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Depression Symptom Patterns as Predictors of Metabolic Syndrome and Cardiac Events in Symptomatic Women with Suspected Myocardial Ischemia: The Women's Ischemia Syndrome Evaluation (WISE and WISE-CVD) Projects

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Abstract

Background: Ischemic heart disease (IHD) risk in women includes biomedical, behavioral, and psychosocial contributors. The purpose of this study was to build upon previous research suggesting that in women, somatic symptoms (SS) of depression may be important to the development of IHD risk factors and major adverse cardiovascular events (MACE). Based on previous findings, we hypothesized that: (1) SS would be associated with robust biomedical predictors of heart disease and functional capacity, while cognitive symptoms (CS) of depression would not, and (2) SS would independently predict adverse health outcomes while CS would not.

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Conflicts of interest

There are no conflicts of interest.

Methods: We examined the relationships between symptoms of depression (SS/CS), metabolic syndrome (MetS), inflammatory markers (IM), coronary artery disease (CAD) severity, and functional capacity in two independent cohorts of women with suspected IHD. In the Women's Ischemia Syndrome Evaluation (WISE), we also examined these variables as predictors of all-cause mortality (ACM) + MACE over a median 9.3-year follow-up. The WISE sample included 641 women with suspected ischemia with or without obstructive CAD. The WISE-Coronary Vascular Dysfunction (WISE-CVD) sample consisted of 359 women with suspected ischemia and no obstructive CAD. All study measures were collected uniformly at baseline. Depressive symptoms were measured via the Beck Depression Inventory. MetS was assessed according to Adult Treatment Panel III (ATP-III) criteria.

Results: In both studies, SS was associated with MetS (Cohen's $d = 0.18, 0.26$, $P < 0.05$, respectively), while CS was not. Within WISE, using Cox Proportional Hazard Regression, SS (Hazard ratio [HR] = 1.08, 95% confidence interval [CI] = 1.01–1.15; HR = 1.07, 95% CI = 1.00–1.13) and MetS (HR = 1.89, 95% CI = 1.16–3.08; HR = 1.74, 95% CI=1.07–2.84) were independent predictors of ACM + MACE after controlling for demographics, IM, and CAD severity, while CS was not.

Conclusions: In two independent samples of women undergoing coronary angiography due to suspected ischemia, SS but not CS of depression were associated with MetS, and both SS and MetS independently predicted ACM and MACE. These results add to previous studies suggesting that SS of depression may warrant specific attention in women with elevated cardiovascular disease (CVD) risk. Future research evaluating the biobehavioral basis of the relationship between depression, MetS, and CVD is needed.

Keywords

Cardiovascular disease; cognitive and somatic symptoms; depression; ischemia; women

Introduction

Among women with known or suspected cardiovascular disease (CVD), clinical depression is both a common comorbidity and a predictor of major adverse cardiovascular events (MACE), CVD risk factors, and functional impairment.[1–3] In addition, in both individuals with coronary disease and in healthy populations, depression is predictive of incident metabolic syndrome (MetS), a cluster of abnormalities that include obesity, hyperglycemia, dyslipidemia, and hypertension.[4–6]

The presence of depression predicts the development of MetS in women with known and suspected coronary disease.[1] Women with elevated depressive symptoms or a previous diagnosis of depression in the National Heart, Lung, and Blood Institute (NHLBI) Women's Ischemia Syndrome Evaluation (WISE) study[7] were observed to be at increased risk of MetS.[1] Depression is associated with multiple biological and behavioral changes that promote the development and progression of CVD. Two physiological mechanisms that may account for associations between depression, MetS, and CVD are coronary artery disease (CAD) severity[8] and increased inflammation (e.g., increased levels of inflammatory cytokines).[9,10] Importantly, studies suggest that the impact of reproductive

hormone fluctuation on inflammatory biomarkers renders women particularly vulnerable to the development of both depressive symptoms and CVD.[11] Therefore, incorporating measures of inflammation may help further improve the identification of women most at-risk for heart disease and adverse cardiac events.

