

# Depression and Heart Rate Variability in Patients With Stable Coronary Heart Disease

## Findings From the Heart and Soul Study

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**Context:** Depression is associated with low heart rate variability (HRV) in patients following myocardial infarction, suggesting that alterations in the autonomic nervous system may contribute to the adverse cardiac outcomes associated with depression. Whether depression is associated with low HRV in patients with stable coronary heart disease (CHD) is not known.

**Objective:** To examine the association between major depression and 24-hour HRV in patients with stable CHD.

**Design, Setting, and Participants:** Cross-sectional study of 873 outpatients with stable CHD recruited from outpatient clinics in the San Francisco Bay Area, California.

**Main Outcome Measures:** Major depression was assessed using the Computerized National Institute of Mental Health Diagnostic Interview Schedule. Heart

rate variability was measured by 24-hour ambulatory electrocardiography.

**Results:** A total of 195 participants (22%) had major depression. Overall, we observed no association between depression and HRV as measured by time domain or frequency domain variables. Mean HRV was similar in participants with and without depression (all *P* values > .10), and participants with depression were no more likely than those without depression to have low HRV (all *P* values > .10).

**Conclusions:** We found no evidence of an association between depression and HRV in 873 outpatients with stable CHD. These findings raise questions about the potential role of HRV in the association between depression and cardiovascular disease.

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**M**AJOR DEPRESSION IS AN independent predictor of morbidity and mortality in patients with stable coronary heart disease (CHD) and after myocardial infarction (MI).<sup>1-10</sup> Several factors have been proposed as potential mechanisms by which depression may lead to CHD events, including increased sympathetic tone, elevated catecholamine levels, alterations in cortisol levels, increased platelet aggregation, inflammatory processes, antidepressant cardiotoxicity, and nonadherence to cardiac prevention and treatment regimens.<sup>11</sup> Of these, the potential effect of depression on the autonomic nervous system has emerged as one of the most intriguing pathways by which depression may lead to CHD events.

A recent large study demonstrated a strong association between depression and low heart rate variability (HRV) in patients post MI,<sup>12</sup> suggesting that acute alterations in cardiac autonomic tone may contribute to the increased risk of CHD events and mor-

tality in post-MI patients with depression. Since low HRV is associated with increased longer-term cardiac mortality,<sup>13-19</sup> an imbalance of cardiac autonomic tone, as measured by low HRV, may contribute to the increased risk of CHD events in patients with depression.<sup>20</sup> Because of this purported effect of depression on HRV and the clear association of worsened HRV with increased cardiac mortality, low HRV may act as an intermediary between major depression and adverse outcomes in post-MI patients.

Although the strength of association between depression and HRV in post-MI patients is compelling, it is not known whether depression is associated with HRV in patients with stable CHD. Since the pathophysiologic features of stable and unstable atherosclerotic plaques are markedly different, it is possible that the association of depression with HRV following an acute coronary syndrome may not persist once CHD has stabilized. However, previous studies of depression and HRV in patients with stable CHD have been limited by small sample sizes.<sup>21-24</sup> To determine whether de-

pression is associated with HRV in patients with stable CHD, we measured depression and 24-hour HRV in 873 outpatients with stable CHD who were participating in the Heart and Soul Study.

## METHODS

### CHARACTERISTICS OF PARTICIPANTS

The Heart and Soul Study is a prospective cohort study of psychosocial factors and health outcomes in patients with CHD. Details regarding our recruitment procedures have been published previously.<sup>25</sup> In brief, we used administrative databases to identify outpatients with documented CHD at 2 Veterans Affairs medical centers, one university medical center, and 9 public health clinics in northern California. Patients were eligible to participate if they had at least 1 of the following: a history of MI or coronary revascularization, angiographic evidence of 50% or more stenosis in at least 1 coronary vessel, or a diagnosis of CHD by an internist or cardiologist (based on abnormal angiogram or exercise treadmill test results in >98% of cases). Patients were excluded if they were unable to walk 1 block or were planning to move from the local area within 3 years.

Between September 2000 and December 2002, a total of 1024 participants enrolled and completed a daylong study appointment at the San Francisco Veterans Affairs Medical Center in California. Of these, 151 were excluded because they had a paced rhythm, atrial fibrillation, or their 24-hour Holter measurement of HRV was unable to be collected, leaving 873 participants for this cross-sectional analysis. All participants completed a daylong baseline study examination that included a comprehensive health interview and medical history questionnaire, an exercise treadmill test with stress echocardiography, and a 24-hour ambulatory Holter monitoring to determine HRV. The protocol was approved by the appropriate institutional review boards, and all participants provided written informed consent.

