

Psychological Distress and Subsequent Cardiovascular Events in Individuals With Coronary Artery Disease

Pratik Pimple, MBBS, MPH, PhD; Bruno B. Lima, MD, PhD; Muhammad Hammadah, MD; Kobina Wilmot, MD, MSCR; Ronnie Ramadan, MD; Oleksiy Levantsevych, MD; Samaah Sullivan, PhD; Jeong Hwan Kim, MD; Belal Kaseer, MD; Amit J. Shah, MD, MSCR; Laura Ward, MPH; Paolo Raggi, MD; J. Douglas Bremner, MD; John Hanfelt, PhD; Tene Lewis, PhD; Arshed A. Quyyumi, MD; Viola Vaccarino, MD, PhD

Background—Higher symptom levels of a variety of measures of emotional distress have been associated with cardiovascular disease (CVD), especially among women. Here, our goal was to investigate the association between a composite measure of psychological distress and incident cardiovascular events.

Methods and Results—In a prospective cohort study, we assessed 662 individuals (28% women; 30% blacks) with stable coronary artery disease. We used a composite score of psychological distress derived through summation of Z-transformed psychological distress symptom scales (depression, posttraumatic stress, anxiety, anger, hostility, and perceived stress) as a predictor of an adjudicated composite end point of adverse events (cardiovascular death, myocardial infarction, stroke, heart failure, or unstable angina). During a mean follow-up of 2.8 years, 120 (18%) subjects developed CVD events. In the overall population, there was no association between the psychological distress measure and CVD events, but there was a sex-based interaction ($P=0.004$). In women, higher psychological distress was associated with a higher incidence of CVD events; each SD increase in the composite score of psychological distress was associated with 1.44 times adjusted hazard of CVD events (95% CI, 1.09–1.92). No such association was found in men.

Conclusions—Among patients with coronary artery disease, higher psychological distress is associated with future cardiovascular events in women only. (*J Am Heart Assoc.* 2019;8:e011866. DOI: 10.1161/JAHA.118.011866.)

Key Words: cardiovascular disease • depression • latent class analysis • psychological stress • sex differences • women

The prevalence of mental health disorders in the US population is growing steadily. In 2013, an estimated 18.1% of US adults aged 18 years or older had a diagnosed mental illness, of which 6.7% (15.7 million) had at least 1 major depressive episode.^{1,2} In addition to significantly contributing to disability and healthcare costs, psychological disturbances have been increasingly associated with physical

health consequences, especially cardiovascular disease (CVD).³ For example, the association between depression, or depressive symptoms, and cardiac events or mortality is well established, both in individuals without coronary artery disease (CAD) at baseline and among those with established CAD.^{4,5} Similar associations have been reported for other psychological factors, including posttraumatic stress disorder (PTSD),⁶ anxiety,⁷ anger, hostility,⁸ and perceived stress,⁹ but results remain either mixed or limited.

The majority of studies investigating the association between psychological factors and CVD have treated each psychological phenotype as an independent exposure, and none have taken into account and integrated individual psychological attributes more broadly. One reason why an integrative approach may be useful is that psychological factors may share biological or behavioral substrates, explaining why they tend to correlate with each other.¹⁰ Examining them together may provide new insights onto specific psychological phenotypes that are relevant for cardiovascular risk.

In the current study, we investigated the association between a composite measure of psychological distress,

From the Department of Epidemiology, Rollins School of Public Health (P.P., S.S., A.J.S., T.L., V.V.), Division of Cardiology, Department of Medicine (B.B.L., M.H., K.W., R.R., O.L., J.H.K., B.K., A.J.S., A.A.Q., V.V.), and Department of Biostatistics & Bioinformatics, Rollins School of Public Health (L.W., J.H.), Emory University, Atlanta, GA; Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, Alberta, Canada (P.R.); Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA (J.D.B.).

Correspondence to: Viola Vaccarino, MD, PhD, Department of Epidemiology, Rollins School of Public Health, Emory University, 1518 Clifton Rd NE, Room 3011, Atlanta, GA 30322. E-mail: viola.vaccarino@emory.edu

Received December 21, 2018; accepted April 2, 2019.

© 2019 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

Clinical Perspective

What Is New?

- Among patients with coronary artery disease, women with higher psychological distress have a significantly higher incidence of subsequent cardiovascular events.
- This association is not observed in men and is independent of coronary artery disease risk factors and indicators of coronary artery disease severity.

What Are the Clinical Implications?

