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Relationships Between Cardiovascular Disease Risk Factors and Depressive Symptoms as Predictors of Cardiovascular Disease Events in Women

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Abstract

Background: Modifiable risk factors for cardiovascular disease (CVD) account for much of the variability in CVD outcomes and are also related to psychosocial variables. There is evidence that depression can undermine the treatment and advance the progression of CVD risk factors, suggesting that CVD risk factor relationships with CVD events may differ among those with depression.

Methods: This study tracked CVD events and mortality over a median of 5.9 years among a prospective cohort of 620 women (mean age 59.6 years [11.6]) completing a diagnostic protocol including coronary angiography and CVD risk factor assessment. Depressive symptoms were assessed using the Beck Depression Inventory (BDI). The study outcome was combined cardiovascular mortality and events.

Results: Over the follow-up interval, 16.1% of the sample experienced one or more of the cardiovascular outcomes. In separate Cox regression models adjusting for age, education history, ethnicity, and coronary angiogram scores, we observed statistically significant CVD risk factor × BDI score interactions for diabetes, smoking, and waist–hip ratio factors. Simple effect analyses indicated that diabetes and smoking status were more strongly associated with cardiovascular outcomes among participants with lower BDI scores, whereas waist–hip ratio values predicted outcomes only among those with higher BDI scores.

Conclusions: These results suggest that the relationship between modifiable CVD risk factors and CVD outcomes may vary with depression status in clinical samples of women. This evidence augments prior research by demonstrating that depression may influence CVD risk jointly with or independent of CVD risk factors. It also provides further support for the inclusion of depression assessment in cardiovascular clinic settings.

Introduction

Modifiable risk factors for cardiovascular disease (CVD; e.g., diabetes, dyslipidemia, hypertension, physical inactivity, obesity, and smoking) are the most important causes of premature morbidity and mortality, explaining upwards of 90% of the variation in cardiovascular events.[1–7] These risk factors appear disproportionately among those with psychosocial stressors such as depression, low socioeconomic status, and social isolation.[8–12] Depression is

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the most robust psychosocial predictor of CVD outcomes, with multiple cohort studies suggesting a relationship between depression and CVD incidence and progression independent of established CVD risk factors.[13–16] However, whereas most of the existing literature has demonstrated that associations between depression and CVD outcomes are independent of established risk factors, depression may also affect CVD risk in combination with these risk factors; for example, depression is associated with poorer adherence to prescribed treatments for conditions such as hyperlipidemia,[17] less successful smoking cessation efforts,[18] lower physical activity,[19] poorer blood pressure control,[20] and more rapid progression of diabetes.[21] Thus, studying the combination of CVD risk factors and depression may yield insights into CVD risk not observed from approaches that examine CVD risk factors and depression independently.

In this article, we assessed relationships between modifiable CVD risk factors, depression symptoms, and CVD events and mortality among women presenting with symptoms of myocardial ischemia and enrolled in the Women's Ischemia Syndrome Evaluation (WISE) study. Prior WISE publications[22,23] reported evidence of independent relationships between depression or CVD risk factors and clinical outcomes. In this paper, we examined the combination of depression and CVD risk factors as event predictors, with the hypothesis that prospective relationships between CVD risk factors and CVD deaths and events would vary according to depressive symptom status as measured by Beck Depression Inventory (BDI) scores.

Materials and Methods

Participant recruitment and entrance criteria

Women (≥18 years old) undergoing a clinically indicated coronary angiogram for suspected myocardial ischemia were recruited for the WISE study from four participating study sites (University of Alabama at Birmingham; University of Florida, Gainesville; University of Pittsburgh; and Allegheny General Hospital, Pittsburgh).[24] The WISE study was designed to improve the understanding and diagnosis of ischemic heart disease in women. Exclusion criteria included major comorbidity compromising follow-up, pregnancy, contraindication to provocative diagnostic testing, cardiomyopathy, New York Heart Association class IV heart failure, recent myocardial infarction or revascularization procedure, significant valvular or congenital heart disease, and language barrier. This report includes data on 620 women with complete data on study variables. All participants provided written informed consent, and all participating sites obtained Institutional Review Board approval.

