Depression, the Metabolic Syndrome and Cardiovascular Risk

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Background: The relationship between depression and the metabolic syndrome is unclear, and whether metabolic syndrome explains the association between depression and cardiovascular disease (CVD) risk is unknown. **Methods:** We studied 652 women who received coronary angiography as part of the Women's Ischemia Syndrome Evaluation (WISE) study and completed the Beck Depression Inventory (BDI). Women who had both elevated depressive symptoms (BDI $\geq$10) and a previous diagnosis of depression were considered at highest risk, whereas those with one of the two conditions represented an intermediate group. The metabolic syndrome was defined according to the ATP-III criteria. The main outcome was incidence of adverse CVD events (hospitalizations for myocardial infarction, stroke, congestive heart failure, and CVD-related mortality) over a median follow-up of 5.9 years. **Results:** After adjusting for demographic factors, lifestyle and functional status, both depression categories were associated with about 60% increased odds for metabolic syndrome compared with no depression (p = .03). The number of metabolic syndrome risk factors increased gradually across the three depression categories (p = .003). During follow-up, 104 women (15.9%) experienced CVD events. In multivariable analysis, women with both elevated symptoms and a previous diagnosis of depression had 2.6 times higher risk of CVD. When metabolic syndrome was added to the model, the risk associated with depression only decreased by 7%, and both depression and metabolic syndrome remained significant predictors of CVD. **Conclusions:** In women with suspected coronary artery disease, the metabolic syndrome is independently associated with depression but explains only a small portion of the association between depression and incident CVD. **Key words:** depression, cardiovascular disease, women, metabolic syndrome, obesity.

BDI = Beck Depression Inventory; **CAD** = coronary artery disease; **CVD** = cardiovascular disease; **DASI** = Duke Activity Status Inventory; **HDL** = high-density lipoprotein; **LDL** = low-density lipoprotein; **WISE** = Women's Ischemia Syndrome Evaluation; **NHLBI** = National Heart, Lung, and Blood Institute.

INTRODUCTION

Depression is common in the general population (1) and in cardiac patients (2,3), particularly among women (1,4,5). Observational studies have provided strong evidence that depression is associated with cardiovascular disease (CVD) or total mortality, both among individuals initially free of CVD (6), and in cardiac patients (7). The mechanisms underlying these effects, however, are still debated (8).

Recently, depression has been linked to the metabolic syndrome (9–12), a growing problem in the United States and an important risk factor for CVD and all-cause mortality (13,14). The reasons for this association may reside in the unhealthy lifestyles of persons with depression, and/or enduring dysregulation of the adrenocortical and autonomic nervous system, which may lead to increased visceral adiposity and insulin resistance (15,16). If the relationship between depression and the metabolic syndrome is confirmed, the latter may well play a role in the increased CVD risk associated with depression. However, depression and the metabolic syndrome have not been consistently linked to each other, with a recent study failing to demonstrate such an association (17). Furthermore, no previous study has addressed the question of whether the metabolic syndrome, entirely or in part, accounts for the observed connection between depression and CVD.

In this study we explored the role played by the metabolic syndrome in the relationship between depression and incident CVD in women with suspected myocardial ischemia, a group with significant psychosocial burden (4). Our key aims were a) to clarify whether the metabolic syndrome and its various components are associated with depression, independent of demographic and lifestyle factors; and b) to investigate to what extent the metabolic syndrome explains the effect of depression on incidence of CVD events over a median follow-up of 5.9 years.

METHODS

Study Sample and General Procedures

The Women's Ischemia Syndrome Evaluation (WISE) is a multicenter study sponsored by the National Heart, Lung, and Blood Institute (NHLBI) for the study of ischemic heart disease in women. Details of the WISE design and methods have been published (18). Briefly, between 1996 and 2000, 936 women with chest discomfort, suspected myocardial ischemia, or both were enrolled at the time of referral for clinically indicated coronary angiography. Exclusion criteria included emergency referral, major comorbidity compromising follow-up, pregnancy, contraindication to provocative diagnostic test-

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ing, cardiomyopathy, severe heart failure, acute myocardial infarction, or unstable angina within 1 month before study entry, coronary revascularization procedures within 6 months before study entry, significant valvular or congenital heart disease, language barrier, and any condition likely to affect study retention (alcoholism, drug abuse, or severe psychiatric illness). The WISE study received institutional review board approval from each participating site and all participants provided informed consent. All enrolled patients received a baseline evaluation that included collection of demographic information, medical history, medication use, symptom and psychosocial evaluation, a physical examination with blood pressure and physical measurements, and a fasting blood draw for the measurement of lipids and glucose.