- Women with coronary artery disease should be recognized as a vulnerable group toward the effect of psychological stress on adverse outcomes.
- Consideration should be given to incorporating psychological distress measures in the assessment of patients with coronary disease, especially women.

derived using a summation score of individual symptoms scales, and future incident cardiovascular events, in 695 individuals with preexisting, stable CAD. Our composite measure integrated symptoms of depression, PTSD, anxiety, anger, hostility, and perceived stress. A similar composite measure of psychological distress was recently developed in stable CAD patients and found to be modifiable.¹¹ We also explored a possible effect modification by sex, given emerging data suggesting that women may be more vulnerable to the effects of psychological stress on CVD risk than men.¹²

Methods

Study Sample

The data that support the findings of this study are available from the corresponding author upon reasonable request. Between June 2011 and October 2014, we enrolled 695 individuals with stable CAD from Emory University–affiliated hospitals and clinics for the Mental Stress Ischemia: Prognosis and Genetic Influences Study. This research was approved by the Emory University Institutional Review Board, and all participants provided informed consent. A detailed protocol with inclusion and exclusion criteria has been previously described.¹³ Briefly, subjects between ages 30 and 80 years were enrolled if they had significant history of CAD during their lifetime (previous myocardial infarction [MI], bypass surgery or percutaneous intervention, positive nuclear scan/exercise stress test, angiographically proven major coronary vessel disease, or abnormal coronary ultrasound). Subjects were excluded if they had a history of unstable angina or acute MI within the previous week of enrollment, severe comorbid medical or psychiatric disorders, uncontrolled

hypertension, pregnancy or breastfeeding, chronic inflammatory disorders, organ transplant, or were receiving dialysis.

Cardiovascular Events Assessment

Each person was followed for a maximum of 36 months after the baseline visit. Individuals were examined in person at 12 and 24 months in the Emory University clinic and queried by telephone at 6 and 36 months. At each follow-up time, research staff queried participants regarding occurrence of hospitalizations, cardiac procedures, and/or cardiac events. If individuals reported such events, study coordinators contacted their physicians or admitting hospitals and obtained medical records for those hospitalizations. If the patient did not come back for the in-person clinic visit, information was obtained by telephone regarding their current status and occurrence of intervening events. For all patients lost to follow-up, a National Death Index search was made, in addition to Social Security and Medicare list searches. For patients who died, a member of their immediate family was interviewed by telephone about the cause of death. We also queried electronic health records to capture any missed cardiovascular events. A total of 8 participants were lost to follow-up.

Our main end point in this study was a composite outcome of cardiovascular death (cardiac death or death attributed to stroke or congestive heart failure), cardiac arrest, nonfatal MI, nonfatal stroke, congestive heart failure, or unstable angina. All of the events were adjudicated by a team of study cardiologists (A.S., P.R., and A.Q.).

Assessment of Psychological Distress

Our global distress measure integrated established symptoms scales measuring psychological characteristics or symptoms with known association with cardiovascular disease and that were previously used in a composite measure developed by Blumenthal et al.¹¹ These included symptoms of depression, anxiety, anger, and perceived general stress. To these we added symptoms of posttraumatic stress disorder (PTSD) and hostility, given their recognized importance for cardiovascular risk.^{8,14}

We assessed depressive symptoms using the Beck Depression Inventory-II, a 21-item self-administered scale.¹⁵ Given that symptom dimensions of the Beck Depression Inventory may differ in their association with cardiovascular outcomes,¹⁶ we calculated 2 separate subscales: negative affect (8 items) and somatic symptoms (13 items).¹⁵ PTSD symptoms were assessed using the PTSD Symptom Checklist, civilian version, a 17-item scale.¹⁷ Trait anxiety was measured with the State-Trait Anxiety Inventory.¹⁸ To measure trait anger symptoms, we used the Spielberger's State-Trait Anger

Expression Inventory¹⁹; to measure hostility, we administered the Cook-Medley Hostility Scale,²⁰ and to assess general perceived stress, we used the Perceived Stress Scale.²¹

These scales were standardized and combined in a composite psychological distress index, as previously published²² and described under the Statistical Analysis section. We also performed a cluster analysis using latent class analysis (LCA),^{23,24} where we constructed a categorical latent variable through observed related variables.^{23,24} A latent construct is a variable that is not directly observed or measured, but that is constructed through observed correlated variables.^{23,24} LCA models are based on the assumption that observed indicator variables are associated with each other because of an underlying unobserved factor, rather than being directly related with each other.^{23,24} Using structural equation modeling, LCA creates a categorical latent variable

based on the designated observed indicators through maximum likelihood estimation.^{23,24} Our primary objective for using LCA was to identify specific psychological phenotypes in our study sample (ie, specific combinations of psychological characteristics or symptoms), and whether these psychological characteristics are associated with CVD outcomes. We have used this same approach in a recent publication.²²

Other Study Measures

We used validated instruments to collect demographic, behavioral, social, and health status data. Race was self-reported and classified as black versus nonblack. Socioeconomic status was assessed using educational level (categorized as \leq high school or $>$ high school graduation); smoking status was categorized into current smokers or nonsmokers.

