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Depression, Inflammation, and Incident Cardiovascular Disease in Women With Suspected Coronary Ischemia

The National Heart, Lung, and Blood Institute–Sponsored WISE Study

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Objectives The purpose of this study was to examine prospectively whether inflammation explains the relationship between depression and cardiovascular disease (CVD).

Background It is unclear whether inflammation is a mechanism linking depression to CVD.

Methods We measured C-reactive protein (CRP) and interleukin (IL)-6 in 559 women with suspected coronary ischemia who completed the Beck Depression Inventory (BDI) at baseline and were followed over 5.9 years. We considered indicators of past and current depression to classify women into 3 groups: 1) depression, having both elevated depressive symptoms (BDI ≥10) and a previous diagnosis of depression requiring treatment; 2) possible depression, having either indicator but not both; and 3) no depression, having neither indicator of depression. The main outcome was incidence of CVD events (hospital stays for nonfatal myocardial infarction, stroke, congestive heart failure, and CVD-related mortality).

Results Compared with women without depression, women with depression had a 70% higher CRP ($p = 0.0008$) and a 25% higher IL-6 ($p = 0.04$), whereas women with possible depression had 30% higher CRP ($p = 0.02$) and 28% higher IL-6 ($p = 0.01$). Depression was a significant predictor of CVD (hazard ratio 2.58, $p = 0.0009$), but possible depression was not (hazard ratio 1.12, $p = 0.68$). Adjustment for other patient factors did not substantially affect the results. Addition of CRP decreased the estimate for depression by 13% and addition of IL-6 decreased it by 4%. Both depression and inflammatory biomarkers remained independent predictors of outcome.

Conclusions Despite their robust association with depression, inflammatory biomarkers explain only a small portion of the association between depression and CVD incidence. (J Am Coll Cardiol 2007;50:2044–50) © 2007 by the American College of Cardiology Foundation

Major depression is common in cardiac patients, particularly among women (1–3), and both clinical depression and elevated depressive symptoms have been associated with a higher risk of adverse outcome events in both men and women (4–6). However, the mechanisms underlying this association remain unclear (7).

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Recently, clinical depression and elevated levels of depressive symptoms were linked to inflammation, in both younger (8,9) and older (10–12) community-dwelling persons. A similar association was observed in patients with a diagnosis of major depression during an active depressive episode (13–16). Given the well-established role of inflammation in the pathogenesis and risk prediction of atherosclerotic cardiovascular disease (CVD) and acute coronary syndromes (17–20), it is possible that inflammation modulates the relationship between depression and CVD incidence or mortality. This question is fundamentally unexplored, because prospective studies have rarely included both depression and inflammatory markers as covariables in prediction models for incident CVD events (21). In addition, the exact nature of the inter-relationships among depression, inflammation, and outcome is not well characterized. Specifically, it is not clear to what extent these associations are due to coexisting risk factors and comorbidity or greater severity of atherosclerotic disease among persons with depression (21).

The purpose of this study was to explore the role of inflammation in explaining the relationship between depressive symptoms and major outcome events in a well-characterized sample of women with suspected coronary ischemia, a group distinctively affected by depression (3). First, we sought to determine whether, at baseline, depressive mood was associated with 2 inflammatory markers, C-reactive protein (CRP) and interleukin (IL)-6, and to what extent this relationship was due to concurrent CVD risk factors and comorbidity and to severity of coronary artery disease (CAD) measured by quantitative coronary angiography. Second, we sought to determine to what extent inflammation modulates the association between depressive mood and outcome after adjusting for other patient factors.

Methods

Study sample and general procedures. The WISE (Women's Ischemia Syndrome Evaluation) study is a multicenter study sponsored by the National Heart, Lung, and Blood Institute designed to address ischemic heart disease evaluation in women. Details of the WISE study design and methods have been published (22). Women were eligible for participation in the WISE study if they were older than 18 years of age and were referred for a coronary angiogram for the evaluation of chest pain symptoms or suspected myocardial ischemia. Exclusion criteria included major comorbidity compromising follow-up, pregnancy, contraindications to provocative diagnostic testing, cardiomyopathy, severe heart failure, recent myocardial infarction or revascularization procedures, significant valvular or congenital heart disease, and a language barrier preventing questionnaire completion. The WISE study received institutional review board approval from each participating site, and all participating women provided informed consent.