The WISE lipid core laboratory was enrolled in the Centers for Disease Control and Prevention lipid standardization program previously used in multiple NHLBI-sponsored lipid-lowering intervention trials. The coefficients of variation for total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were 1.80%, 1.23%, and 3.93%, respectively. Low-density lipoprotein (LDL) cholesterol was obtained using the Friedewald formula (19). The Homeostasis Model Assessment of Insulin Resistance index was calculated from fasting glucose and insulin values (20).

Waist circumference was measured at the umbilicus. Functional capacity was assessed by means of the Duke Activity Status Inventory (DASI), a validated 12-item questionnaire which correlates with exercise treadmill results (21) and is a strong prognostic indicator (22). Physical activity was evaluated with the Postmenopausal Estrogen-Progestin Intervention questionnaire, a self-reported estimate of average physical activity level at home, work, and leisure (23). In addition, all medications taken within the last week, including antidepressants, were recorded and classified into major medication classes.

Measurement of Depression

Recruitment in WISE preceded the administration of the psychological questionnaire by about 4 months, therefore psychological data were not available in early participants. As part of the psychosocial battery, participants completed the Beck Depression Inventory (BDI), a self-administered validated 21-item scale of depressive symptoms which was shown to predict cardiovascular outcomes in many studies (24–26). The BDI provides a continuous score of depressive symptoms ranging from 0 to 63, and a score $\geq$10 indicates at least moderate symptoms of depression (27). A lifetime history of major depressive disorder was not formally assessed, but participants were asked whether they had a previous diagnosis of depression requiring treatment. This question did not query the type or duration of the treatment. After previous work in WISE (28), information on depressive symptoms and self-reported treatment history of depression was used to classify women into three groups of increasing depression severity. Women with both elevated symptoms of depression (BDI $\geq$10) and a reported previous diagnosis of depression were considered the most severe or longstanding cases of depression, presumably including many cases of major depressive disorder. This group was previously shown to exhibit a remarkably higher risk of death and cardiac events compared with women with none or only one of these two depression indicators (28). Those with either BDI $\geq$10 or a previous diagnosis of depression, but not both, represented an intermediate group; and women with neither condition were considered nondepressed.

Assessment of Metabolic Syndrome

We used the ATP-III criteria, recently revised by the American Heart Association and the NHLBI (29), to classify women as being with or without the metabolic syndrome on the basis of the presence or absence of three or more of the following factors: a) waist circumference $>$88 cm; b) fasting triglycerides $\geq$150 mg/dl or taking lipid-lowering medications; c) HDL cholesterol $<$50 mg/dl or taking lipid-lowering medications; d) systolic blood pressure $\geq$130 mm Hg, or diastolic blood pressure $\geq$85 mm Hg, or use of antihypertensive drug therapy; and e) fasting glucose $\geq$100 mg/dl or taking antidiabetic drugs. In addition to classifying women based on diagnosis of metabolic syndrome, we calculated a score counting the number of metabolic syndrome risk factors, ranging from 0 to 5.

Assessment of Angiographic Coronary Artery Disease

Quantitative analysis of coronary angiograms was performed off-line at the WISE Angiographic Core Laboratory (Rhode Island Hospital, Providence, RI) by investigators blinded to all other subject data (30). 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, NY). The presence of one or more stenoses $\geq$50% in diameter was classified as "obstructive" coronary artery disease (CAD). A CAD severity score was also developed by assigning increasing points to increasing percent stenosis (0–19, 20–49, 50–69, 70–89, 90–98, 99–100), after adjusting for presence of collaterals. Lesion location was taken into account in the scoring, with more proximal lesions receiving higher weighting.

Ascertainment of Cardiovascular Events

Follow-up for the occurrence of CVD events was obtained by telephone interview at 6-weeks and then yearly thereafter. Using a scripted interview, an experienced nurse or physician queried each patient for the occurrence of hospitalizations and the reason for hospitalization. The main outcome of interest was a composite end point of major cardiovascular events, including death due to CVD or hospitalizations for nonfatal myocardial infarction, stroke, or congestive heart failure (ICD-9 codes 390–459). In the event of death, a death certificate was obtained and causes of death were adjudicated by WISE investigators blinded to other study data. In case of disagreement, a consensus and final adjudication were obtained by the Steering Committee. The median length of follow-up was 5.9 years (interquartile range 3.6–6.9 years).