Table 1. Descriptive Characteristics of the Study Population According to Quartiles of Psychological Distress Score (Summed Z-Score)

Variables	Quartile 1 (Low Symptoms) (N=167)	Quartile 2 (Mild Symptoms) (N=166)	Quartile 3 (Moderate Symptoms) (N=164)	Quartile 4 (High Symptoms) (N=165)	Total Population (N=662)
Demographic factors					
Age, y, mean (SD)*	66 (8)	65 (8)	62 (9)	59 (9)	63 (9)
Women, N (%)*	39 (23)	38 (23)	47 (29)	61 (37)	185 (28)
Black, N (%)*	38 (23)	39 (23)	49 (30)	71 (43)	197 (30)
Education \leq high-school, N (%)	28 (17)	39 (23)	47 (29)	53 (32)	167 (25)
Lifestyle factors and medical history					
Current smokers, N (%)*	11 (7)	21 (13)	28 (17)	34 (21)	94 (14)
Hypertension, N (%)	123 (74)	131 (79)	124 (76)	127 (77)	505 (76)
Dyslipidemia, N (%)	130 (78)	143 (86)	133 (81)	135 (82)	541 (82)
Diabetes mellitus, N (%)	45 (27)	55 (33)	56 (34)	58 (35)	214 (32)
BMI, mean (SD)*	28 (4)	30 (5)	30 (6)	31 (6)	30 (5)
Previous MI, N (%)	62 (37)	54 (32)	59 (35)	72 (44)	247 (37)
History of heart failure, N (%)	16 (10)	22 (13)	22 (13)	32 (19)	92 (14)
Previous revascularization, N (%)	127 (76)	123 (74)	128 (78)	131 (79)	509 (77)
Ejection fraction in %, mean (SD)	68 (14)	69 (14)	67 (13)	69 (14)	69 (14)
CAD \geq 70% stenosis, N (%) [†]	133 (85)	129 (88)	113 (81)	112 (83)	487 (84)
Current medications					
Statins, N (%)	140 (84)	140 (84)	146 (89)	139 (85)	565 (86)
Beta-blockers, N (%)*	106 (64)	125 (75)	129 (79)	132 (80)	492 (74)
ACE inhibitors, N (%)	79 (47)	75 (45)	67 (41)	78 (48)	299 (45)
Aspirin, N (%)	146 (87)	145 (87)	144 (87)	134 (81)	569 (86)
Antidepressants, N (%)*	16 (10)	27 (16)	47 (28)	61 (37)	151 (23)
Anxiolytics, N (%)	8 (5)	13 (8)	18 (11)	16 (10)	55 (8)

ACE indicates angiotensin-converting enzyme; BMI, indicates body mass index; CAD, coronary artery disease; MI, myocardial infarction.

* $P<0.05$.

[†]CAD severity based on coronary angiography results before revascularization procedures (if any); 85 observations missing.

Table 2. Descriptive Characteristics of the Study Population According to Sex

Variables	Men (N=477)	Women (N=185)	Total Population (N=662)
Demographic factors			
Age, y, mean (SD)	63 (9)	63 (9)	63 (9)
Black, N (%) [*]	118 (25)	79 (43)	197 (30)
Education ≤high school, N (%)	116 (24)	51 (28)	167 (25)
Lifestyle factors and medical history			
Current smokers, N (%)	66 (14)	28 (15)	94 (14)
Hypertension, N (%)	359 (75)	146 (79)	505 (76)
Dyslipidemia, N (%)	397 (83)	144 (78)	541 (82)
Diabetes mellitus, N (%)	144 (30)	70 (38)	214 (32)
BMI, mean (SD)	29 (5)	30 (6)	30 (5)
Previous MI, N (%)	176 (37)	71 (38)	247 (37)
History of heart failure, N (%)	63 (13)	29 (16)	92 (14)
Previous revascularization, N (%)	364 (76)	145 (78)	509 (77)
Ejection fraction in %, mean (SD) [*]	66 (12)	74 (14)	69 (14)
CAD ≥70% stenosis, N (%) [†]	356 (85)	131 (82)	487 (84)
Current medications			
Statins, N (%)	411 (86)	154 (84)	565 (86)
Beta-blockers, N (%)	349 (73)	143 (77)	492 (74)
ACE inhibitors, N (%) [*]	234 (49)	65 (35)	299 (45)
Aspirin, N (%)	416 (87)	153 (83)	569 (86)
Antidepressants, N (%) [*]	91 (19)	60 (32)	151 (23)
Anxiolytics, N (%)	36 (8)	19 (10)	55 (8)

ACE indicates angiotensin-converting enzyme; BMI, body mass index; CAD, coronary artery disease; MI, myocardial infarction.

^{*}P<0.05.

[†]CAD severity based on coronary angiography results before revascularization procedures (if any); 85 observations missing.

Hypertension, hyperlipidemia, and diabetes mellitus were ascertained by research staff during the clinic visit through a detailed medical history. Angiographic data and left ventricular ejection fraction were obtained from the most recent coronary angiogram documented in the patient's medical record. CAD severity was quantified using a cutoff of 70% blockage in any major arteries.