### DEPRESSION

Our primary predictor variable was current major depression. We measured the presence of current (past month) major depression according to *DSM-IV* criteria. We used the modified Computerized National Institute of Mental Health Diagnostic Interview Schedule (CDIS-IV), a highly structured interview designed to yield psychiatric diagnoses.<sup>26</sup> The CDIS-IV is a validated computerized version of the health care professional-administered, structured, clinical interview for the diagnosis of psychiatric illness. Trained research assistants administered the interview during the daylong baseline study appointment. Participants found to have current depression were informed that they had depression, instructed to discuss these symptoms with their primary care physician, and provided a list of local resources available for further evaluation and treatment.

Our secondary predictor variable was severe depression. We administered the 9-item Patient Health Questionnaire (PHQ),<sup>27</sup> which assesses the severity of depressive symptoms during the past 2 weeks. We categorized scores on this scale as representing no to minimal depressive symptoms (PHQ score, 0-3), mild to moderate depressive symptoms (PHQ score, 4-9), or severe depressive symptoms (PHQ score,  $\geq 10$ ).<sup>28</sup> Severe depression was defined as current depression by the CDIS-IV interview and severe depressive symptoms on the PHQ. To determine whether severe depression was associated with HRV, we compared HRV in participants who had severe depression with those who had no evidence of depressive symptoms (no current depression by CDIS-IV and PHQ score <4).

## HEART RATE VARIABILITY

Heart rate variability parameters (the outcome variables) were obtained via 3-channel 24-hour ambulatory Holter electrocardiographic recording as recommended by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.<sup>29</sup> Using standardized protocols, tapes were scanned at 500 times real time, and electrocardiography data were digitized at a sampling frequency of 128 Hz. Computer software (General Electric Medical System Software for Holter Analysis; GE Healthcare, Waukesha, Wis) was used to detect and label each QRS complex (part of electrocardiographic wave representing ventricular depolarization) using beats that had normal morphologic characteristics and a cycle length less than 20% duration of the preceding cycle length. An independent and blinded reviewer processed all Holter electrocardiograms and modified any inappropriate computer labels, with particular focus on periods with the highest and lowest average RR intervals.

The annotated QRS data were processed to allow time-domain characterization (General Electric Medical System Software for Holter Analysis; GE Healthcare), including standard deviation of NN intervals in milliseconds and standard deviation of 5-minute mean NN intervals in milliseconds. Frequency-domain assessment was executed using standardized fast Fourier transformation, including very low-frequency power (0.0033-0.04 Hz) in milliseconds squared; low-frequency power (0.04-0.15 Hz) in milliseconds squared; high-frequency power (0.15-0.40 Hz) in milliseconds squared; and wideband-frequency power (0.0033-0.4 Hz) in milliseconds squared. Very low-frequency power and wideband-frequency power were only available for 478 participants because we changed software programs halfway through the study.

### OTHER PARTICIPANT CHARACTERISTICS

Age, sex, ethnicity, marital status, medical history, smoking status, and alcohol use were determined by questionnaire. We measured weight and height and calculated body mass index (weight in kilograms divided by the square of height in meters). Physical activity was determined using the multiple-choice question, "Which of the following statements best describes how physically active you have been during the last month, that is, done activities such as 15-20 minutes of brisk walking, swimming, general conditioning, or recreational sports?" Participants who answered fairly, quite, very, or extremely active (vs not at all or a little active) were considered physically active. We used the CDIS-IV to determine the presence of comorbid posttraumatic stress disorder (PTSD) and generalized anxiety disorder during the past year.<sup>26</sup>

We assessed left ventricular ejection fraction using a resting echocardiogram. To measure ischemia, we performed a symptom-limited, graded exercise treadmill test according to a standard Bruce protocol and calculated the wall motion score index at peak exercise using stress echocardiography.<sup>30</sup> Participants were instructed to bring their medication bottles to the study appointment, and study personnel recorded all current medications. We measured systolic and diastolic blood pressure and assayed glycosylated hemoglobin, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol levels after a 12-hour fast.

### STATISTICAL ANALYSIS

Differences in characteristics between participants with and without current depression were compared using 2-tailed *t* tests (or nonparametric equivalent) for continuous variables and  $\chi^2$  tests for dichotomous variables. The frequency domain variables were

log transformed to produce normal distributions. We then used analysis of covariance to compare mean HRV in participants with and without depression, adjusting for potential confounding variables.