Depressive symptoms can be divided into “cognitive symptoms (CS)” such as sadness, guilt, and suicidal ideation, and “somatic symptoms (SS)” such as fatigue, anhedonia, and sleep and weight changes. SS, theoretically, may more closely reflect shared disease processes underlying depression and CVD. Indeed, SS of depression, compared to CS, have shown stronger associations with CVD risk factors and MACE outcomes in several previous studies.[12] However, most of these studies fail to adjust for potentially explanatory biological variables, including CAD severity and inflammation.

This study builds upon several previous WISE reports[1,13,14] examining different types of depressive symptoms as cardiac outcome predictors. In the current paper, we extended previous findings in two ways: (1) We examined relationships between depressive symptom subtypes, MetS, CAD severity, inflammatory markers (IM), and functional capacity across two independent cohorts of women presenting with symptoms consistent with the presence of myocardial ischemia (WISE[7] and WISE-Coronary Vascular Dysfunction [WISE-CVD] [15] studies, respectively), and (2) We evaluated these baseline variables as predictors of all-cause mortality (ACM) and MACE outcomes among WISE women over an extended median 9.3-year follow-up. Based on previous research, we hypothesized that somatic depressive symptoms would be associated with MetS, CAD severity, IM, and functional capacity while cognitive depressive symptoms would not. We further hypothesized that SS of depression would independently predict adverse outcomes (ACM + MACE) in the WISE study but that cognitive depressive symptoms would not.

Methods

Study samples

This study utilized the data from two independent samples of women participating in the WISE[7] (sample one) and WISE-CVD[15] (sample two) prospective cohort studies. The designs and protocols of both studies have been outlined in previous publications.[7,15] These multi-site NHLBI-sponsored studies aimed to improve detection and diagnosis of ischemic heart disease in women, a population in which signs and symptoms of CVD have been historically both misunderstood and poorly identified.[16–18] All WISE study research sites received institutional review board (IRB) approval for study procedures, and participants provided written informed consent. All demographic, psychosocial, physiological, and functional variables used in the present study were assessed once during the baseline evaluation prior to coronary angiography. Participants who completed a battery of psychosocial assessments at baseline the components of which have been described elsewhere in detail[19] were included in the analyses for the current paper.

Sample one (WISE), recruited between 1996 and 2001, consisted of 641 women undergoing a clinically indicated coronary angiogram for chest pain symptoms and/or suspected myocardial ischemia. This sample was comprised of women with (40%) and without (60%)

obstructive CAD. Sample two (WISE-CVD) recruited between 2008 and 2015 and consisted of 359 women without obstructive CAD. Both samples shared identical exclusion criteria, including age <18, the presence of existing medical conditions representing contraindication to the safety and validity of physiological assessments (e.g., pregnancy, heart failure, valvular disease, previous myocardial infarction, recent cardiac surgery), and the indication of a language barrier.[7,15]

Measurement of depression and functional capacity

The WISE studies assessed depressive symptoms at baseline with the Beck Depression Inventory (BDI).[20] The BDI is a 21-item self-report inventory that measures both CS (e.g., sadness, suicidality, guilt; BDI-CS) and SS (e.g., anhedonia, fatigue, weight change; BDI-SS) of depression, providing subscale scores for each symptom cluster in addition to a total depressive symptom severity score. BDI-CS subscale scores range from 0 to 42, BDI-SS subscale scores range from 0 to 21, and BDI total scores range from 0 to 63. The BDI demonstrates high internal consistency in both psychiatric (alpha coefficient = 0.86) and non-psychiatric samples (alpha coefficient = 0.81).[21]

Functional capacity was assessed at baseline via the Duke Activity Status Index (DASI). The DASI measures the self-reported ability to perform 12 different activities requiring varying levels of cardiovascular effort (e.g., grooming and self-care activities, performing yard work, and participating in strenuous sports).[22] Possible scores range from 12 to 48, with higher scores reflecting more severe levels of functional impairment. DASI scores have been shown to correlate with both peak oxygen uptake levels during cardiovascular exercise stress testing[22] and obstructive CAD diagnosis,[23] providing evidence for the measure's concurrent and predictive validity.