Statistical Analysis

First, we performed a descriptive comparison of baseline factors according to depression status. Because some variables (body mass index, waist circumference, physical activity score, functional capacity score, lipid and glucose levels) were not normally distributed, the median value, rather than the mean, was calculated according to BDI groups, and the p value for trend was obtained using nonparametric tests. To calculate trend statistics, we used the Mantel-Haenszel test for categorical data, and the Jonckheere-Terpstra method for continuous data (31).

Next, logistic regression models were used to examine the relationship between the depression group and metabolic syndrome, and odds ratios and 95% confidence intervals for metabolic syndrome according to depression status were obtained after adjusting for other factors. In separate steps, models were adjusted for demographic factors (age, race, education, and marital status), behavioral and functional status variables (current and past smoking, physical activity, and functional capacity measured with the DASI), and beta blocker use. To examine the association between depression and individual components of the metabolic syndrome, we conducted a similar series of logistic regression models in which each component was the dependent variable. We also constructed cumulative logit regression models for ordered categories to examine the relationship between depression and number of metabolic syndrome risk factors as an ordinal variable ranging from 0 to 5. Additional analyses were conducted with BDI as a continuous variable.

The individual and joint association of depression and metabolic syndrome with incident CVD events was tested using Cox proportional hazards models. Modeling was conducted in subsequent steps: a) adjusting for demographic factors (age, race, education, and marital status); b) adding behavioral variables (smoking and physical activity), functional capacity, and use of beta blockers; c) adding the CAD severity score; and, finally, d) adding metabolic syndrome, to determine whether the latter modulated the association between depression and outcome. We also examined whether the addition of number of metabolic syndrome risk factors, rather than metabolic syndrome, would provide similar results. The proportional hazards assumption of invariant hazards ratio over the follow-up was tested and found to be satisfied.

Because persons may become depressed as a consequence of a diagnosis of coronary heart disease, we repeated the analyses after excluding women with a previous history of coronary heart disease, defined as history of

myocardial infarction, percutaneous coronary intervention, or coronary artery bypass graft surgery, or with a previous history of diagnosed diabetes. All analyses were conducted using SAS software, version 9 (Cary, NC), and all tests for statistical significance were 2-tailed.

RESULTS

A total of 936 women were enrolled in WISE. Of this group, 283 women were excluded because information on BDI was not obtained, and an additional two women were excluded because of missing depression diagnosis information, leaving 652 women available for analysis. Ten additional women had missing follow-up data and were excluded from the analyses of CVD events. Women without depression information were significantly less likely to be white (75% versus 84%), had more severe CAD on angiogram (severity score 9.25 versus 7.50), and were slightly more likely to meet the metabolic syndrome criteria (67% versus 60%).

A comparison of baseline characteristics according to depression group (Table 1) showed that women with an elevated BDI score or a previous depression diagnosis were younger, less educated, and less likely to be married. They were also less physically active, had lower functional capacity and were more likely to smoke. However, presence and severity of CAD based on angiographic results did not differ by depression status. Menopausal status was not related to depression, but depressed women were more likely to use hormone replacement therapy.

Depression and Metabolic Syndrome

Of the metabolic syndrome risk factors, triglyceride levels and waist circumference were those most strongly associated with depression, showing a graded association with respect to depression severity group (Table 1). Except glucose, all the metabolic syndrome risk factors tended to be more common in women with depression (Figure 1). As a result, the prevalence of the metabolic syndrome was higher in women with either elevated BDI or a previous depression diagnosis (66.7%), or both (63.3%), compared with women with no depression (53.4%, $p < .001$; test for trend: $p = .01$). The number of metabolic syndrome risk factors meeting the ATP-III criteria increased progressively across the depression severity groups, 2.7, 3.0, and 3.1, respectively ($p = .003$).