All participants completed a baseline evaluation including health status, psychosocial factors, medical history, physical exam, use of medications in past week, and collection of fasting blood samples. Physical function was assessed by means of the Duke Activity Status Index, a validated 12-item questionnaire of functional capability for cardiac patients (23).

Abbreviations and Acronyms

BDI = Beck Depression Inventory
CAD = coronary artery disease
CRP = C-reactive protein
CVD = cardiovascular disease
HR = hazard ratio
IL = interleukin

Measurement of depression. Of the 936 participants enrolled in the WISE study, 674 completed at baseline the Beck Depression Inventory (BDI) (24), a self-administered validated 21-item scale of depressive symptoms that was shown to predict CVD outcomes in many studies (25,26). The BDI was available only in this subset, because the psychological assessment battery was introduced slightly later (4 months), after the WISE study enrollment had begun. The BDI provides a continuous score of depressive symptoms ranging from 0 to 63, and a score ≥10 indicates at least moderate symptoms of depression. If more than 2 BDI questions were missing, the BDI score was set to missing (n = 20 women); however, if only 1 to 2 questions were missing, the mean response from the non-missing questions was substituted to the missing values (n = 41 women). 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. Patients were not queried about type or duration of the treatment. We considered, consistent with previous work (27), the concomitant presence of 2 depression indicators, a previous diagnosis of depression requiring treatment, and currently elevated depressive symptoms (BDI ≥10). This classification should better capture long-standing or recurrent depression, which presumably included many cases of major depressive disorder. This group was previously shown to have a remarkably higher risk of death and cardiac events compared with having none or only 1 depression indicator (27). Thus, women were classified into 3 groups: 1) no depression, having neither a BDI ≥10 nor a previous diagnosis of depression requiring treatment; 2) possible depression, having either a BDI ≥10 or a previous diagnosis of depression but not both; and 3) depression, having both a BDI ≥10 and a previous diagnosis of depression. As part of the baseline examination, all medications taken within the previous 6 weeks were recorded and classified, including antidepressant medications.

Measurement of inflammatory markers. Plasma sampled at baseline was frozen at −70°C for subsequent measurement of inflammatory markers. Levels of IL-6 were measured with a commercially available enzyme-linked immunosorbent assay kit (Quantikine hs human IL-6, R&D Systems, Minneapolis, Minnesota). Levels of high-sensitivity CRP were measured by a high-sensitivity method

on the Hitachi 911 analyzer (Roche, Basel, Switzerland) with reagents from Denka Seiken (Niigata, Japan). Interleukin-6 was measured at the University of Pittsburgh, and CRP was assayed at a core laboratory (Brigham and Women's Hospital, Boston, Massachusetts) with previously validated techniques (28).

Assessment of angiographic CAD. Quantitative analysis of coronary angiograms was performed off-line at the WISE Angiographic Core Laboratory (Rhode Island Hospital, Providence, Rhode Island) by investigators blinded to all other subject data (29). Luminal diameter was measured at all stenoses and at nearby reference segments with an electronic cine projector-based "cross-hair" technique (Vanguard Instrument Corp., Melville, New York). A CAD severity score was developed by assigning increasing points to increasing percent stenosis (0% to 19%, 20% to 49%, 50% to 69%, 70% to 89%, 90% to 98%, and 99% to 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 CVD outcome events. Follow-up for the occurrence of CVD events was obtained by telephone interview at 6 weeks and then yearly thereafter. With a scripted interview, an experienced nurse or physician queried each patient for the occurrence of and reasons for hospital stays. The outcome of interest was a composite end point of major cardiovascular events, including death due to CVD or hospital stays for nonfatal myocardial infarction, stroke, or congestive heart failure (International Classification of Diseases, Ninth Revision, codes 390 to 459). In the event of death, a death certificate was obtained and the cause of death was blindly reviewed by an events committee. In case of disagreement, a consensus and final adjudication were obtained by the steering committee. The median length of follow-up for ascertainment of survival was 5.9 years (interquartile range 3.6 to 6.9 years).