Assessment of physiological variables

We utilized the American Heart Association's Adult Treatment Panel III (ATP III) criteria to identify individuals who met diagnostic criteria for MetS, a robust independent predictor of cardiac disease in women and men.[24] A diagnosis of MetS requires individuals to have at least three of the following risk factors: (1) waist circumference >88 cm, (2) triglycerides ≥150 mg/dL, (3) high-density lipoprotein (HDL) cholesterol <50 mg/dL, (4) blood pressure ≥130/≥85 mm Hg, and (5) fasting glucose ≥110 mg/dL.[25] Risk factors were measured at baseline via a physical examination and fasting blood draw.

Each participant received a continuous CAD severity score based on quantitive angiogram results performed after the baseline visit. 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 further adjusted according to lesion location, with more proximal lesions receiving a higher weighting factor.[26] CAD severity scores were logarithmically transformed to normalize the distribution. Inflammation was assessed via blood tests for two inflammatory biomarkers – high-sensitivity C-reactive protein (CRP) and interleukin-6 (IL-6) – in the baseline evaluation. Both biomarkers are robustly associated with CVD risk.[27] Of the 641 women in the WISE sample, 548 had CRP measurements and 513 had IL-6 measurements.

Determination of major adverse cardiovascular events

MACE outcomes are currently available only for WISE (not WISE-CVD). Researchers conducted yearly follow-up telephone calls with WISE study participants to assess for the incidence of MACE. Utilizing a standardized interview script, trained medical professionals collected information regarding recent hospitalizations and corresponding illnesses. Incidence of MACE included both fatal and nonfatal instances of stroke, congestive heart failure, and myocardial infarction. Consistent with previous WISE studies, our main WISE outcome of interest was computed into a single variable by combining all incidents of MACE with ACM over a median 9.3-year follow-up period.

Statistical analyses

All analyses were conducted using SPSS software version 28 and conducted as two-tailed tests for statistical significance (P values for significance wer set at 0.05). First, we examined descriptive and frequency distributions of baseline demographic variables in both WISE samples, including age, race, education level, and marital status, and utilized independent samples t-tests to assess for between-samples differences. Scores for all continuous and ordinal variables (age and education level) were normally distributed. Within both samples, we computed BDI-SS and BDI-CS scores for each participant. We expressed relationships between MetS, depression scores (BDI-CS and BDI-SS scores), CAD severity, IM (CRP and IL-6), and functional capacity in the form of effect sizes (Cohen's d values, where values of 0.20–0.49, 0.50–0.79, and ≥0.80 are conventionally considered small, medium, and large effect sizes, respectively).[28]

For our primary analyses, we performed Cox-proportional hazard regression models to examine the individual and combined predictive power of MetS and BDI subscales for ACM + MACE within WISE. In this model (model 1), block one included demographic factors including age, race, education, and marital status. In subsequent blocks, we utilized hierachical regression to include biomedical covariates (MetS, IM, and CAD severity scores), DASI scores, and finally, BDI-CS and BDI-SS scores. Given the high correlation between CRP and IL-6 ($r = 0.45$, $P < 0.001$), when adjusting for IM, we ran separate regression models (models 2a and 2b) looking at the separate impact of CRP and IL-6, respectively.

Results

Sample characteristics

Table 1 describes sociodemographic factors (age, race, education level, and marital status) and baseline measures (CVD risk factors, IM, functional capacity, current medications, and depression scores) for the WISE/WISE-CVD samples. In comparison to the WISE sample, the WISE-CVD sample contained significantly fewer white women (73.3% vs. 83.6%), and had higher levels of education. The prevalence of MetS was more than two-fold higher among WISE (56.8%) versus WISE-CVD participants (24.6%). Condordant with the higher rates of MetS, women in the WISE sample also endorsed significantly higher total depression scores on the BDI versus women in WISE-CVD (10.56 vs. 9.23, $P = 0.01$) and

relatively higher BDI-SS scores (5.47 vs. 4.68, $P < 0.001$). In contrast, BDI-CS scores did not differ between the WISE samples (5.09 vs. 4.60, $P = 0.20$).

