbrink J, de Graaf R, Ten Have M, Beekman A. Economic costs of minor depression: a population-based study. Acta Psychiatr Scand 2007;115:229–36.
21. Mallik S, Spertus JA, Reid KJ, et al. Depressive symptoms after acute myocardial infarction: evidence for highest rates in younger women. Arch Intern Med 2006;166:876–83.
22. Bairey Merz CN, Kelsey SF, Pepine CJ, et al. The Women's Ischemia Syndrome Evaluation (WISE) study: protocol design, methodology, and feasibility report. J Am Coll Cardiol 1999;33:1453–61.
23. Sharaf BL, Pepine CJ, Kerensky RA, et al. Detailed angiographic analysis of women with suspected ischemic chest pain (pilot phase data from the NHLBI-sponsored Women's Ischemia Syndrome Evalua-

tion [WISE] study angiographic core laboratory). Am J Cardiol 2001;87:937–41.
24. Mahoney EM, Jurkovitz CT, Chu H, et al. Cost and cost effectiveness of an early invasive vs conservative strategy for the treatment of unstable angina and non-ST-segment elevation myocardial infarction. JAMA 2002;288:1851–8.
25. Shaw LJ, Merz CN, Pepine CJ, et al., on behalf of Women's Ischemia Syndrome Evaluation (WISE) Investigators. The economic burden of angina in women with suspected ischemic heart disease: results from the National Institutes of Health—National Heart, Lung, and Blood Institute–sponsored Women's Ischemia Syndrome Evaluation. Circulation 2006;114:894–904.
26. Johnson BD, Shaw LJ, Buchthal SD, et al. Prognosis in women with myocardial ischemia in the absence of obstructive coronary disease: results from the National Institutes of Health—National Heart, Lung, and Blood Institute–sponsored Women's Ischemia Syndrome Evaluation (WISE). Circulation 2004;109:2993–9.
27. Shaw LJ, Lewis JF, Hlatky MA, et al. Women's Ischemia Syndrome Evaluation, current status and future research directions: report of the National Heart, Lung, and Blood Institute Workshop October 2–4, 2002: Gender-Related Risk Factors for Ischemic Heart Disease. Circulation 2004;109:e56–8.
28. Mark DB, Hlatky MA. Medical economics in the assessment of value in cardiovascular medicine, part I. Circulation 2002;106:516–20.
29. Mark DB, Hlatky MA. Medical economics in the assessment of value in cardiovascular medicine, part II. Circulation 2002;106:626–30.
30. Shaw LJ, Heller GV, Travin MI, et al. Cost analysis of diagnostic testing for coronary artery disease in women with stable chest pain. J Nucl Cardiol 1999;6:559–69.
31. Thomson Healthcare. PDR bookstore. Available at: http://www.pdrbookstore.com. Accessed July 4, 2004.
32. U.S. Department of Labor, Bureau of Labor Statistics. Consumer Price Index home page. Available at: http://www.bls.gov/cpi/home.htm#data. Accessed August 16, 2006.
33. Beck AT. Depression Inventory. Philadelphia: Center for Cognitive Therapy, 1978.
34. Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. Circulation 1999;99:2192–217.
35. Hlatky MA, Boineau RE, Higginbotham MB, et al. A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). Am J Cardiol 1989;64:651–4.
36. Yusuf S, Hawken S, Ounpuu S, et al., on behalf of INTERHEART Study Investigators. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. Lancet 2005;366:1640–9.
37. The Writing Group for the PEPI trial. Effects of estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions Trial (erratum in JAMA 1995;274:1676). JAMA 1995;273:199–208.
38. Wang PS, Patrick A, Avorn J, et al. The costs and benefits of enhanced depression care to employers. Arch Gen Psychiatry 2006;63:1345–53.
39. Von Korff M, Katon W, Bush T, et al. Treatment costs, cost offset, and cost-effectiveness of collaborative management of depression. Psychosom Med 1998;60:143–9.
40. Musselman DL, Evans DL, Nemeroff CB. The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment. Arch Gen Psychiatry 1998;55:580–92.
41. Unutzer J, Patrick DL, Simon G, et al. Depressive symptoms and the cost of health services in HMO patients aged 65 years and older. A 4-year prospective study. JAMA 1997;277:1618–23.
42. Ziegelstein RC, Kim SY, Kao D, et al. Can doctors and nurses recognize depression in patients hospitalized with an acute myocardial infarction in the absence of formal screening? Psychosom Med 2005;67:393–7.

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