Statistical methods. First, we performed a descriptive comparison of baseline factors according to depression status with analysis of variance models or chi-square tests. To calculate trend statistics, we used the Mantel-Haenszel test for categorical data and the Jonckheere-Terpstra method for continuous data (30). Because the distribution of the inflammatory markers was skewed, analyses of these variables were based on natural log transformations. To ease interpretation, values were transformed back to the original units yielding geometric means.

We fitted linear regression models to test the association between depression group and CRP or IL-6, respectively, after adjusting sequentially for other baseline variables. Because the dependent variables were log-transformed, we expressed the results in terms of percent change by taking the antilog of the regression coefficient. Analyses were conducted in the following separate steps: 1) depression group as sole explanatory variable; 2) demographic factors (age, race, education, marital status) were added; 3) CVD risk factors (history of diabetes, history of hypertension, plasma cholesterol and high-density lipoprotein cholesterol levels, body mass index, and current smoking) were added; and 4) the CAD severity score was added. At each step, we re-examined the association between depression group and inflammatory markers. Additional analyses were conducted with BDI as a continuous variable.

The relationship among depression, inflammation, and incident CVD events was tested with Cox proportional hazards models, which allowed us to obtain the hazard ratio (HR) and the 95% confidence interval (CI) of CVD events associated with depression group before and after adjusting for other factors. In separate steps, as in the preceding description, models were adjusted for demographic factors, CVD risk factors, and CAD severity score. Finally, inflammatory variables were added (in separate models) to determine whether they modulated the association between depression and outcome after other baseline factors were adjusted for. The proportional hazards assumption of invariant HR over the follow-up was tested and found to be met.

Because the WISE study sample includes both women with and without obstructive CAD, and because presence of CAD might affect the levels of inflammatory biomarkers and of depressive symptoms and their inter-relationships, we repeated the Cox proportional hazards analysis in the subgroup of women without obstructive CAD, defined as presence of at least 1 stenosis ≥50% in diameter. All analyses were conducted with SAS software, version 9 (SAS Institute, Cary, North Carolina), and all tests for statistical significance were 2-tailed at an alpha level of 0.05.

Results

Of the 674 women who completed the BDI, 559 (83%) had <3 missing BDI items and had data on depression history, on CVD outcome events, and on at least 1 inflammatory marker. An additional 23 women were excluded from all multivariable models because of missing covariable data, leaving 536 women available for multivariable analysis, of which 527 had data on CRP and 493 had data on IL-6.

Women with elevated BDI score or a previous depression diagnosis were younger, less educated, and more likely to smoke and have hypertension than women without depression (Table 1). They also reported more angina than women without depression although were not more likely to have obstructive CAD.

Association between depression and inflammation. Both depression groups were significantly associated with inflammatory biomarkers (Table 2). Compared with nondepressed women, those with possible depression (having either a BDI ≥10 or a previous depression diagnosis but not both) showed 30% higher CRP level ($p = 0.02$) and 28% higher IL-6 ($p = 0.01$). Women with depression (having both a BDI ≥10 and a previous depression diagnosis) had a 70% higher CRP ($p = 0.0008$) and a 25% higher IL-6 ($p = 0.04$). Adjustment for CVD risk factors, comorbidity,