In logistic regression models, after adjusting for demographic factors, both depression categories were associated with about 80% increased odds for metabolic syndrome com-

TABLE 1. Sample Characteristics According to Depression Status

	BDI <10 and No Previous Depression Diagnosis ($N = 305$)	BDI ≥10 or Previous Depression Diagnosis ($N = 249$)	BDI ≥10 and Previous Depression Diagnosis ($N = 98$)	*p* (Trend)
Age	59.45 ± 11.42	57.49 ± 11.49	53.94 ± 10.22	<.001
White race (%)	86.89	80.32	84.69	.23
High school or more (%)	85.57	78.71	77.55	.03
Married (%)	68.20	57.83	58.16	.02
Current smoker (%)	11.48	23.29	33.67	<.001
Ever smoked (%)	45.90	55.02	63.27	.001
Postmenopausal (%)	77.26	75.52	72.45	.34
History of symptomatic CAD (%)	26.1	30.1	29.2	.39
Presence of obstructive CAD (%)	33.4	38.2	22.5	.23
CAD severity score	7.50 (5–17)	8.25 (5–18)	6.25 (5–11)	.40
BMI, median (IQR)	28.30 (25–32)	28.73 (26–33)	28.21 (26–32)	.25
Physical activity median (IQR)	8.00 (6–9)	7.50 (6–9)	6.50 (6–9)	<.001
Functional capacity (DASI) (median (IQR))	24.7 (15–37)	15.2 (7–26)	7.6 (5–20)	<.001
Systolic BP (mm Hg), mean (SD)	136.11 ± 19.58	135.89 ± 20.54	136.93 ± 20.57	.81
Diastolic BP (mm Hg), mean (SD)	76.43 ± 10.76	76.08 ± 10.51	78.01 ± 11.08	.40
Triglycerides (mg/dl), median (IQR)	117.00 (79–174)	132.00 (90–192)	153.00 (89–231)	<.001
LDL-C (mg/dl), mean (SD)	113.32 ± 35.19	108.75 ± 39.88	117.95 ± 39.65	.53
HDL-C (mg/dl), median (IQR)	53.00 (46–63)	52.00 (46–60)	52.00 (44–59)	.14
Fasting plasma glucose (mg/dl), median (IQR)	98.00 (87–126)	96.00 (84–126)	98.00 (86–116)	.33
HOMA-IR index, median (IQR)	1.86 (0.97–3.25)	2.03 (0.87–3.55)	2.06 (1.13–4.04)	.51
Waist circumference (cm), median (IQR)	86.36 (76–99)	91.44 (81–104)	93.98 (84–102)	<.001
Ever used hormone replacement therapy (%)	49.5	50.4	68.4	.006
Use of beta blockers in past week (%)	40.00	37.65	28.57	.06
Use of antidepressants in past week (%)	3.93	18.15	60.20	<.001

BDI = Beck Depression Inventory; IQR = inter-quartile range; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; HOMA-IR = Homeostasis Model Assessment of Insulin Resistance; SD = standard deviation.