The WISE Angiographic Core Laboratory (Rhode Island Hospital, Providence, RI) performed quantitative analysis of coronary angiograms, with investigators blinded to all other subject data.[25] Luminal diameter was measured at all stenoses and at nearby reference segments using an electronic cine projector-based "cross-hair" technique (Vanguard Instrument Corporation). Each participant received a continuous coronary artery disease (CAD) severity score based on angiogram results and a modified Gensini index.[26] This severity score was developed with points assigned according to the category of severity of the stenosis (0–19, 20–49, 50–69, 70–89, 90–98, 99–100), adjusting for partial and complete collaterals. Scores were then adjusted according to lesion location with more proximal lesions receiving a higher weighting factor.

Women were contacted at 6 weeks post-baseline and annually thereafter for a median of 5.9 years (25th percentile = 2.5 years; 75th percentile = 6.9 years) to track their subsequent experiences of CVD events and cardiovascular mortality. Follow-up consisted of a scripted telephone interview by an experienced research nurse. This data collection tool was validated previously against medical records.[26] Death certificates were obtained and reviewed by the study cardiologists in the event of participants' death. For study purposes, CVD events included myocardial infarction (MI), congestive heart failure, stroke, and deaths judged to have resulted probably or definitely from cardiovascular causes.

Modifiable risk factors

All participants completed a baseline evaluation that included a physical examination with blood pressure and physical measurements, clinical interview, and a fasting blood draw for the measurement of lipids and glucose. Major CVD risk factors in the WISE protocol included smoking status, blood pressure, dyslipidemia, diabetes, obesity, and physical inactivity. We assessed smoking based on self-reported current versus not current smoker status. Blood pressure was measured by a trained study nurse using a standard sphygmomanometer during the physical examination; however, because approximately two thirds of WISE participants reported use of one or more antihypertensive agents in the past week (beta-blockers, calcium antagonists, angiotensin-converting enzyme inhibitors, etc.), we defined hypertension status for this report dichotomously based upon participants' report of a history of hypertension requiring treatment (lifestyle or medication). Dyslipidemia status was also defined dichotomously based upon the participants' reported history of treatment for the purpose of the current study due to approximately one third of the sample missing either one or both lipoprotein blood test results. Fasting blood glucose readings served as our primary measure of diabetic status; we also collected self-reported diabetes treatment histories. We operationally defined obesity in terms of waist–hip ratio values, with waist circumference measured at the umbilicus. Both hip and waist values were rounded to the nearest inch. For the purpose of subgroup analyses, we dichotomously defined elevated waist-to-hip ratio values ≥0.85.[3] Physical inactivity was evaluated with the Postmenopausal Estrogen-Progestin Intervention questionnaire (PEPI-Q),[27] a validated self-report instrument measuring physical activity levels at home, work, and leisure on a 4-point scale, ranging from inactivity to heavy activity. Prior studies show that PEPI-Q scores correlate with aerobic fitness levels determined by treadmill testing.[27] We further collected information about CVD risk factor histories and treatments for use in exploratory analyses.

Participants' self-reported education history served as an estimate of socioeconomic status. Finally, each woman responded to a question assessing her marital status (options included never married, currently married or living together, separated, divorced, or widowed).

Depression

Women completed a validated measure (Beck Depression Inventory[28] [BDI]) of depressive symptom severity and reported their current use of antidepressants as part of the baseline

assessment. We used continuous BDI scores for all primary analyses; for comparisons of lower and higher BDI groups, we categorized BDI scores into those ranging from 0 to 9 versus ≥10, in line with BDI score interpretation guidelines.[29]

Statistical analyses

Comparisons of women with lower versus higher BDI scores on CVD risk factors, demographic factors, and CVD outcomes were completed using *t* tests and chi-square analyses. Separate cardiovascular events and mortality outcomes did not occur at a frequency to provide adequate statistical power; therefore, we combined the event and mortality categories as the primary outcome. Cox regression methods were employed to assess time to event relationships between CVD risk factors, BDI scores, and risk factor × BDI score interaction effects with cardiovascular outcomes. BDI scores were maintained in continuous form in the primary analyses. Participant age, race, education history, marital status, and log-transformed coronary artery disease severity score were each included as covariates. We examined each of the six measured CVD risk factors (i.e., fasting glucose/diabetes, dyslipidemia, hypertension, physical activity, smoking, and waist–hip ratio) in separate Cox regression models. In the case of a significant interaction, we completed simple effect analyses for CVD risk factors with significant interaction results, wherein we tested the CVD risk factor relationship with cardiovascular outcomes among participants with lower and higher BDI scores. All statistical analyses were completed using SPSS software, version 17.0 (SPSS Inc.), with statistical significance declared at $p < 0.05$.