To determine whether the association between depression and HRV differed by the presence of other clinical characteristics, we adjusted for medical comorbidities associated with depression. Furthermore, we tested for interactions between depression and other variables known to be associated with HRV,<sup>24</sup> including age, sex, history of MI, diabetes mellitus, congestive heart failure, revascularization, physical activity,  $\beta$ -blocker use, body mass index, and current smoking. Since HRV may be influenced by severity of cardiovascular disease and by the use of  $\beta$ -blockers or antidepressants, we repeated our analyses stratified by the presence of MI or revascularization, use of  $\beta$ -blockers, and use of antidepressants.

To examine whether severe depression was associated with low HRV, we compared mean HRV in participants who had severe depressive symptoms with those who had no evidence of depressive symptoms. For this analysis, we excluded participants who had a clinical diagnosis of depression by the CDIS-IV without severe symptoms (PHQ score <10) and those who had moderate depressive symptoms without a clinical diagnosis (PHQ score >4). We also examined the association between depression severity (PHQ) score (as a continuous variable) and measures of HRV using the Pearson correlation coefficient.

Finally, we examined the association of depression with low HRV as a dichotomous variable (defined as lowest quartile of HRV), using a  $\chi^2$  statistic. All analyses were performed using SAS software (version 8; SAS Institute, Inc, Cary, NC).

## RESULTS

Of the 873 participants, 22% (195/873) had current depression based on the CDIS-IV interview (**Table 1**). Compared with participants without depression, those with depression were younger and were less likely to be male, married, or have a history of coronary revascularization. Participants with depression were more likely to smoke, have a higher body mass index, and be less physically active. Patients with depression were more likely to be taking an antidepressant, to have higher depression scores, to have PTSD, and to have anxiety. There was no difference in resting heart rate between participants with and without depression (Table 1).

We observed no association between depression and mean time-domain or frequency-domain HRV in unadjusted or adjusted analyses (**Table 2**). There were no significant interactions of depression with age, sex, history of MI, revascularization, congestive heart failure, diabetes mellitus, current smoking, physical activity,  $\beta$ -blocker use, or body mass index in either time-domain or frequency-domain HRV analyses. We observed no association between depression and any measure of HRV in the 644 participants who reported a history of MI or revascularization, in the 353 nonusers of  $\beta$ -blockers, in the 706 nonusers of antidepressant medication, or in the 752 men alone (all *P* values >.10).

Of the 195 participants with current depression, 104 had severe depressive symptoms (current CDIS-IV depression and PHQ score  $\geq 10$ ). We found no association between severe depression and mean HRV indexes in unadjusted or adjusted analyses (**Table 3**). Likewise, there was no significant correlation between severity score on

**Table 1. Characteristics of 873 Study Participants With Stable Coronary Heart Disease, Stratified by the Presence of Current Depression\***

Variable	Participants With Depression (n = 195)	Participants Without Depression (n = 678)	P Value
Age, y, mean (SD)	62 (11)	68 (10)	<.001
Male	132 (68)	580 (86)	<.001
White	115 (59)	391 (58)	.76
Married	64 (33)	300 (44)	.004
Medical history			
Diabetes mellitus	57 (29)	172 (25)	.28
Myocardial infarction	95 (49)	381 (56)	.08
Congestive heart failure	34 (17)	107 (16)	.60
Hypertension	139 (71)	485 (72)	.92
Stroke	30 (15)	96 (14)	.67
Revascularization (CABG or PTCA)	99 (51)	420 (62)	.006
COPD or asthma	35 (20)	103 (16)	.20
Current smoker	56 (29)	115 (17)	.002
Regular alcohol use	56 (29)	191 (28)	.90
Body mass index, kg/m <sup>2</sup> , mean (SD)	29 (5)	28 (5)	.03
Physically active	101 (52)	453 (67)	<.001
Medication use			
$\beta$ -Blocker	113 (58)	406 (60)	.63
Statin	116 (59)	453 (67)	.06
Aspirin	155 (79)	549 (81)	.64
Renin-angiotensin system inhibitor	94 (48)	335 (49)	.77
Antidepressant			
SSRIs	59 (30)	31 (5)	<.001
Tricyclic	14 (7)	22 (3)	.01
Other	42 (22)	30 (4)	<.001
Laboratory test results, mean (SD)			
HDL cholesterol level, mg/dL	46 (15)	46 (14)	.85
LDL cholesterol level, mg/dL	106 (36)	104 (32)	.37
Glycohemoglobin concentration, %	6 (1.4)	6 (1.1)	>.99
Cardiac function			
Resting heart rate, mean (SD)	67.6 (12.5)	67.1 (11.6)	.59
Left ventricular ejection fraction $\leq 55\%$	28 (14)	114 (17)	.41
Wall motion score index, mean (SD)	1.1 (0.3)	1.2 (0.4)	.09
Systolic blood pressure, mean (SD)	133 (22)	133 (21)	.95
Diastolic blood pressure, mean (SD)	75 (12)	74 (11)	.27
Depression score (PHQ <sup>27</sup> ), mean (SD)	11 (6)	4 (4)	<.001
Posttraumatic stress disorder	48 (25)	31 (5)	<.001
Generalized anxiety disorder	72 (37)	18 (3)	<.001