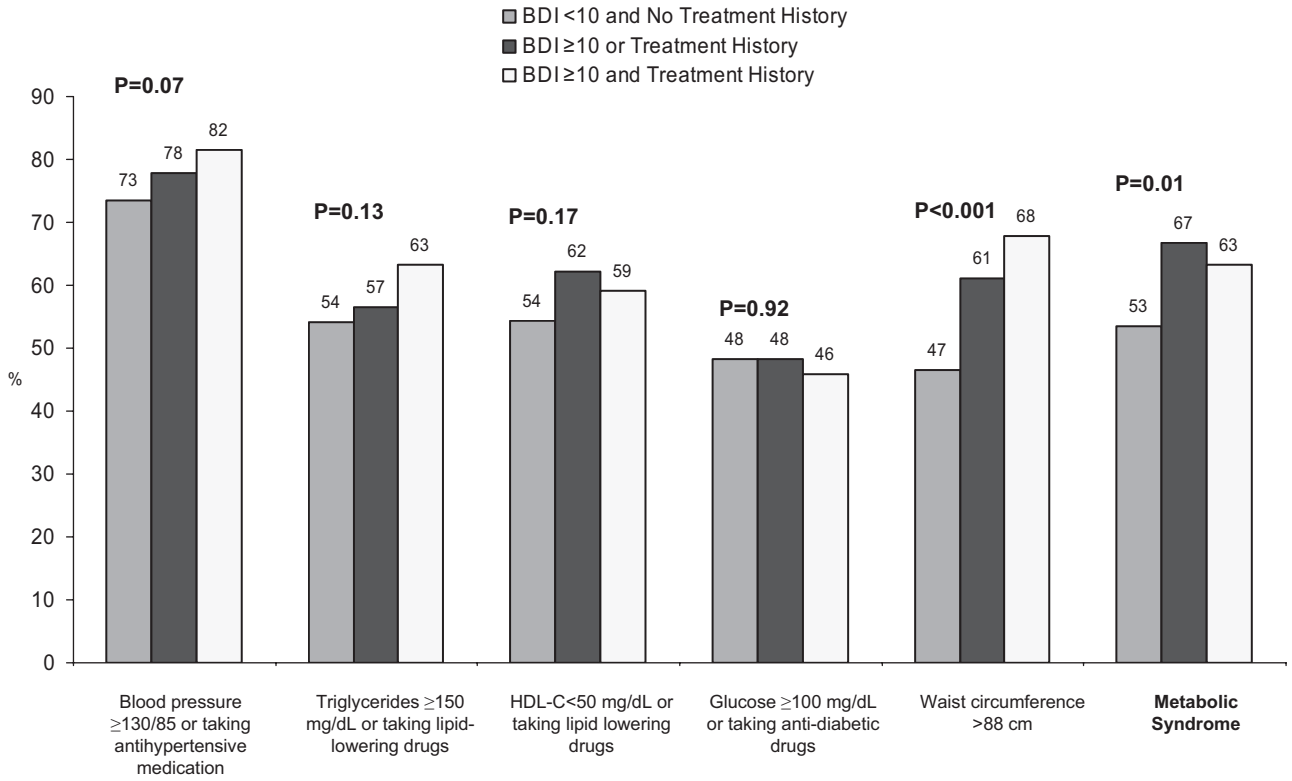

Figure 1. Unadjusted association of depression category with the metabolic syndrome and its individual risk factor components.

pared with no depression (Table 2). The association was slightly weakened, to about 60%, by further adjusting for smoking, physical activity, functional capacity (DASI scores), and use of beta blockers. Depression category was also associated, in a graded fashion, with number of metabolic syndrome risk factors. After adjusting for all the variables mentioned above, having both elevated BDI scores and a previous depression diagnosis increases the odds of having one additional metabolic syndrome risk factor by 58% when compared with those with no depression ($p = .04$). Depressive symptoms were associated with metabolic syndrome also as a continuous variable: in logistic regression models adjusted for all the variables above, for each 5-point increase in BDI score the odds of metabolic syndrome increased 20% ($p = .002$). In contrast, a previous depression diagnosis, without consideration of BDI score level, was not associated with metabolic syndrome: odds ratio = 1.00, $p = .99$.

When subjects with a history of CAD were excluded, the associations were somewhat stronger (Table 2): in multivariable analysis, women with both elevated BDI scores and a previous depression diagnosis had greater than twice the odds of metabolic syndrome compared with nondepressed women ($p < .001$).

Depression was a stronger predictor of the metabolic syndrome as a whole, rather than of separate metabolic syndrome risk factors. When metabolic syndrome risk factor criteria were examined individually in adjusted models as above, only hypertension ($p = .04$) and elevated triglycerides ($p = .03$) were significantly more common in depressed women, although other factors showed borderline associations.

Depression, Metabolic Syndrome, and Incident Cardiovascular Disease

During the 5.9 years of follow-up, there were 104 outcome events, including 31 CVD deaths and 73 nonfatal CVD events. After adjusting for demographic factors, women with both elevated BDI and a previous depression diagnosis had almost two times higher risk of CVD compared with women without depression (Table 3). After further adjusting for behavioral factors, functional capacity, use of beta blockers and CAD severity, the association was minimally reduced. In contrast, the intermediate depression category was not significantly associated with CVD incidence. As shown in Table 3, metabolic syndrome was also strongly related to incident CVD. Once the metabolic syndrome was added to the model, the risk associated with depression decreased by 7%, and both depression and metabolic syndrome remained significant predictors of CVD. When number of metabolic syndrome risk factors was added to the model, in place of metabolic syndrome, the results were almost identical and are not shown. Addition of antidepressant use in the past week to the final model also did not materially change the study estimates. The BDI score as a continuous variable was also significantly associated with CVD: for each 5-points increase in BDI, CVD risk increased 17% ($p = .004$). However, after adjustment for other risk factors the estimate became 8% ($p = .25$). A previous depres-