Results

During the WISE recruitment period 1882/8557 women screened for the resulting 22% meeting eligibility criteria. From this group, 936 (50%) enrolled in WISE. Among the 936 women initially enrolled in WISE, 292 were missing BDI data due to delayed implementation of the psychosocial questionnaires into the baseline assessment. An additional 24 participants were missing CVD risk factor information, follow-up data, or status on one or more covariates, leaving 620 for event analyses. Within this subsample, a total of 100 women experienced one or more CVD events for analysis purposes; 30 cardiovascular deaths, 21 myocardial infarctions, 37 congestive heart failure episodes, and 29 strokes occurred over the follow-up period (events were not independent, accounting for why the number of CVD outcomes was greater than the number of women experiencing one or more of the outcomes). Depression scores were not associated with follow-up length.

Demographic and CVD risk factor information appears in Table 1. A total of 278 women (44.8%) had BDI scores ≥10. Women with BDI scores ≥10 were less likely to report being married and significantly more likely to have less education, a nonwhite ethnicity increased rates of several measured CVD risk factors, greater usage of antidepressants, and higher rates of CVD events (9.1% vs. 15.8% event rates for those with BDI scores <10 and ≥10, respectively, $p = 0.01$) over follow-up.

CVD risk factors, depression, and cardiovascular outcomes

Table 2 presents Cox regression results modeling predictors of combined cardiovascular death and events. Results are separated in Table 2 by CVD risk factor. In each model, covariate terms including age, education history, ethnicity, and angiogram-derived CAD severity scores were entered at the first step of the model, followed by the specific CVD risk factor and continuous BDI scores and finally the CVD risk factor × BDI score interaction term. In each model, CAD severity scores were a highly significant predictor ($p < 0.001$) of cardiovascular events. The main study hypothesis was that CVD risk factor relationships with cardiovascular outcomes would vary by depression status (i.e., significant interaction effects). In partial support of the study hypotheses, statistically significant interaction effects were observed in three of the six CVD risk factor models (fasting glucose or diabetes, smoking, and waist–hip ratio).

We subsequently performed separate simple effect analyses for the three risk factors with significant interactions, in which we computed Cox regression models assessing the covariate-adjusted CVD risk factor at both lower (BDI scores of 0–9) and higher (BDI scores ≥10) depressive symptom levels. For the fasting glucose or diabetes factor, simple effect

Table 1. Demographic, Cardiovascular Disease Risk Factor, and Clinical Event Characteristics of Women's Ischemia Syndrome Evaluation Participants by Beck Depression Inventory Category ($N = 620$)

	BDI score <10 (n=*342*)[a]	*BDI score ≥10* (n=*278*)	*p value for group difference*
Age, mean (sd)	59.3 (11.4)	56.2 (11.1)	0.001
CAD score, mean (sd)[b]	13.7 (13.5)	12.8 (11.9)	0.40
Race (% nonwhite)	13.2%	19.8%	0.03
Completed high school	85.4%	77.7%	0.01
Married	67.6%	57.9%	0.01
Hypertension	55.3%	59.7%	0.26
Current smokers	12.0%	27.0%	<0.001
Dyslipidemia	56.7%	65.8%	0.10
Diabetes	20.8%	24.6%	0.25
Physically inactive	22.7%	35.7%	0.001
Elevated waist–hip ratio[c]	38.3%	48.4%	0.02
Antidepressant use	11.4%	25.6%	<0.001

[a]BDI, Beck Depression Inventory.
[b]CAD, coronary artery disease.
[c]Waist–hip ratio ≥0.85.