Table 1 Distribution of Baseline Factors According to Depression Status

	No Depression (n = 265)	Possible Depression (n = 211)	Depression (n = 83)	p Value ANOVA or Chi-Square	p Value Trend
Age, yrs	59.2 ± 11.5	57.8 ± 11.5	53.9 ± 10.2	0.0009	0.0008
White, %	86	78	84	0.056	0.21
≥ high school education, %	85	80	77	0.13	0.049
Married, %	67	59	61	0.22	0.18
Diabetes mellitus, %	19	28	20	0.056	0.37
Hypertension, %	53	53	72	0.004	0.009
Total cholesterol, mg/dl	195 ± 41	192 ± 45	202 ± 47	0.22	0.86
HDL-C, mg/dl	55 ± 13	53 ± 11	54 ± 13	0.12	0.14
Body mass index, kg/m^2	29.1 ± 6.4	29.7 ± 6.7	29.6 ± 6.2	0.55	0.32
Current smoker, %	11	20	32	<0.0001	<0.0001
Use of aspirin in past week, %	63	57	48	0.056	0.02
Use of statins in past week, %	26	31	20	0.14	0.75
Angina frequency (1 or more daily episode), %	32	37	49	0.01	0.004
Antidepressant medications in past 6 weeks, %	4	18	60	<0.0001	<0.0001
Mean BDI	4.8 ± 2.7	14.0 ± 7.1	20.0 ± 8.4	<0.0001	<0.0001
IL-6, pg/ml (geometric mean ± SD)	2.6 ± 2.2	3.3 ± 2.1	3.2 ± 2.4	0.001	0.0008
CRP, mg/l (geometric mean ± SD)	2.9 ± 3.3	4.1 ± 3.6	5.3 ± 3.2	0.0001	<0.0001
CAD at coronary angiography, %					
Absent	41	37	46	0.11	0.38
Minimal	26	26	34		
Obstructive	33	37	20		
CAD severity score	13.8 ± 13.2	14.0 ± 13.9	10.0 ± 8.6	0.047	0.41

No depression: Beck Depression Inventory (BDI) <10 and no previous depression diagnosis; possible depression: BDI ≥10 or previous depression diagnosis; depression: BDI ≥10 and previous depression diagnosis.

ANOVA = analysis of variance; CAD = coronary artery disease; CRP = C-reactive protein; HDL-C = high-density lipoprotein cholesterol; IL = interleukin.

health status, and CAD severity did not substantially change these associations.

Depressive symptoms as a continuous variable were also associated with inflammation: after adjusting for all the factors listed in Table 2, 1 SD-higher BDI score was associated with 12% higher IL-6 ($p = 0.004$) and 13% higher CRP ($p = 0.04$).

Depression, inflammation, and incident CVD. During the 5.9 years of follow-up, there were 79 outcome events, including 23 CVD deaths and 56 nonfatal CVD events. In unadjusted analysis, women with depression had a HR of 2.56 for CVD (95% CI 1.44 to 4.51) compared with women without depression, whereas women with possible depression did not show a significantly elevated risk (HR 1.12, 95% CI 0.66 to 1.90) (Table 3). In exploratory analyses, we examined the event subcomponents of the combined CVD end point for their individual relationship with depression. Except for nonfatal stroke, all event types showed a trend for an increased rate in the depression group.

Adjustment for demographic factors, traditional CVD risk factors, and CAD severity score did not substantially affect the study estimates for the relationship between depression group and CVD incidence (Table 3). Addition of CRP, however, decreased slightly the estimate for depression, by 13%. When IL-6 was added in place of CRP, it decreased the estimate for depression by 4%. In these models, CRP (HR 1.27, 95% CI 1.04 to 1.55) and IL-6 (HR 1.41, 95% CI 1.05 to 1.88) remained significantly associated with the outcome, independent of depression and of all the other variables in the models.

Restricting the analysis to women without obstructive CAD did not decrease the strength of the association between depression and outcome (Table 3). In this group, women with depression had more than 3-fold higher risk of CVD compared with nondepressed women ($p = 0.002$). Addition of CRP, again, decreased the estimate by approximately 13%, and addition of IL-6 decreased it by 4%. The interaction between depression group and CAD status was not significant in any of the models.

Discussion

In a prospective study of women with well-characterized CVD risk status, we found a significant association between depression, defined as having elevated depressive symptoms and a previous depression diagnosis, and 2 established biomarkers of inflammation, IL-6 and CRP. This association was not explained by CVD risk factors, comorbidity, and CAD severity. We also found that, despite being associated with each other, depression and inflammation predicted future events for the most part independently. Thus, despite a clear relationship between depression and inflammation, the latter plays only a