TABLE 2. Relationship Between Depression Group, Metabolic Syndrome, and Number of Metabolic Syndrome Risk Factors

	Outcome Variable: Metabolic Syndrome			Outcome Variable: No. Metabolic Syndrome Risk Factors		
	OR	95% CI	*p*	OR[a]	95% CI	*p*
All subjects (N = 652)						
Adjusted for demographic factors (age, race, education, marital status)						
BDI <10 and no previous depression diagnosis	1.00	—	—	1.00	—	—
BDI ≥10 or previous depression diagnosis	1.82	1.27–2.61	.001	1.47	1.09–1.99	.01
BDI ≥10 and previous depression diagnosis	1.77	1.09–2.89	.02	1.87	1.23–2.82	.003
p for trend	$p = .002$			$p < .001$		
Adjusted for all above plus ever smoking, physical activity, functional capacity (DASI) and beta blocker use						
BDI <10 and no previous depression diagnosis	1.00	—	—	1.00	—	—
BDI ≥10 or previous depression diagnosis	1.67	1.15–2.44	.007	1.31	0.96–1.80	.09
BDI ≥10 and previous depression diagnosis	1.59	0.94–2.67	.08	1.58	1.02–2.44	.04
p for trend	$p = .02$			$p = .02$		
Subjects without a history of coronary heart disease (N = 384)						
Adjusted for demographic factors (age, race, education, marital status)						
BDI <10 and no previous depression diagnosis	1.00	—	—	1.00	—	—
BDI ≥10 or previous depression diagnosis	1.65	1.04–2.62	.03	1.26	0.85–1.88	.25
BDI ≥10 and previous depression diagnosis	3.05	1.63–5.70	<.001	3.06	1.79–5.24	<.001
p for trend	$p < .001$			$p < .001$		
Adjusted for all above plus ever smoking, physical activity, functional capacity (DASI) and beta blocker use						
BDI <10 and no previous depression diagnosis	1.00	—	—	1.00	—	—
BDI ≥10 or previous depression diagnosis	1.63	1.01–2.64	.05	1.18	0.79–1.78	.42
BDI ≥10 and previous depression diagnosis	3.16	1.62–6.17	<.001	2.73	1.55–4.80	<.001
p for trend	$p < .001$			$p = .002$		

OR = odds ratio; CI = confidence interval; BDI = Beck Depression Inventory.

[a] OR for one additional metabolic syndrome risk factor, by means of cumulative logit regression models for ordered categories.

sion diagnosis was associated with CVD risk (adjusted hazards ratio = 1.87, $p = .04$).

Again, exclusion of women with previous CAD strengthened the associations providing a larger relative risk (Table 4). Women with both elevated BDI and a previous depression diagnosis had more than four times higher risk of CVD compared with nondepressed women ($p = .004$), and addition of the metabolic syndrome had, again, a modest effect, weakening the association by only 7%.

DISCUSSION

Although a connection between depression and metabolic syndrome has been suspected for some time, no previous studies have addressed whether, and to what extent, metabolic syndrome is an important mediator in the relationship between depression and CVD. In a cohort of women with suspected CAD, we report a strong association between depression and prevalence of the metabolic syndrome, independent of demographic factors, lifestyle, and functional status. Women with

TABLE 3. Relationship Between Depression Group, Metabolic Syndrome and CVD Incidence in the Entire Sample