Statistical Analysis

We converted each psychological symptom scale into a Z-score variable by subtracting the mean of each scale from each individual's reported score and then dividing this by the SD of each scale. We then summed these individual Z-scores (a total of 7 Z-scores, corresponding to 7 symptom scales) to

Table 3. Numbers and Percentages of Patients Who Developed Cardiovascular Outcomes, According to Sex

Variables	Men (N=477)	Women (N=185)	Total Population (N=662)
Total cardiovascular events, N (%) [*]	82 (17)	38 (21)	120 (18)
Cardiovascular death, N (%)	8 (2)	1 (1)	9 (1)
Cardiac arrest, N (%)	5 (1)	1 (1)	6 (1)
Myocardial infarction, N (%)	18 (4)	8 (4)	26 (4)
Stroke, N (%)	7 (1)	3 (2)	10 (2)
Heart failure, N (%)	19 (4)	6 (3)	25 (4)
Unstable angina, N (%)	46 (10)	25 (14)	71 (11)

^{*}Individual events do not sum up to total events because of overlap (same individuals having multiple events during follow-up).

derive a composite psychological distress index. We compared subject characteristics according to quartiles of the psychological distress index, using either the ANOVA test for normally distributed variables or the chi-square test for categorical variables. We also compared baseline characteristics according to the presence of CVD events and by sex. For our main analysis, we performed multivariable Cox proportional hazard regression models with the composite CVD end point as the outcome and the psychological distress

Table 4. Association of Psychological Distress Indicators With Future Cardiovascular Outcomes in the Overall Population.

Exposure Comparison	Full Sample: Unadjusted HR (95% CI)	Full Sample: Adjusted HR (95% CI)
Composite psychological distress index (summed Z-scores)		
Continuous Z-score	1.19 (1.00–1.41)	1.03 (0.86–1.24)
Quartile 1 (low)	Reference	Reference
Quartile 2 (mild)	1.22 (0.73–2.06)	1.09 (0.63–1.87)
Quartile 3 (moderate)	1.01 (0.59–1.75)	0.85 (0.48–1.50)
Quartile 4 (high)	1.53 (0.93–2.52)	1.03 (0.60–1.78)
Latent class analysis (cluster analysis)		
LCA class 1 (low)	Reference	Reference
LCA class 2 (mild)	0.49 (0.26–0.91)	0.54 (0.29–1.00)
LCA class 3 (moderate)	0.72 (0.47–1.11)	0.64 (0.41–1.01)
LCA class 4 (high)	1.38 (0.83–2.30)	1.04 (0.61–1.78)

HR represents estimated increase in future cardiovascular disease events hazard when comparing low symptoms (reference) to upper quartiles/LCA classes (mild, moderate, and high symptoms). Results adjusted for age, sex, race, education status, body mass index, smoking, hypertension, diabetes mellitus, dyslipidemia, previous myocardial infarction, heart failure, and past revascularization. HR, hazard ratio; LCA, latent class analysis.

indicator as the main predictor variable. For these analyses, the end of the follow-up was considered as either the end date of the study (follow-up to 36 months) for patients who did not experience the end point or the date of occurrence of the study end point, or death, or loss to follow-up. We also checked whether the proportional hazard assumption was met in each of our individual models. We adjusted for a priori chosen covariates, which included sociodemographic characteristics (age, sex, race, and education less than or equal to high school education), CAD risk factors, and severity indicators (smoking status, hypertension, dyslipidemia, diabetes mellitus, body mass index, history of MI, previous revascularization, and history of congestive heart failure). For women-specific models, we also adjusted for hormone replacement therapy use. In addition, there were no differences by psychological distress level or by sex in most of these variables. However, we ran a final model with these variables included, to examine whether results changed. We

performed LCA using Latent Gold software,²⁵ and model fit (ie, the minimum number of latent classes needed to get the best fit of the maximum likelihood) was assessed using established criteria.^{23,24} We performed similar analyses as above with LCA-derived categorical variable too. In separate models, we explored sex as an effect modifier for the association between psychological distress and CVD events. We used SAS software (version 9.3; SAS Institute Inc., Cary, NC) for the analysis, with an alpha level of 0.05 for statistical significance.

Results

Sample Characteristics

Thirty-three subjects of the total of 695 had missing information on either exposure or outcome, leaving an analytical sample size of 662. Mean age of the study