Table 2. Time to Event Rates of Cardiovascular Mortality and Events Among Women Categorized by Cardiovascular Risk Factor and Beck Depression Inventory Scores ($N = 620$)

Risk factor	*Hazard ratio*	*95% CI*
Fasting glucose levels	1.01	1.01–1.02
BDI	1.1	1.03–1.2
Diabetes × BDI[a]	p = 0.01	
Diabetes at BDI < 10	5.3	2.7–10.2
Diabetes at BDI ≥ 10	1.4	0.7–2.6
Dyslipidemia	0.92	0.49–1.7
BDI	0.98	0.94–1.03
Dyslipidemia × BDI	$p = 0.06$	
Hypertension	1.4	0.64–3.1
BDI	1.0	0.95–1.1
Hypertension × BDI	$p = 0.80$	
Physical inactivity	0.46	0.22–0.96
BDI	1.01	0.98–1.04
Physical inactivity × BDI	0.85	
Smoking	3.3	1.4–7.4
BDI	1.03	1.0–1.07
Smoking × BDI[a]	$p = 0.04$	
Smoking at BDI < 10	1.9	0.90–4.5
Smoking at BDI ≥ 10	1.4	0.7–2.7
Waist–hip ratio	0.06	0.01–3.5
BDI	0.72	0.56–0.93
Waist–hip ratio × BDI[a]	$p = 0.01$	
Waist–hip ratio at BDI < 10	0.74	0.38–1.4
Waist–hip ratio at BDI ≥ 10	1.9	0.95–3.7

[a]Interaction $p < 0.05$.

Adjusted for age, education history, ethnicity, and CAD severity scores.

Events included myocardial infarction, stroke, and hospitalization for congestive heart failure.

Table 3. Percent of Women Experiencing a Cardiovascular Disease (CVD) Death and Event Risk Over Follow-Up, Categorized by CVD Risk Factor and Beck Depression Inventory Status ($N = 620$)

	BDI score status	
CVD risk factor status	*BDI < 10*	*BDI ≥ 10*
Diabetic (no)	8.9%	31.9%
Diabetic (yes)	20.5%	44.1%
Dyslipidemic (no)	10.3%	16.7%
Dyslipidemic (yes)	15.5%	33.6%
Hypertensive (no)	11.8%	15.3%
Hypertensive (yes)	15.2%	32.5%
Physically inactive (no)	11.1%	21.8%
Physically inactive (yes)	16.7%	43.3%
Current smoker (no)	12.3%	23.0%
Current smoker (yes)	24.4%	34.2%
Elevated waist–hip ratio (no)	12.0%	17.8%
Elevated waist–hip ratio (yes)	14.4%	36.3%

analyses revealed that fasting glucose scores were a highly significant predictor of cardiovascular outcomes among WISE participants with lower BDI scores (hazard ratio [HR] 1.009, 95% confidence interval [CI] 1.005–1.013), but not statistically associated with outcomes among those with higher BDI scores (HR 1.003, 95% CI 0.99–1.005). The same pattern was observed replacing fasting glucose values with dichotomous diabetic status (HR 5.3, 95% CI 2.7–10.2 and HR 1.4, 95% CI 0.7–2.6, respectively). Current smoking status was likewise more strongly associated with cardiovascular outcomes among lower BDI participants (HR 1.9, 95% CI 0.9–4.5, $p = 0.10$) than among higher BDI scorers (HR 1.4, 95% CI 0.7–2.7). Finally, waist–hip ratio status showed the opposite pattern, with waist–hip ratio values marginally predictive of outcomes among higher BDI scores (HR 1.9, 95% CI 0.95–3.7, $p = 0.07$) but not lower scorers (HR 0.74, 95% CI 0.38–1.4). The decrease in statistical significance patterns in the simple effects analyses was largely attributable to the reduction in power resulting from examining results within BDI subgroups.