Depression and CVD Incidence				Metabolic Syndrome and CVD Incidence			
	RR	95% CI	*p*		RR	95% CI	*p*
Adjusted for demographic factors[a]				Adjusted for demographic factors[a]	2.44	1.51–3.92	<.001
BDI <10 and no previous depression diagnosis	1.00	—	—				
BDI ≥10 or previous depression diagnosis	1.35	0.86–2.12	.20				
BDI ≥10 and previous depression diagnosis	2.78	1.68–4.62	<.001				
Adjusted for all above plus ever smoking, physical activity, functional capacity (DASI), and beta-blocker use				Adjusted for all above plus ever smoking, physical activity, functional capacity (DASI), and beta-blocker use	2.08	1.28–3.38	.003
BDI <10 and no previous depression diagnosis	1.00	—	—				
BDI ≥10 or previous depression diagnosis	1.08	0.67–1.73	.76				
BDI ≥10 and previous depression diagnosis	1.95	1.13–3.37	.02				
Adjusted for all above plus CAD at coronary angiography (CAD severity score)				Adjusted for all above plus CAD at coronary angiography (CAD severity score)	1.79	1.09–2.94	.02
BDI <10 and no previous depression diagnosis	1.00	—	—				
BDI ≥10 or previous depression diagnosis	0.98	0.59–1.61	.93				
BDI ≥10 and previous depression diagnosis	2.59	1.45–4.62	.001				
Adjusted for all above plus metabolic syndrome				Adjusted for all above plus depression category	1.81	1.10–2.99	.02
BDI <10 and no previous depression diagnosis	1.00	—	—				
BDI ≥10 or previous depression diagnosis	0.90	0.55–1.49	.69				
BDI ≥10 and previous depression diagnosis	2.47	1.38–4.42	.002				

BDI = Beck Depression Inventory; CAD = coronary artery disease; RR = relative risk.

[a] Age, race (white versus nonwhite), education (high school education versus less than high school), and marital status (married versus not married).

depression had approximately 80% higher odds of having the metabolic syndrome compared with nondepressed women; this estimate decreased to approximately 60% after adjusting for lifestyle factors, functional status, and use of beta blockers. In addition, the number of metabolic syndrome risk factors increased gradually across the three categories of increasing depression severity. However, the metabolic syndrome only explained a small portion, 20%, of the association between depression and incident CVD.

A relationship between major depression and the metabolic syndrome has been examined in three previous studies (9,10,17). Among young adults (<40 years of age) in the Third National Health and Nutrition Examination Survey, the prevalence of metabolic syndrome was approximately twice as high in women with a history of major depressive episode compared with women without (9). This association was not explained by demographic and behavioral factors, including age, race, education, smoking history, physical activity, and carbohydrate and alcohol consumption. No such relationship was found in men, suggesting that women may be especially susceptible to metabolic derangements secondary to depression. Similarly, in a sample of middle-aged women, depressive symptoms and metabolic syndrome were significantly correlated, but the results were unadjusted for demographic and lifestyle factors (10). In contrast, a recent study in a young Finnish sample failed to find an association between depression and metabolic syndrome (17). This study, however, did not examine women separately from men.

When metabolic syndrome risk factors were examined separately, only hypertension and elevated triglycerides were significantly associated with depression in multivariable analysis. However, the number of risk factors went up with increasing depression category, therefore supporting the usefulness of their combination as a cluster under the definition of metabolic syndrome in this study.

In this study, we used a classification of depression that incorporated both treatment history and current levels of depressive symptoms. As reported before (28), the combination

TABLE 4. Relationship Between Depression Group, Metabolic Syndrome and CVD Incidence Among Women Without a History of Previous Coronary Heart Disease

Depression and CVD Incidence	RR	95% CI	*p*
Adjusted for demographic factors[a]			
BDI <10 and no previous depression diagnosis	1.00	—	—
BDI ≥10 or previous depression diagnosis	1.40	0.59–3.32	.45
BDI ≥10 and previous depression diagnosis	4.01	1.74–9.28	.001
Adjusted for all above plus ever smoking, physical activity, functional capacity (DASI), and beta-blocker use			
BDI <10 and no previous depression diagnosis	1.00	—	—
BDI ≥10 or previous depression diagnosis	1.25	0.51–3.07	.62
BDI ≥10 and previous depression diagnosis	3.39	1.37–8.42	.008
Adjusted for all above plus CAD at coronary angiography (CAD severity score)			
BDI <10 and no previous depression diagnosis	1.00	—	—
BDI ≥10 or previous depression diagnosis	1.41	0.56–3.58	.47
BDI ≥10 and previous depression diagnosis	4.44	1.62–12.12	.004
Adjusted for all above plus metabolic syndrome			
BDI <10 and no previous depression diagnosis	1.00	—	—
BDI ≥10 or previous depression diagnosis	1.38	0.54–3.51	.50
BDI ≥10 and previous depression diagnosis	4.21	1.51–11.76	.006

BDI = Beck Depression Inventory; CAD = coronary artery disease; RR = relative risk.