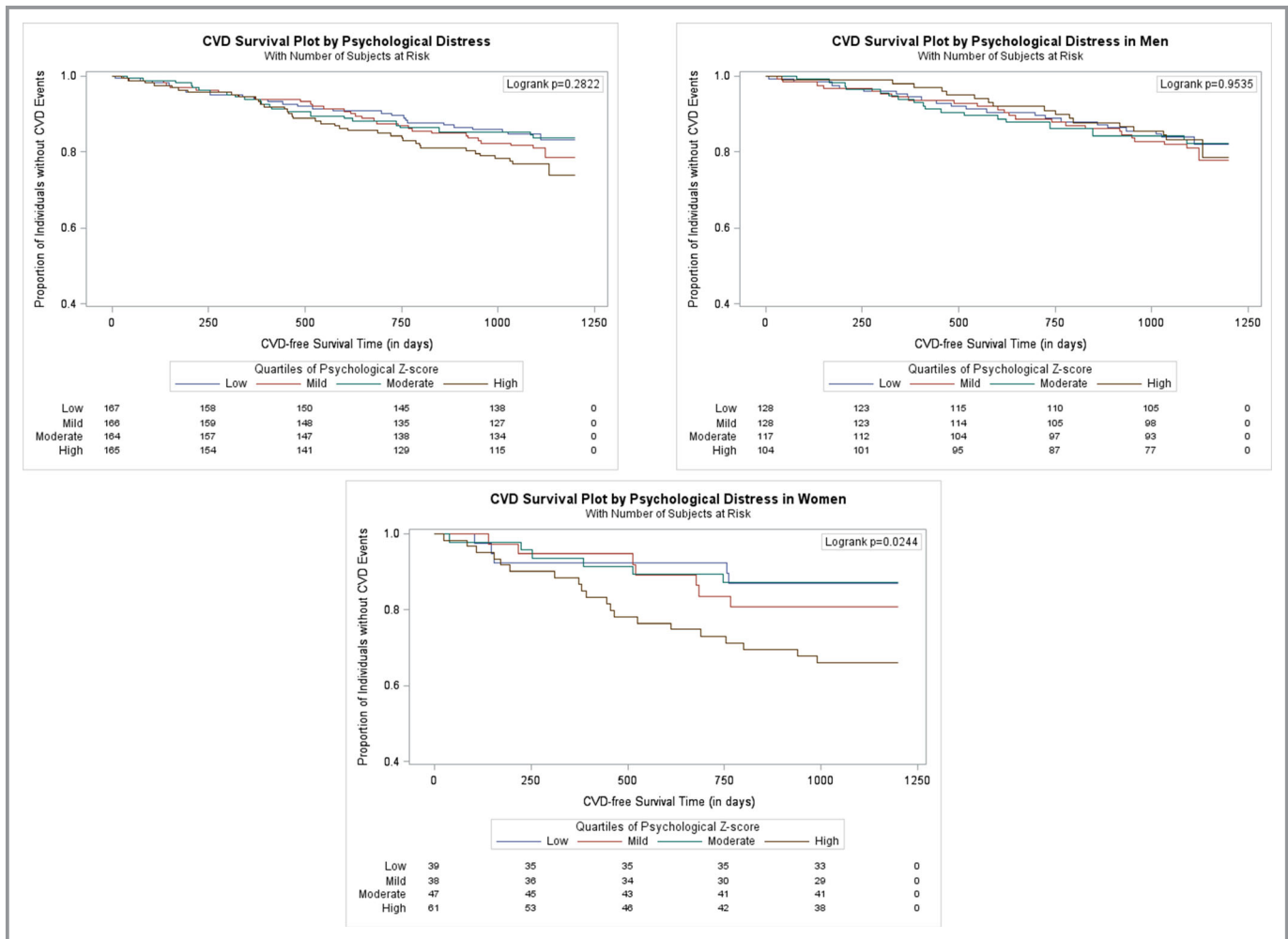


Figure. Cardiovascular survival by psychological distress: (1) overall population, (2) men, and (3) women. CVD indicates cardiovascular disease.

Table 5. Association of Psychological Distress Indicators With Future Cardiovascular Outcomes, According to Sex

Exposure Comparison	Men: Adjusted HR (95% CI)	Women: Adjusted HR (95% CI)	P Value for Sex Interaction
Composite psychological distress index (summed Z-scores)			
Continuous Z-score	0.85 (0.66–1.08)	1.44 (1.09–1.92)	0.004
Quartile 1 (low)	Reference	Reference	0.03
Quartile 2 (mild)	1.09 (0.60–1.99)	1.46 (0.46–4.60)	
Quartile 3 (moderate)	0.96 (0.51–1.80)	0.85 (0.26–2.81)	
Quartile 4 (high)	0.74 (0.38–1.46)	2.70 (1.00–7.30)	
Latent class analysis (cluster analysis)			
LCA class 1 (low)	Reference	Reference	0.009
LCA class 2 (mild)	0.38 (0.18–0.80)	1.61 (0.50–5.26)	
LCA class 3 (moderate)	0.57 (0.33–0.97)	1.00 (0.43–2.37)	
LCA class 4 (high)	0.57 (0.26–1.24)	2.71 (1.12–6.49)	

HR: represents estimated increase in future cardiovascular disease events hazard when comparing low symptoms (reference) to upper quartiles/LCA classes (mild, moderate, and high symptoms). Results adjusted for age, sex, race, education status, body mass index, smoking, hypertension, diabetes mellitus, dyslipidemia, previous myocardial infarction, heart failure, past revascularization, and hormone replacement therapy (for women). HR indicates hazard ratio; LCA, latent class analysis.

population was 63 years (SD, 9 years), 185 (28%) were women, 197 (30%) were blacks, and 167 (25%) had less than or equal to high school education (Table 1). As expected, the prevalence of cardiovascular risk factors was high in this population, including hypertension (76%), dyslipidemia (82%), and type 2 diabetes mellitus (32%). Furthermore, 37% had a previous MI, and 77% had a previous revascularization procedure.