The direction of the interaction effects for diabetic and smoking status—showing stronger relationships with outcomes among those with lower BDI scores—appears potentially counterintuitive. Therefore, we performed follow-up analyses in order to provide a clear interpretation of these patterns. The above hazard ratios indicated relative, not absolute, prediction of events across risk factor and BDI categories. As shown in Table 3, for diabetes, smoking, and waist–hip ratio factors, the absolute event risk was highest among those with a combination of the risk factor and higher BDI scores. From Table 3, we can see that the significant Cox regression interaction between diabetes and lower BDI was a result of the relatively greater difference in event risk between nondiabetics and diabetics among those with lower BDI scores compared with women with higher BDI scores. Specifically, for those with lower BDI scores, 9% of nondiabetics experienced an event over follow-up, compared with 21% of those with diabetes. This represented a more than twofold relative risk difference associated with diabetes among those with lower BDI scores. In contrast, among patients with higher BDI scores, 32% of nondiabetics experienced a CVD event, compared with 44% of those with diabetes. This represented a 38% increase in event risk across the nondiabetic versus diabetic groups. Thus, the significant interaction hazard ratio indicated that the relative difference in event risk among nondiabetics versus diabetics was larger among those with lower BDI scores than among those with higher BDI scores. It does not suggest that higher BDI scores were "protective" among diabetics. Again, as seen in Table 3, the absolute risk of CVD events was highest among those with both diabetes and higher BDI scores, indicating that the joint presence of higher BDI scores was associated with a larger absolute risk.

The same pattern held true for smoking status. Specifically, among women with lower BDI scores, 12% of nonsmokers experienced an event compared with 24% of smokers (a 200% relative risk difference). Among women with higher BDI scores, however, 23% of nonsmokers and 34% of smokers experienced a CVD event over follow-up (a 48% relative risk difference). Thus, while the joint presence of higher BDI scores increased the absolute event risk associated with smoking, the relative risk difference for smoking status as a predictor was stronger for women with lower BDI scores. Notably, the pattern observed for diabetes and smoking status was reversed for waist–hip ratio. Here, the relative risk difference associated with a lower versus higher waist–hip ratio was larger among those with higher BDI scores (an 18% versus 36% rate of events, respectively) than among those with lower

BDI scores (12% versus 14%). These patterns of relative versus absolute risk explain what might have first appeared as paradoxical findings.

Discussion

This investigation assessed the interrelationships among six established CVD risk factors, depressive symptoms, and CVD-related death and events. Many previous studies have identified relationships between depression and CVD development and prognosis independent of established CVD risk factors.[30–33] This analysis differs in that we assessed combined effects between CVD risk factors and depressive symptoms in the form of interactions. The results indicated that associations between several established CVD risk factors—including diabetes, smoking, and elevated waist–hip ratio—and CVD death and events varied according to depressive symptom severity. This pattern was robust to covariate adjustment that included demographic characteristics and quantitative angiogram-derived CAD severity.

These results carry at least two implications for future research. First, the findings suggest that depression may be associated with cardiovascular outcomes through different pathways. Depression, for example, may be related to CVD independent of CVD risk factors[12–14] or, as suggested here, in combination with CVD risk factors. Many studies have described depression's relationships with greater numbers and severity of CVD risk factors; however, few have examined the possibility of interactive associations among depression, CVD risk factors, and cardiovascular events. Second, among women presenting with suspected myocardial ischemia, elevated depressive symptoms appear to be common and closely linked to CVD risk factor status, which may have implications for managing CVD risk factors in this population. Because cooccurring depression appears to undermine CVD risk factor management based on prior research,[9,18,19] and the potential interactions between elevated depression and CVD risk factor implications observed here, depression screening performed in accordance with American Heart Association (AHA) recommendations could be a tool to help providers identify patients that warrant more attention to risk factor management as a means of improving health outcomes.[34]

The pattern of interaction effects observed proved difficult to interpret on the surface. Our results showed that CVD risk was highest among women with risk factors and higher BDI scores, a pattern that was consistent across each of the six measured risk factors. However, in the cases of the significant interaction tests for diabetes and smoking, the hazard ratios showed that risk factor status better predicted events among women with lower BDI scores rather than what may have seemed the more intuitive higher BDI scores. The presentation of absolute event risk numbers, however, explained this apparent discrepancy, showing that the above two interactions were based upon relative risk differences that were, in fact, entirely consistent with the stronger absolute risk associated with higher BDI scores.