[a] Age, race (white versus nonwhite), education (high school education versus less than high school), and marital status (married versus not married).

of these two depression markers was a powerful predictor of subsequent CVD, and a more robust risk indicator than just the BDI score or treatment history alone. Women with both factors likely include those with more severe, persistent, or recurrent depression. Previous studies have shown that women with a recurrent history of major depression have a higher risk of carotid plaque (32) and coronary and aortic calcification (33) compared with women with a single episode of depression or no history, suggesting that exposure to multiple episodes of depression may be particularly detrimental for women's cardiovascular health.

Potential Mechanisms

It is well known that depressed individuals tend to follow unhealthy lifestyles such as smoking, sedentary behavior, unhealthy diet, and poor compliance with medical treatments (34,35). However in our study, as in the report by Kinder et al. (9), the association remained strong after adjusting for behavioral factors, suggesting that the latter play only a minor role.

Depression has been associated with physiological abnormalities that may have metabolic consequences, including hypothalamus-pituitary-adrenal axis hyperactivity and autonomic nervous system dysfunction (36). These same abnormalities have been linked to several, if not all, of the components of the metabolic syndrome (16,37,38), and psychosocial factors explain a large portion of the association between adrenal/autonomic disturbances and the metabolic syndrome (16).

Despite numerous plausible mechanisms, our study cannot determine whether depression is a cause, a consequence, or simply a marker of the metabolic syndrome. For example, physical limitations or social stigma caused by obesity may predispose to depression, however, our study adjusted for functional capacity. Emotional problems in obese persons may also be secondary to excess cytokine production, which may have a role in the etiology of depression (39). Nonetheless, the strong association found and the dose-response pattern, with increasing levels of depressive symptoms, suggest a causal relationship. Whatever the predominant direction, it is important to recognize that behavioral/emotional problems and the metabolic syndrome are interconnected and may enhance each other in a feed-forward pattern. For example, in a longitudinal study of women, depression, tension, and anger at baseline predicted the development of the metabolic syndrome during the follow-up, but having the metabolic syndrome at baseline also predicted increasing anger and anxiety in the following years (10).

Relation to Cardiovascular Risk

In view of our prospective design we were able to evaluate, for the first time, the relative importance of depression and metabolic syndrome on CVD risk. We found that only 20% of the CVD risk associated with depression was explained by the metabolic syndrome. Once depression and metabolic syndrome were both included in the same model, they both remained independent predictors of CVD. Given the prognostic role of the metabolic syndrome (13,14), and its strong association with depression in this study, it is somewhat surprising that it explained only a small fraction of the increased CVD risk associated with depression. On the other hand, the link between depression and CVD is multifactorial (8). In addition to lifestyle and traditional CVD risk factors, evidence is mounting on the role of autonomic dysfunction, coagulation, and inflammation, which may provide a more direct pathophysiological link between depression and CVD (36,40).

Limitations

The WISE study included a selected sample of women referred for coronary angiography due to suspected coronary ischemia, which may limit generalizability. Nonetheless, this is a relevant patient group to study, given their high level of

psychosocial distress and coronary risk factor burden, particularly metabolic syndrome risk factors. The psychosocial questionnaire was not available for the initial participants, limiting somewhat the sample size for analysis. In addition, women without depression information had more severe CAD and more metabolic syndrome risk factors than the remaining women had, suggesting that earlier participants had a higher risk status. Furthermore, we did not have information on major depression from a diagnostic interview, or on duration of depression. We also did not have information on type or duration of antidepressant treatments. However, our classification based on current depressive symptoms in conjunction with a previous diagnosis of depression requiring treatment should be a better approximation of major depressive disorder than a definition focusing only on current depressive symptoms. On the other hand, the multicenter design, the detailed collection of patient data, the core laboratory assessment of CVD risk factors, and CAD assessment with coronary angiography represent unique strengths of this study and add to the validity of our findings.

CONCLUSIONS

In women with suspected CAD, depression and the metabolic syndrome are associated with each other independent of lifestyle factors and functional status. Surprisingly, however, the metabolic syndrome only explains a small portion of the association between depression and incident CVD, suggesting that depression and metabolic syndrome increase CVD risk mostly through independent pathways. Although our findings highlight the importance of both depression and the metabolic syndrome as independent risk factors for CVD in women, they indicate the need for more research aimed at uncovering the complex mechanisms linking depression to CVD risk.

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