Abbreviations: CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PHQ, Patient Health Questionnaire; PTCA, percutaneous transluminal coronary angioplasty; SSRI, selective serotonin reuptake inhibitor.

To convert to SI factors: HDL and LDL cholesterol to millimoles per liter, multiply by 0.0259.

\*Per the Computerized National Institute of Mental Health Diagnostic Interview Schedule.<sup>26</sup> Values are expressed as number (percentage) of patients unless otherwise indicated.

the depressive symptoms scale (PHQ) and any measure of HRV (all *P* values >.10). The proportion of participants with low HRV was similar in participants with and

**Table 2. Mean Heart Rate Variability in 873 Participants With Coronary Heart Disease, Stratified by the Presence of Depression**

Variable	Sample Size	Unadjusted Mean (SD)			Adjusted Mean (95% CI)*		
		Participants With Depression (n = 195)	Participants Without Depression (n = 678)	P Value	Participants With Depression (n = 195)	Participants Without Depression (n = 678)	P Value
SDNN, ms	873	122 (40)	121 (37)	.93	109 (100-118)	104 (95-112)	.15
SDANN, ms	873	109 (36)	109 (36)	.82	97 (88-105)	92 (84-100)	.14
LnVLF, ms <sup>2</sup>	478	6.3 (0.9)	6.4 (0.7)	.26	6.0 (5.7-6.2)	6.0 (5.7-6.2)	.73
LnLF, ms <sup>2</sup>	872	5.3 (1.1)	5.3 (1.0)	.84	5.1 (4.9-5.4)	5.1 (4.8-5.3)	.44
LnHF, ms <sup>2</sup>	872	4.3 (1.0)	4.4 (1.1)	.12	4.3 (4.0-4.5)	4.3 (4.1-4.6)	.66
LnWBF, ms <sup>2</sup>	478	6.8 (0.9)	6.9 (0.8)	.35	6.5 (6.3-6.8)	6.5 (6.3-6.8)	.95

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; HDL, high-density lipoprotein; HF, high-frequency power (0.15-0.40 Hz); LF, low-frequency power (0.04-0.15 Hz); Ln, natural log; SDANN, standard deviation of 5-minute mean NN intervals; SDNN, standard deviation of NN intervals; VLF, very low-frequency power (0.0033-0.04 Hz); WBF, wideband-frequency power (0.0033-1.7070 Hz).

\*All variables from Table 1 (except depression score) were entered into the multivariable models. Other variables associated with SDNN (at  $P < .05$ ) were  $\beta$ -blockers, resting heart rate, diabetes mellitus, congestive heart failure, COPD or asthma, and current smoking. Other variables associated with SDANN were diabetes mellitus, COPD or asthma,  $\beta$ -blockers, angiotensin receptor blockers, and resting heart rate. Other variables associated with VLF were aspirin and resting heart rate. Other variables associated with LF were diabetes mellitus, HDL cholesterol level, use of tricyclic antidepressant, resting heart rate, and posttraumatic stress disorder. Other variables associated with HF were age, HDL cholesterol level, and resting heart rate. The other variable associated with WBF was resting heart rate.