The population mean of the composite psychological distress index was 0 (SD=5.3). Subjects with higher psychological distress (quartile 4=high symptoms) were younger (59 years in quartile 4 versus 66 years in quartile 1) and more likely to be female and black (Table 1). Among lifestyle and medical history factors, only body mass index and current smoking were significantly different according to psychological distress level, with patients in higher symptom quartiles showing greater body mass index and a higher prevalence of smoking. None of the CAD severity indicators, like history of MI, heart failure, previous revascularization, and significant CAD stenosis, were statistically different according to psychological distress level. Medication use

was similar across the groups, except for beta-blockers and antidepressants, which were more common in higher symptoms quartiles. When patient characteristics were examined by sex, women were more likely to be black and had a higher ejection fraction, whereas all other cardiovascular risk factors and severity indicators were similar between men and women. Among medications, women had lower prescriptions for angiotensin-converting enzyme inhibitors and higher prescriptions for antidepressants (Table 2).

LCA classified the study population into 4 classes, with overall excellent gradation of symptoms across classes, except for some similarity between classes 1 and 2. Details are presented in a previous publication.²²

Association With CVD Outcomes

Subjects were followed for 2.8 years on average. In total, 120 (18%) subjects had cardiovascular events during follow-up and women tended to have a higher incidence of CVD events than men (21% versus 17%; Table 3). The majority of events were hospitalizations for unstable angina (N=71; 11%), followed by nonfatal MI and congestive heart failure (4% each).

In the overall sample, there was no association between the psychological distress indicator (either the summed Z-score or quartiles of summed Z-score) and future CVD outcomes (Table 4; Figure). However, a significant interaction by sex was noted ($P=0.004$ for sex \times summed Z-score interaction). In women, higher psychological distress was associated with a higher risk of CVD events: Each SD increase in the summed Z-score was associated with 1.44 times hazard of CVD events (95% CI, 1.09–1.92). Women with higher psychological distress (quartile 4) had an estimated 33% events at the end of 3 years, as compared with 13% events in women with low distress (quartile 1; Figure). As compared with quartile 1, quartile 4 was associated with an adjusted 2.70 higher hazard of cardiovascular events (95% CI, 1.00–7.30) among women (Table 5). Among men, there were no differences in cardiovascular outcomes by psychological distress level, and interaction between sex and psychological distress quartiles was significant ($P=0.03$). Analysis done with LCA-derived classes showed similar results (Table 5). When we performed these analyses using individual scales instead of the summed Z-score variable, we found similar results; with the exception for the anger-trait score, all the psychological measures were associated with CVD events in women, but not in men (Table 6).

Discussion

In individuals with preexisting, stable CAD, women with higher psychological distress, defined as a composite measure of

Table 6. Association of Individual Psychological Indicators With the CVD Events Composite End Point, According to Sex

Exposure Comparison	Full Sample: Adjusted HR (95% CI)	Men: Adjusted HR (95% CI)	Women: Adjusted HR (95% CI)	P Value for Sex Interaction
CVD events (cardiovascular death/cardiac arrest/MI/stroke/CHF/UA)				
BDI-somatic score	1.13 (0.96–1.34)	0.94 (0.75–1.18)	1.45 (1.11–1.89)	0.01
BDI-negative affect score	1.08 (0.92–1.28)	0.91 (0.72–1.15)	1.47 (1.13–1.90)	0.007
PCL score	1.18 (1.01–1.38)	1.00 (0.79–1.26)	1.45 (1.14–1.83)	0.03
STAI Anxiety-Trait score	1.06 (0.89–1.28)	0.88 (0.69–1.12)	1.41 (1.04–1.91)	0.01
STAXI Anger-Trait score	1.08 (0.91–1.28)	0.98 (0.79–1.22)	1.25 (0.94–1.68)	0.19
CMHS hostility score	1.00 (0.82–1.18)	0.83 (0.66–1.04)	1.39 (1.02–1.90)	0.007
Perceived-stress score	0.99 (0.89–1.26)	0.78 (0.61–1.00)	1.36 (1.00–1.86)	0.005

Results adjusted for age, sex (in full sample), race, education status, body mass index, smoking, hypertension, diabetes mellitus, dyslipidemia, previous myocardial infarction, heart failure, past revascularization, and hormone replacement therapy (for women). BDI indicates Beck Depression Inventory; CMHS, Cook–Medley Hostility Score; CVD, cardiovascular disease; HR, represents estimated increased hazard in future CVD events with each standard deviation increase in the individual psychosocial scale; PCL, PTSD Symptom Checklist (Civilian); STAI, State-Trait Anxiety Inventory; STAXI, State-Trait Anger Expression Inventory.

psychological symptom scales (depression, PTSD, anxiety, anger, hostility, and perceived stress) showed significantly higher incidence of CVD events, whereas there was no such association found in men. The sex difference in the association was robust to the adjustment of sociodemographic factors and even traditional cardiovascular risk factors and clinical disease severity indicators.