Depression, metabolic syndrome, inflammation, and functional capacity

In the WISE sample, BDI-SS scores were associated with MetS (Cohen's $d = 0.18$, $P = 0.021$) while BDI-CS scores were not (Cohen's $d = 0.05$, $P = 0.40$). Similarly, in the smaller WISE-CVD sample, BDI-SS scores were associated with MetS (Cohen's $d = 0.26$, $P = 0.015$) while BDI-CS scores were not (Cohen's $d = 0.15$, $P = 0.13$). While DASI scores were correlated with MetS (Cohen's $d = 0.23$, $P = 0.005$), BDI-CS scores (Cohen's $d = 0.32$, $P < 0.001$), and BDI-SS scores (Cohen's $d = 0.70$, $P < 0.001$) in the WISE sample, they correlated only with MetS (Cohen's $d = 0.33$, $P = 0.003$) and BDI-SS scores (Cohen's $d = 0.47$, $P < 0.001$) in the WISE-CVD sample.

In the WISE sample, CRP was related to both BDI-CS scores (Cohen's $d = 0.28$, $P = 0.002$) and BDI-SS scores (Cohen's $d = 0.31$, $P < 0.001$). IL-6 was also associated with both depression symptom subtypes (Cohen's $d = 0.30, 0.44$, $P < 0.001$, respectively). Similarly, although CRP was related to MetS (Cohen's $d = 0.17$) at $P = 0.049$, IL-6 demonstrated larger associations with MetS (Cohen's $d = 0.31$, $P < 0.001$). DASI scores were not correlated with CAD severity (Cohen's $d = 0.08$, $P = 0.343$) or IM variables (CRP: Cohen's $d = 0.08$, $P = 0.370$; IL-6: Cohen's $d = 0.16$, $P = 0.066$). However, CAD severity scores were correlated with MetS (Cohen's $d = 0.47$, $P < 0.001$) and IM (Cohen's $d = 0.18$ for both CRP and IL-6, $P = 0.038$ and 0.040, respectively) but not BDI-CS (Cohen's $d = -0.08$, $P = 0.311$) or BDI-SS (Cohen's $d = 0.06$, $P = 0.440$).

Predictors of adverse events in WISE

Over a median 9.3 years of follow-up, 79 WISE study participants experienced MACE and 55 participants experienced ACM. In total, 121 participants met criteria for the composite outcome variable (ACM + MACE).

After adjusting for demographic factors [Table 2], women meeting MetS criteria experienced a greater than two-fold increase in time-to-event risk (Hazard ratio [HR] = 2.11, 95% confidence interval [CI] = 1.39–3.20) compared with women who did not meet criteria for MetS. BDI-SS was a significant independent predictor of time to adverse event risk (HR = 1.08, 95% CI = 1.03–1.14), while BDI-CS was not (HR = 1.02, 95% CI = 0.99–1.05). Further, CRP (HR = 1.01, 95% CI = 1.01–1.02), IL-6 (HR = 1.04, 95% CI = 1.01–1.08), CAD severity (HR = 1.04, 95% CI = 1.03–1.05), and DASI scores (HR = 1.16, 95% CI = 1.08–1.24) were also significant independent predictors.

After adjusting for demographic factors and CAD severity, MetS (HR = 1.82, 95% CI = 1.19–2.79) and BDI-SS (HR = 1.08, 95% CI = 1.02–1.14) remained significantly associated with time to outcome events. Finally, in models 2a and 2b [Table 3], after adjusting for demographic factors, MetS, IM, and CAD severity – despite the loss of 100–150 participants from missing data in the CRP and IL-6 variables – BDI-SS remained an independent predictor when controlling for both CRP (HR = 1.08, 95% CI = 1.01–1.15) and IL-6 (HR = 1.07, 95% CI = 1.00–1.13). MetS also retained independent predictive power when controlling for both CRP (HR = 1.89, 95% CI = 1.16–3.08) and IL-6 (HR = 1.74, 95% CI =

1.07–2.84). When DASI scores were added to models 2a and 2b, neither BDI-SS nor MetS retained independent predictive power. Notably, BDI-CS was not significantly associated with time to outcome events in any of the model iterations.