In practice, these results indicate that CVD event risk associated with established risk factors is consistently higher among women who also report higher depressive symptoms in the form of BDI scores. The significant interaction patterns further suggest that the ability to predict event risk using diabetes, smoking, or waist–hip ratio information is enhanced by the concurrent knowledge of BDI scores. The correlational nature of these data, however, leaves us to speculate regarding the precise mechanisms underlying these interactions. For factors such as waist–hip ratio, for example, it is important to recognize that weight gain is a common depressive symptom, suggesting that higher waist–hip ratios and depression levels share similar etiologies and may exacerbate one another. This conceptual overlap is not true for smoking or diabetes; however, depression may confound smoking cessation efforts[12] and interfere with medication or exercise adherence among patients with diabetes.[13]

This study focused on depressive symptoms assessed by BDI scores. Among women with elevated BDI scores, more than 25% reported current use of antidepressants; this pattern could suggest that some antidepressant-treated WISE participants were experiencing only partial symptom relief from treatment or, alternatively, that the BDI ≥ 10 cutoff used here to identify elevated depressive symptom levels overestimated the prevalence of clinically significant depression. Even with state-of-the-art treatments, achieving lasting reductions in depressive symptoms often requires careful monitoring and follow-up care by a mental health provider.[35,36] Effective depression treatment is likewise dependent upon the accurate identification of depression, which evidence suggests is often under-recognized.[37,38] Any possible underestimate of true depressive rates in this sample, however, should have resulted in an attenuation of the group differences observed. That the pattern of statistical relationships we observed remained despite this possible treatment-selection factor and moderate sample sizes for event analyses may be seen as further support for the observed interrelationships between depressive symptoms and CVD risk factors as outcome predictors.

Study limitations

The WISE study was not specifically designed to study depression status or treatment effects. Thus, no information concerning the type, duration, or effectiveness of past or present depression treatment was collected. Extending these results to those with interview-diagnosed mood disorders and in protocols with more detailed information concerning patterns of antidepressant use and depression treatment (and effectiveness) over time will be important future steps. Further, women with higher BDI scores may have differed in a variety of unmeasured ways from those with lower scores and depression severity may vary over time.

Although our analyses demonstrated differential associations for CVD risk factors and CVD outcomes in relation to depressive symptoms, we cannot exclude that these associations may be due to variables such as diet or medication adherence, for which higher BDI scores may be a marker. Due to the moderate sample size, the current results should be viewed as preliminary support for interaction testing in a larger cohort. In some analyses, our results were based upon dichotomously defined CVD risk factors rather than continuously measured forms of these factors. Although logistical factors such as high levels of treatment (blood pressure) and missing data (lipids) favored this approach for assessing participants standing on these risk factors, the loss of data from artificial dichotomies is also an important limitation.

Finally, the enrollment criteria for the WISE study sample limit our ability to make generalizations to men or to similarly

aged women with different cardiac risk profiles. WISE participants were recruited in tertiary care centers for evaluation of suspected myocardial ischemia. The clinical characteristics of the WISE sample were intended to resemble as closely as possible women undergoing routine coronary assessments. However, these same characteristics set the WISE sample apart from asymptomatic women or women with other medical complications, limiting the ability to generalize our study findings.

Conclusions

In a sample of women with suspected myocardial ischemia, the impact of several modifiable CVD risk factors (diabetes, smoking, and waist–hip ratio as a measure of obesity) on clinical outcomes including CVD death and events (congestive heart failure, stroke, MI) varied depending on women's concurrent levels of depressive symptom severity as measured by the BDI. Although depression is an established independent predictor of CVD events, these results offer an alternative perspective regarding the mechanisms by which depression may affect the development or course of CVD, implying that a second pathway may be via influencing the event risk associated with risk factors for CVD. These results reinforce AHA guidelines for the assessment of depression in coronary heart disease patients[39] and suggest that further research should be aimed at understanding the modulating mechanisms involving depression and traditional CVD risk factors.

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Disclosure Statement

The listed authors have no financial disclosures or conflicts of interest with the findings in this paper.

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