Table 2 Relationship Between Depression Group and Inflammatory Biomarkers

	% Difference in CRP	95% CI	p Value	% Difference in IL-6	95% CI	p Value
Unadjusted						
No depression	Ref	—	—	Ref	—	—
Possible depression	+30%	1.04–1.63	0.022	+28%	1.10–1.49	0.001
Depression	+70%	1.25–2.32	0.0008	+25%	1.01–1.52	0.036
p for trend			0.0004			0.004
Adjusted for demographic factors*						
No depression	Ref	—	—	Ref	—	—
Possible depression	+31%	1.04–1.65	0.022	+27%	1.09–1.49	0.002
Depression	+72%	1.25–2.36	0.0008	+28%	1.04–1.58	0.017
p for trend			0.0004			0.002
Further adjusted for CVD risk factors†						
No depression	Ref	—	—	Ref	—	—
Possible depression	+30%	1.03–1.62	0.028	+22%	1.05–1.43	0.010
Depression	+65%	1.21–2.27	0.002	+22%	1.00–1.52	0.056
p for trend			0.0008			0.013
Further adjusted for CAD severity score						
No depression	Ref	—	—	Ref	—	—
Possible depression	+30%	1.04–1.63	0.023	+22%	1.05–1.43	0.010
Depression	+73%	1.26–2.36	0.0007	+23%	1.00–1.52	0.046
p for trend			0.0003			0.010

No depression: BDI <10 and no previous depression diagnosis; possible depression: BDI ≥10 or previous depression diagnosis; depression: BDI ≥10 and previous depression diagnosis. *Age, race (white vs. non-white), education (high school education vs. < high school), and marital status (married vs. not married). †History of diabetes, history of hypertension, plasma cholesterol and high-density lipoprotein cholesterol (HDL) levels, body mass index, and current smoking.

CI = confidence interval; CVD = cardiovascular disease; Ref = reference category; other abbreviations as in Table 1.

minor role in the higher risk of adverse outcomes for women with depression.

Many previous studies examined the link between depression (or depressive symptoms) and CVD (31,32). However, only 1 previous investigation, among men, assessed the joint contribution of depression and inflammation on CVD outcomes (9). These authors found, consistent with our results, that depressive symptoms and inflammatory markers independently predicted outcome and the estimate for depression remained unchanged after adjusting for inflam-

Table 3 Relationship Between Depression Group, CRP, and CVD Incidence

	All Women (n = 527)			Women Without CAD (n = 363)		
	HR	95% CI	p Value	HR	95% CI	p Value
Unadjusted						
No depression	1.00	—	—	1.00	—	—
Possible depression	1.12	0.66–1.90	0.68	1.35	0.61–3.01	0.46
Depression	2.58	1.47–4.51	0.0009	4.09	1.91–8.75	0.0003
Adjusted for demographic factors*						
No depression	1.00	—	—	1.00	—	—
Possible depression	1.06	0.62–1.80	0.84	1.42	0.63–3.18	0.40
Depression	2.56	1.44–4.52	0.001	4.21	1.93–9.18	0.0003
Further adjusted for CVD risk factors† and CAD severity score						
No depression	1.00	—	—	1.00	—	—
Possible depression	0.91	0.52–1.60	0.74	1.16	0.50–2.69	0.72
Depression	2.65	1.39–5.04	0.003	4.23	1.81–9.88	0.0009
Further adjusted for CRP						
No depression	1.00	—	—	1.00	—	—
Possible depression	0.92	0.52–1.62	0.77	1.12	0.48–2.59	0.79
Depression	2.43	1.26–4.67	0.008	3.82	1.60–9.09	0.002

No depression: BDI <10 and no previous depression diagnosis; possible depression: BDI ≥10 or previous depression diagnosis; depression: BDI ≥10 and previous depression diagnosis. *Age, race (white vs. non-white), education (high school education vs. < high school), and marital status (married vs. not married). †History of diabetes, history of hypertension, plasma cholesterol and HDL levels, body mass index, and current smoking.

HR = hazard ratio; other abbreviations as in Tables 1 and 2.

mation. Thus, on the basis of our results, also in women does inflammation contribute only modestly to the association between depression and CVD.