Discussion

This paper described relationships between depressive symptom subtypes (CS and SS), MetS, CAD severity, IM, and functional capacity in two independent cohorts of women experiencing symptoms consistent with myocardial ischemia. Correlational results indicated that in both the WISE and WISE-CVD samples, SS of depression were significantly associated with MetS, IM, and functional capacity, while the associations between CS and relevant biological and functional markers were either relatively weaker or nonsignificant. Importantly, when using depression scores and MetS to predict ACM + MACE events over a median 9.3 years of follow-up available in the WISE cohort, we observed that somatic depression scores – but not cognitive depression scores – were a significant predictor of time to adverse outcomes, independent of demographic variables, MetS, CAD severity, and inflammation. The inclusion of established CVD risk factors and relevant biomarkers, coupled with the extended follow-up period, represent novel contributions to the literature examining psychosocial predictors of cardiac risk in women. Instead of by CVD risk or other biomedical severity markers, the relationship between somatic depressive symptoms and adverse events in WISE was best explained in our analyses by functional capacity (in the form of DASI scores). Combined with findings from previous WISE reports[1,13,14] and from non-WISE cohort studies[29] also identifying associations between somatic depression symptoms and CVD risk, the current paper adds further support for routinely assessing both general depression and specific SS of depression in at-risk populations of women.

Three previous WISE reports described relationships between overall depressive symptoms, depressive symptom clusters – SS vs. CS – and markers of CVD risk. In the first finding reported in 2008,[1] we described one of the first prospective relationships between overall symptoms of depression, MetS, and CVD events (CVD mortality and nonfatal stroke, myocardial infarction, and heart failure events over a median 5.8 years) in women. A second study in 2009 found that SS of depression, but not CS, were associated with the increased risk of ACM + MACE.[14] Third, in 2021, a follow-up WISE report[13] described a statistical relationship between depression symptoms and the presence of obstructive CAD (defined by coronary angiography results). This relationship was observed with SS but not with either total depression symptoms or CS. Multiple – although not all – other studies have observed similar patterns when separately examining somatic depression symptoms.[29] For example, previous prospective studies have reported somatic symptom-linked increases in outcomes including CVD death, CVD hospital admissions, increases in proinflammatory cytokines, and progression in atherosclerotic disease, among others.[30–36] In addition, studies such as the Coronary Artery Risk Development in Young Adults (CARDIA) study of young adult men and women report predictive associations between depression and MetS using measures such as the Center for Epidemiological Studies Depression Scale (CESD), which include fewer items assessing somatic components of depression.[37] The current findings, therefore, are extending a small but growing literature assessing somatic symptom links to cardiovascular endpoints.

Collectively, this literature indicates that somatic depression symptoms are often more strongly linked to markers of CVD risk than either total depressive symptoms or cognitive depression symptoms. Notably, however, many studies measuring depression do not assess SS despite these findings. For example, many CVD studies and studies enrolling older-aged or medically ill participants intentionally assess depression using questionnaires that exclude SS.[38,39] The rationale in these studies is usually that SS of depression may be confounded with medical conditions and spuriously inflate the prevalence of clinical depression. Omitting SS, however, could – consistent with findings from the current study – also reduce information about symptoms potentially important to accurate risk assessment that are otherwise not effectively captured through conventional medical diagnosis such as CVD risk factors or MetS.

A common interpretation of the SS-CVD relationship is that SS – at least in CVD or other medical populations – may be indicative of physical disease rather than a psychiatric condition like depression. From this perspective, SS of depression, medical conditions such as MetS, and CVD-related outcomes may represent partly overlapping markers of disease severity or reflect shared pathophysiological mechanisms of CVD such as CAD severity, inflammation, mitochondrial dysfunction, and insulin resistance.[5–6] For example, although the relationship between inflammation, insulin resistance, and MetS is well-known, fewer are aware of the research demonstrating both inflammation and insulin resistance as potential causes of depression symptoms.[40]