**Table 3. Mean Heart Rate Variability in Participants With Severe Depressive Symptoms and in Those With No Depressive Symptoms\***

Variable	Sample Size	Unadjusted Mean (SD)			Adjusted Mean (95% CI)†		
		Severe Depressive Symptoms (n = 104)	No Depressive Symptoms (n = 418)	P Value	Severe Depressive Symptoms (n = 104)	No Depressive Symptoms (n = 418)	P Value
SDNN, ms	522	120 (37)	124 (40)	.42	110 (97-122)	104 (92-116)	.31
SDANN, ms	522	108 (36)	110 (37)	.50	99 (86-111)	92 (80-104)	.24
LnVLF, ms <sup>2</sup>	288	6.4 (0.8)	6.4 (0.9)	.94	6.2 (5.9-6.6)	6.1 (5.8-6.4)	.41
LnLF, ms <sup>2</sup>	521	5.3 (1.0)	5.3 (1.0)	.96	5.1 (4.7-5.4)	4.9 (4.6-5.3)	.39
LnHF, ms <sup>2</sup>	521	4.3 (1.0)	4.5 (1.0)	.22	4.2 (3.8-4.5)	4.2 (3.9-4.6)	.77
LnWBF, ms <sup>2</sup>	288	6.8 (0.8)	6.9 (0.9)	.90	6.7 (6.3-7.1)	6.6 (6.3-7.0)	.56

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; HDL, high-density lipoprotein; HF, high-frequency power (0.15-0.40 Hz); LF, low-frequency power (0.04-0.15 Hz); Ln, natural log; SDANN, standard deviation of 5-minute mean NN intervals; SDNN, standard deviation of NN intervals; VLF, very low-frequency power (0.0033-0.04 Hz); WBF, wideband-frequency power (0.0033-1.7070 Hz).

\*Severe depressive symptoms defined as current depression by the Computerized National Institute of Mental Health Diagnostic Interview Schedule<sup>26</sup> and score of 10 or more on Patient Health Questionnaire.<sup>27</sup> No depressive symptoms defined as no current depression by the Computerized National Institute of Mental Health Diagnostic Interview Schedule and score less than 4 on Patient Health Questionnaire. All other participants were excluded from the analysis.

†All variables from Table 1 (except depression score) were entered into the multivariable models. Other variables associated with SDNN (at  $P < .05$ ) were white ethnicity, diabetes mellitus, COPD or asthma, current smoking, physical activity,  $\beta$ -blockers, angiotensin receptor blockers, and resting heart rate. Other variables associated with SDANN were diabetes mellitus, COPD or asthma,  $\beta$ -blockers, angiotensin receptor blockers, and resting heart rate. Other variables associated with VLF were current smoking, glycohemoglobin level, and resting heart rate. Other variables associated with LF were current smoking and resting heart rate. Other variables associated with HF were age, current smoking, HDL cholesterol level, and resting heart rate. Other variables associated with WBF were current smoking and resting heart rate.

without depression (**Table 4**). There was no association between severe depression and low HRV.

#### COMMENT

We found no evidence of an association between depression and low HRV in 873 outpatients with stable CHD. Overall, we observed no difference in time domain or frequency domain measures of HRV in participants with and without depression. Moreover, there was no correlation between continuous measures of depression severity and measures of HRV nor was there any association be-

tween severe depressive symptoms and HRV. These findings raise questions about whether HRV is a mediator in the association of depression with adverse outcomes among patients with stable CHD.

In patients with CHD, depression is associated with an almost 2-fold increased risk of CHD events and mortality,<sup>1-10</sup> but no study has determined how depression leads to adverse outcomes. Several recent studies have suggested that autonomic dysfunction, represented by low HRV, may be one of the more promising potential explanations. Depression has been associated with low HRV in the setting of acute MI,<sup>12,17</sup> and low HRV is associated

**Table 4. Number and Proportion of Participants With Abnormal (Low) Heart Rate Variability by Presence of Depression\***

Variable	Current Depression (n = 195)	No Current Depression (n = 678)	P Value	Severe Depressive Symptoms (n = 104)	No Depressive Symptoms (n = 418)	P Value
Lowest quartile SDNN, $\leq 95$ ms	51 (26)	176 (26)	.96	27 (26)	105 (25)	.86
Lowest quartile SDANN, $\leq 83$ ms	52 (27)	170 (25)	.65	29 (28)	111 (27)	.78
Lowest quartile LnVLF, $\leq 5.85$ ms <sup>2</sup>	34 (23)	91 (27)	.38	16 (21)	55 (26)	.36
Lowest quartile LnLF, $\leq 4.67$ ms <sup>2</sup>	45 (23)	175 (26)	.43	23 (22)	104 (25)	.55
Lowest quartile LnHF, $\leq 3.66$ ms <sup>2</sup>	52 (27)	168 (25)	.60	28 (27)	97 (23)	.43
Lowest quartile LnWBF, $\leq 6.29$ ms <sup>2</sup>	34 (23)	86 (26)	.58	17 (22)	51 (24)	.71

Abbreviations: HF, high-frequency power (0.15-0.40 Hz); LF, low-frequency power (0.04-0.15 Hz); Ln, natural log; SDANN, standard deviation of 5-min mean NN intervals; SDNN, standard deviation of NN intervals; VLF, very low-frequency power (0.0033-0.04 Hz); WBF, wideband-frequency power (0.0033-1.7070 Hz).