Although the overall relationship between psychological distress indicators, like depression and future cardiovascular events, is fairly established,^{4,5,26} previous literature regarding sex differences in the association between psychological distress and cardiovascular disease is mixed.^{12,27} However, 2 recent nationally representative studies, 1 from the United States using the National Health and Nutrition Examination Survey²⁸ and the second from Canada using the National Population Health Survey,²⁹ have shown an association of depression and other psychological factors with CVD in women and not in men. Also, the large, 52-countries Interheart study found a differential effect of the impact of psychological distress on MI by sex.³⁰ In this study, a composite measure of psychological symptoms yielded a 40% population-attributable risk for acute MI in women, whereas for men the same attributable risk was only 25%. Our results of an association between a composite psychological distress measure and future cardiovascular events in women further add to this evolving literature, and highlight the potential advantage of measuring an individual's psychological distress as a whole.

The proposed mechanisms through which psychological distress affects CVD are multifactorial and can be grouped in 2 broad categories of behavioral factors (increased smoking, unhealthy diet, sedentary lifestyle, and medication nonadherence) and biological mechanisms, mainly through autonomic nervous system dysfunction leading to lower heart-rate

variability, increased sympathetic nervous system activation and inflammatory activity, as well as endothelial and platelet abnormalities.³¹ Women have been shown to be more prone to the postulated ill effects of psychological stress on biological mechanisms like increased inflammatory activity,³² increased platelet activation,³³ and lower heart-rate variability.³⁴ However, the effect of these potential mediators on the association between psychological distress and CVD events needs to be explored further.

Potentially, the association between psychological distress and future CVD events among women with preexisting CAD could be attributed to “reverse-causation,” that is, higher baseline CVD burden can lead to higher psychological symptoms and to more future events. However, there were no sex differences in these factors, and the sex differences in the association between psychological distress and future CVD events persisted even after adjusting for validated indicators of CAD severity like history of MI and heart failure.

Our study has several strengths. To the best of our knowledge, this is the first study to investigate the association between a comprehensive measure of psychological distress and future cardiovascular events. Our study population was well characterized clinically and with thorough exposure assessment of psychological factors across multiple domains. Also, cardiovascular events and causes of death were adjudicated by experienced cardiologists using an established protocol. Our study, however, is not without limitations. Measurement bias for the exposure (psychological distress) is an important issue, given that all these factors are self-reported, and can be an explanation for the lack of association between distress and CVD events in men, given that men might under-report depressive symptoms, as compared with women.³⁵ Also, because we studied individuals with

established CAD, we cannot exclude a possible collider bias,³⁶ and traditional confounding adjustment may not be sufficient to correct for this bias. We also could not account for the time lag between the last CAD event and the study baseline visit. Finally, the number of events for specific CVD events was small, precluding the ability to analyze these events separately.

In conclusion, we found that, among CAD patients, a higher level of psychological distress, measured as a composite measure of a variety of symptom scales, is associated with higher cardiovascular events in women, but not in men. These findings suggest that the value of a regular assessment of psychological measures in cardiovascular practices, especially for women, should be considered. Equally important should be the exploration of treatment modalities for ameliorating psychological distress in patients with CAD,³⁷ especially among women, including holistic approaches, like meditation or relaxation techniques, in addition to traditional medical therapy.

Sources of Funding

This work was supported by the NIH, through the following grants: P01 HL101398, R01 HL109413, R01HL109413-02S1, R01HL125246, K24HL077506, K24 MH076955, UL1TR000454, KL2TR000455, K23HL127251, and T32HL130025A.

Disclosures

None.