Notably, however, the above shared pathophysiology model is not consistent with our findings that somatic depression symptoms predicted ACM + MACE in WISE independent of known biological risk factors (CAD severity, IM, and MetS) for adverse cardiac events. Instead, SS, inflammation, and MetS – while robustly interrelated in both the WISE and WISE-CVD cohorts – appeared to contribute to CVD risk in WISE through a combination of shared and independent mechanisms [Figure 1]. A potential means to explore the question of the role of early disease symptoms or subclinical pathophysiologic processes more comprehensively in future research is to include measures of mitochondrial function, insulin resistance (e.g., glucose tolerance test, homeostasis model assessment of insulin resistance [HOMA-IR], fasting insulin, etc.) and other additional pathophysiological mechanisms.[9] The latter tests may offer greater insight into potentially shared biological and behavioral pathways between somatic depression symptoms, MetS, and adverse cardiac outcomes.

Study limitations and directions for future research

The WISE and WISE-CVD studies overlapped closely in their protocol and design to enable comparable analyses in the current paper between depression and MetS. At present, data concerning mortality and MACE events among WISE-CVD remain in collection, preventing a full replication of the survival analyses at this time. Additionally, current medications, IM, and CAD severity were not assessed in the WISE-CVD study.

Despite the methodological similarities between WISE and WISE-CVD, the WISE-CVD sample reflected a more demographically diverse group of participants. However, neither sample included enough non-Caucasian participants to allow for separate examination of relationships between symptoms of depression, MetS, and ACM + MACE within female

minority populations. Therefore, additional research regarding psychosocial and CVD risk factors within female minority populations is warranted.[41]

Finally, use of the BDI allowed us to assess the presence of CS and SS of depression central to the findings of the current paper. Given that the BDI is a self-report measure, however, designed only to capture the presence and severity of symptoms – not diagnose psychiatric conditions – we were unable to generalize these findings to patients experiencing major depressive disorder or other mood disorders. Further, the WISE studies did not collect information regarding current depression diagnoses, nor did they require participants to indicate the specific types or doses of antidepressant medications they were taking. Given that the impact of antidepressant medication on cardiac symptoms has been shown to depend greatly upon medication type (e.g., selective serotonin reuptake inhibitors, serotonin and noradrenaline reuptake inhibitors, tricyclics, monoamine oxidase inhibitors), future research investigating adverse outcomes in cardiac patient samples would benefit from including this important information as part of data collection and analysis.

Summary

In the two prospective cohorts of women with suspected myocardial ischemia, SS but not CS of depression were associated with MetS and adverse outcomes (ACM + MACE). Among WISE participants, SS of depression predicted ACM + MACE independently of robust biomedical predictors of CVD and MACE (MetS, CAD severity, and inflammation), while CS did not. Parallel to this finding, SS of depression were consistently associated with MetS status and were more strongly related to MetS than either overall depression symptoms or CS of depression. These results add to previous studies suggesting that SS may warrant specific attention in populations with elevated CVD risk and encourage additional research evaluating the biobehavioral basis of the relationship between depression, MetS, and CVD.