\*Values are expressed as number (percentage) of participants.

with increased mortality following MI.<sup>13,15,16</sup> In the ENRICH study, Carney et al<sup>12</sup> found a strong association between depression and low HRV (frequency domain variables) in 307 patients with depression compared with 366 patients without depression following acute MI. Furthermore, a number of small studies have reported improvements in HRV after treatment for depression,<sup>31,32</sup> including 2 studies in patients with CHD.<sup>33,34</sup> However, stable and unstable CHD have different pathophysiologic features, and it is thus possible that low HRV may act as a mediator between depression and adverse outcomes in patients with unstable but not stable CHD.

Our results differ from those of several small studies that have examined the association between depression and HRV in patients with stable CHD. Carney et al,<sup>21</sup> in a study of 77 patients undergoing elective coronary angiography, found only a trend toward lower HRV in stable CHD. In another study, Carney et al<sup>22</sup> reported lower HRV in 19 patients with depression compared with 19 patients without depression who were undergoing elective coronary angiography. Krittayaphong et al<sup>23</sup> found an association between low HRV and higher depression scores in 42 patients with exercise-induced ischemia. Stein et al<sup>24</sup> found lower HRV in 40 patients with depression compared with 32 patients without depression with documented CHD by angiography recruited from cardiac rehabilitation centers and newspaper advertisements. Conversely, Yeragani et al<sup>35</sup> found no difference in HRV between 19 patients with depression and 20 control patients.

There are several possible explanations for the difference between our results and those of prior studies. First, recent trends in therapy for patients with CHD may eliminate the previously reported association between depression and HRV. However, we observed no evidence of an interaction between depression and  $\beta$ -blockers in our analysis and no association of depression with HRV in the subset of participants who were not taking  $\beta$ -blockers. Second, antidepressant medications, which have been shown to improve HRV post-MI, may blunt the effect of depression on HRV.<sup>34</sup> However, the majority of patients with depression in our study were not taking antidepressants, and even after excluding those taking antidepressants, we still found no association between depression and HRV.

Third, 79 (9%) of our study participants had a diagnosis of PTSD within the past year, and comorbid PTSD

may confound the association between depression and HRV. However, with the exception of an association between PTSD and low-frequency power, neither generalized anxiety disorder nor PTSD was associated with any HRV indexes in our analysis. Finally, we determined the presence of depression in the past month, and it is possible that the effect of depression may have been attenuated if the participant was not actually depressed during the same 24 hours as the HRV measurement. However, even when we limited our analysis to those who reported severe depressive symptoms in the prior 2 weeks, we observed no association between depression and HRV.

Another potential explanation is that participants with depression were healthier than participants without depression in our study or that the CDIS-IV misclassified some participants without depression as having depression, thus diluting the effect of depression on HRV. However, even after adjusting for the presence of medical illness, we observed no association between depression and HRV. Furthermore, after excluding the "healthier" subset of participants (ie, those who did not have a history of MI or revascularization), there was still no association between depression and HRV.

Several limitations must be considered in interpreting our results. First, only 161 (18%) of our participants were women, so our results may not generalize to other patient populations. However, our subset of women was larger than the total combined number of women enrolled in all previously published studies of depression and HRV in patients with stable CHD, and the total number of participants in our study was also greater than 3 times the total combined number of participants in these previously published studies. Second, we changed our HRV analysis software halfway through the study, so half of the Holter tapes were run using different software. However, in a blinded repeat analysis of 20 tapes, we found more than 99% concordance in readings between the 2 software programs. Finally, we did not use nonlinear techniques to measure HRV in our participants, and nonlinear techniques may be more sensitive to depression than those used in our study.<sup>36</sup>

In summary, we found no evidence that depression is associated with low HRV in a study of 873 patients with stable CHD. These findings raise questions about whether low HRV mediates the association between depression and adverse cardiovascular events.

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