Depression and inflammation. The precise nature of the relationship between depression and inflammation is not clear. An obvious explanation is the higher prevalence of coexisting risk factors and comorbidity in persons with depression or a greater severity of atherosclerotic disease (21). Comorbid conditions and severity of CAD, however, did not substantially affect the association between depression and inflammatory biomarkers in our study, and thus, these factors are not likely to play a major role. As with other forms of psychological stress (33,34), depression might induce inflammation through a number of mechanisms via sympathetic nervous system activation. For example, stress activates the transcription factor nuclear factor kappa B (NF-κB) in peripheral blood mononuclear cells, an effect that is dependent on norepinephrine and is abolished by alpha 1-adrenoceptor blockade (35). In addition, beta-adrenoceptor stimulation increases gene expression and protein production of several inflammatory cytokines (36). Inflammation might also play a role in the pathogenesis of depression (37). Given the cross-sectional assessment of depression and inflammatory biomarkers, our analysis cannot clarify the causal relationship between the two.

Depression, inflammation, and CVD. The inter-relationships among depression, inflammation, and incident CVD or mortality also remain unclear and might be multidirectional (21). Depression might induce inflammation, and the latter might mediate or amplify the relationship between depression and CVD; however, a number of other scenarios are possible. For example, both depression and inflammation might cause CVD but through separate pathways. Alternatively, depression and inflammation might have a common precursor that is linked to CVD. Finally, inflammation might cause both depression and CVD, without depression having a causal role on CVD. We were able, in view of our prospective study design, to evaluate the relative importance of depression and inflammation on CVD incidence. Our results indicate that depression and inflammation act mostly independently of each other. Therefore, it is unlikely that depression is just an epiphenomenon of inflammation or that a common precursor to both depression and inflammation explains a large part of their association with CVD.

Taken together, our results suggest that, in women with suspected coronary ischemia, depression and inflammation influence CVD risk for the most part through independent pathways. Given the prognostic role of inflammatory biomarkers and their robust association with depression, it is surprising that inflammation explained only a small fraction of the increased CVD risk associated with depression. In contrast, the link between depression and CVD is multifactorial (7). For example, evidence is mounting on the role of autonomic dysfunction and coagulation, which might provide alternative pathophysiological links between depression and CVD (38,39).

Study limitations. We studied women referred for coronary angiography due to suspected coronary ischemia; therefore, our sample might not be generalizable to all women in the community or all women with heart disease. However, this is an important patient group to study, given the high level of psychosocial distress in these patients and, at the same time, their well-characterized CVD risk status, including severity of CAD measured by coronary angiography. Another possible limitation is that the sample was relatively heterogeneous, because it included both women with and without obstructive CAD. However, few women in the WISE study were completely normal (i.e., had no history of coronary heart disease and also a normal angiogram) (29). To assess whether results would differ according to whether women had or did not have obstructive CAD, we repeated the analysis among women without CAD, which provided similar conclusions. Other limitations include delayed implementation of the psychosocial questionnaire reducing the sample size and the relatively low rate of outcome events, thus precluding us from examining such events separately by type or cause. However, exploratory analyses showed similar trends of higher rates in the depression group for almost all the cardiovascular events when examined separately. Additionally, we did not have information on major depressive disorder from a diagnostic interview or on duration, severity, or type of treatment of past depression. However, our classification on the basis of current depressive symptoms in conjunction with a previous diagnosis of depression requiring treatment is presumably a better approximation of major depressive disorder than a definition focusing only on current depressive symptoms. It is possible, however, that depression treatment is one reason for the higher CVD risk in depressed women. Two recent observational studies have linked the use of selective serotonin reuptake inhibitor antidepressant drugs to a higher rate of cardiovascular events and mortality in patients with heart failure (40) and after bypass surgery (41). However, these results might be confounded by indication, because many other studies have documented the safety and possible benefit of selective serotonin reuptake inhibitor use in cardiac patients (42,43), including 2 randomized trials (44,45). Although there are some limitations, unique strengths of this study include the longitudinal design, multisite recruitment, richness of patient data, long-term follow-up, and core laboratory–blinded assessments of coronary angiograms and inflammatory biomarkers.

Conclusions

In women with suspected coronary ischemia, inflammation is independently correlated with depression; however, it plays a minor role in modulating the association between depression and CVD outcome events. Our results emphasize the need for further study to better understand the multifactorial pathophysiological pathways linking depression to CVD risk.

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