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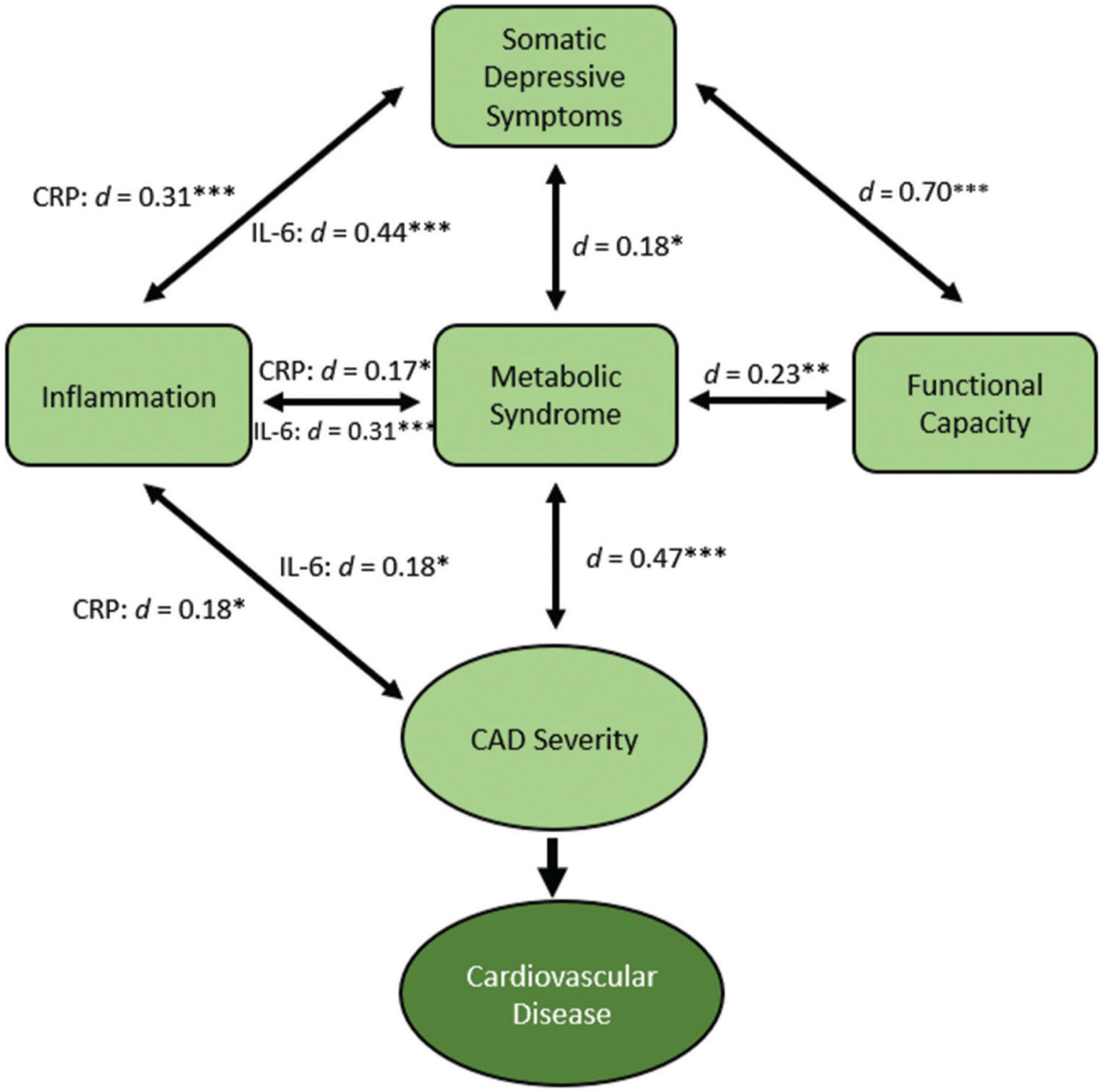

Figure 1:

Observed Effect Sizes of Relationships Between Depression and Cardiometabolic Variables Within the WISE Sample. $P < 0.05$. ** $P < 0.01$. *** $P < 0.001$. CRP=C-reactive protein, IL-6=Interleukin-6, *d*=Cohen's *d* measure of effect size, CAD=Coronary artery disease

Table 1:

Sociodemographic characteristics and baseline measures for Women's Ischemia Syndrome Evaluation and Women's Ischemia Syndrom Evaluation-Coronary Vascular Dysfunction participants

Variable	WISE	WISE-CVD	*P*
Sample size (*n*), mean (SD)	641	359	
Age, mean (SD)	57.97 (11.4)	54.62 (10.8)	<0.001
BDI total, mean (SD)	10.56 (8.36)	9.23 (8.06)	0.01
BDI CS, mean (SD)	5.09 (5.92)	4.60 (5.66)	0.20
BDI SS, mean (SD)	5.47 (3.37)	4.68 (3.19)	<0.001
CRP (mg/dL), mean (SD)	4.07 (3.81)		
IL-6 (pg/mL), mean (SD)	8.04 (15.10)		
CAD severity score, mean (SD)	13.32 (12.75)		
DASI score, mean (SD)	13.57 (2.24)	13.54 (2.27)	0.84
Race, *n* (%)			
Black or African-American	99 (15.4)	26 (7.2)	<0.001
White	536 (83.6)	263 (73.3)	<0.001
Other	6 (1.0)	61 (17.0)	<0.001
Education level (> high school), *n* (%)	266 (41.5)	263 (75.1)	<0.001
Marital status (married), *n* (%)	402 (62.7)	254 (72.6)	0.002
MetS diagnosis, *n* (%)	364 (56.8)	100 (24.6)	<0.001
MetS severity, *n* (%)			
0 risk factors	25 (3.9)	77 (22.0)	<0.001
1 risk factor	92 (14.4)	101 (28.9)	<0.001
2 risk factors	160 (25)	72 (20.6)	0.12
3 risk factors	165 (25.7)	56 (16.0)	<0.001
4 risk factors	117 (18.3)	35 (10.0)	<0.001
5 risk factors	82 (12.8)	9 (2.6)	<0.001
Current medications, *n* (%)			
Ace inhibitors	162 (25.3)		
Antidepressants	114 (17.8)		
Anxiolytics	129 (20.1)		
Asprin	376 (58.7)		
Beta blockers	241 (37.6)		
Calcium antagonists	171 (26.7)		
Diuretics	181 (28.2)		
Nitrates	216 (33.7)		
Statins	176 (27.5)		

MetS severity reflects the number of MetS risk factors endorsed by each participant. WISE=Women's ischemia syndrome evaluation, WISE-CVD=WISE-coronary vascular dysfunction, BDI=Beck depression inventory, MetS=Metabolic syndrome, CAD=Coronary artery disease, DASI=Duke Activity Status Index, SD=Standard deviation, CRP=C-reactive protein, IL-6=Interleukin-6, CS=Cognitive subscale, SS=Somatic subscale

Table 2:

Independent Women's Ischemia Syndrome Evaluation predictors of all-cause mortality + major adverse cardiovascular events adjusted for demographic factors (*n*=639)

Variable	HR	95% CI	*P*
MetS diagnosis	2.11	1.39–3.20	<0.001
BDI CS	1.02	0.99–1.05	0.183
BDI SS	1.08	1.03–1.14	0.003
CRP	1.01	1.01–1.02	0.001
IL-6	1.04	1.01–1.08	0.025
CAD severity	1.04	1.03–1.05	<0.001
DASI	1.16	1.08–1.24	<0.001

Adjusted for age, education, and race. MetS=Metabolic syndrome, BDI=Beck depression inventory, CAD=Coronary artery disease, DASI=Duke Activity Status Index, CRP=C-reactive protein, IL-6=Interleukin-6, CI=Confidence interval, CS=Cognitive subscale, SS=Somatic subscale, HR=Hazard ratio

Table 3:

Models 2a and 2b: Women's Ischemia Syndrom Evaluation depression subscores as predictors of all-cause mortality + major adverse cardiovascular events adjusted for inflammatory markers

Model 2a (n=546)				Model 2b (n=512)			
CRP				IL-6			
Variable	**HR**	**95% CI**	***P***	**Variable**	**HR**	**95% CI**	***P***
Adjusted for demographics, MetS + IM							
BDI-CS	1.00	0.97–1.04	0.904	BDI-CS	1.01	0.97–1.05	0.641
BDI-SS	1.07	1.01–1.14	0.032	BDI-SS	1.07	1.00–1.14	0.037
Adjusted for demographics, MetS, IM + CAD severity							
BDI-CS	1.00	0.97–1.04	0.760	BDI-CS	1.01	0.98–1.05	0.476
BDI-SS	1.08	1.01–1.15	0.016	BDI-SS	1.07	1.00–1.13	0.049
Adjusted for demographics, MetS, IM, CAD severity + DASI							
BDI-CS	1.00	0.97–1.04	0.977	BDI-CS	1.01	0.98–1.05	0.558
BDI-SS	1.05	0.99–1.12	0.119	BDI-SS	1.04	0.98–1.11	0.216

CRP=C-reactive protein, IL-6=Interleukin-6, BDI=Beck depression inventory, CS=Cognitive subscale, SS=Somatic subscale, MetS=Metabolic syndrome, CAD=Coronary artery disease, DASI=Duke Activity Status Index, CI=Confidence interval, IM=Inflammatory markers, HR=Hazard ratio