References

- Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62:617–627.
- National Institute of Mental Health (NIMH). Mental health information. Bethesda, MD: NIMH; 2013.
- Strike PC, Steptoe A. Psychosocial factors in the development of coronary artery disease. *Prog Cardiovasc Dis*. 2004;46:337–347.
- Lichtman JH, Froelicher ES, Blumenthal JA, Carney RM, Doering LV, Frasure-Smith N, Freedland KE, Jaffe AS, Leifheit-Limson EC, Sheps DS, Vaccarino V, Wulsin L; American Heart Association Statistics Committee of the Council on Epidemiology and Prevention and the Council on Cardiovascular and Stroke Nursing. Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: systematic review and recommendations: a scientific statement from the American Heart Association. *Circulation*. 2014;129:1350–1369.
- Carney RM, Freedland KE. Depression and coronary heart disease. *Nat Rev Cardiol*. 2017;14:145–155.
- Edmondson D, Kronish IM, Shaffer JA, Falzon L, Burg MM. Posttraumatic stress disorder and risk for coronary heart disease: a meta-analytic review. *Am Heart J*. 2013;166:806–814.
- Batelaan NM, Seldenrijk A, Bot M, van Balkom AJ, Penninx BW. Anxiety and new onset of cardiovascular disease: critical review and meta-analysis. *Br J Psychiatry*. 2016;208:223–231.
- Chida Y, Steptoe A. The association of anger and hostility with future coronary heart disease: a meta-analytic review of prospective evidence. *J Am Coll Cardiol*. 2009;53:936–946.
- Richardson S, Shaffer JA, Falzon L, Krupka D, Davidson KW, Edmondson D. Meta-analysis of perceived stress and its association with incident coronary heart disease. *Am J Cardiol*. 2012;110:1711–1716.
- Suls J, Bunde J. Anger, anxiety, and depression as risk factors for cardiovascular disease: the problems and implications of overlapping affective dispositions. *Psychol Bull*. 2005;131:260–300.
- Blumenthal JA, Sherwood A, Smith PJ, Watkins L, Mabe S, Kraus WE, Ingle K, Miller P, Hinderliter A. Enhancing cardiac rehabilitation with stress management training: a randomized, clinical efficacy trial. *Circulation*. 2016;133:1341–1350.
- Vaccarino V, Bremner JD. Behavioral, emotional and neurobiological determinants of coronary heart disease risk in women. *Neurosci Biobehav Rev*. 2017;74:297–309.
- Hammadah M, Al Mheid I, Wilmot K, Ramadan R, Shah AJ, Sun Y, Pearce B, Garcia EV, Kutner M, Bremner JD, Esteves F, Raggi P, Sheps DS, Vaccarino V, Quyyumi AA. The mental stress ischemia prognosis study: objectives, study design, and prevalence of inducible ischemia. *Psychosom Med*. 2017;79:311–317.
- Edmondson D, von Kanel R. Post-traumatic stress disorder and cardiovascular disease. *Lancet Psychiatry*. 2017;4:320–329.
- Beck AT, Steer RA, Brown GK. *BDI-II. Beck Depression Inventory*. 2nd ed. San Antonio, TX: The Psychological Corporation; 1996.
- Carney RM, Freedland KE. Are somatic symptoms of depression better predictors of cardiac events than cognitive symptoms in coronary heart disease? *Psychosom Med*. 2012;74:33–38.
- Blanchard EB, Jones-Alexander J, Buckley TC, Forneris CA. Psychometric properties of the PTSD checklist (PCL). *Behav Res Ther*. 1996;34:669–673.
- Spielberger CD, Gorsuch RL, Lushene RE. *State-Trait Anxiety (STAI) Manual*. Palo Alto, CA: Consulting Psychologists Press; 1970.
- Spielberger CD. *Professional Manual for the State-Trait Anger Expression Inventory*. Research ed. Tampa, FL: University of South Florida; 1988.
- Cook WW, Medley DM. Proposed hostility and pharisaic-virtue scales for the MMPI. *J Appl Psychol*. 1954;38:414–418.
- Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav*. 1983;24:385–396.
- Pimple P, Hammadah M, Wilmot K, Ramadan R, Al Mheid I, Levantsevych O, Sullivan S, Lima BB, Kim JH, Garcia EV, Nye J, Shah AJ, Ward L, Raggi P, Bremner JD, Hanfelt J, Lewis TT, Quyyumi AA, Vaccarino V. The relation of psychosocial distress with myocardial perfusion and stress-induced myocardial ischemia. *Psychosom Med*. 2019 Jan 23. doi: 10.1097/psy.0000000000000674. [Epub ahead of print].
- Hagenaars JA, McCutcheon AL. *Applied Latent Class Analysis*. New York, NY: Cambridge University Press; 2002.
- Collins LM, Lanza ST. *Latent Class and Latent Transition Analysis: With Applications in the Social, Behavioral, and Health Sciences*. Hoboken, New Jersey: John Wiley & Sons; 2013.
- Vermunt JK, Magidson J. *Technical Guide for Latent Gold 5.0: Basic, Advanced, and Syntax*. Belmont, MA: Statistical Innovations; 2013.
- Lichtman JH, Bigger JT Jr, Blumenthal JA, Frasure-Smith N, Kaufmann PG, Lesperance F, Mark DB, Sheps DS, Taylor CB, Froelicher ES. Depression and coronary heart disease: recommendations for screening, referral, and treatment: a science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Psychiatric Association. *Circulation*. 2008;118:1768–1775.
- Gan Y, Gong Y, Tong X, Sun H, Cong Y, Dong X, Wang Y, Xu X, Yin X, Deng J, Li L, Cao S, Lu Z. Depression and the risk of coronary heart disease: a meta-analysis of prospective cohort studies. *BMC Psychiatry*. 2014;14:371.
- Shah AJ, Veledar E, Hong Y, Bremner JD, Vaccarino V. Depression and history of attempted suicide as risk factors for heart disease mortality in young individuals. *Arch Gen Psychiatry*. 2011;68:1135–1142.
- Garad Y, Maximova K, MacKinnon N, McGrath JJ, Kozyrskyj AL, Colman I. Sex-specific differences in the association between childhood adversity and cardiovascular disease in adulthood: evidence from a national cohort study. *Can J Cardiol*. 2017;33:1013–1019.
- Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:937–952.
- Vaccarino V, Bremner JD. Psychiatric and behavioral aspects of cardiovascular disease. In: Zipes DP, Libby P, Bonow RO, Mann DL, Tomaselli GF, eds. *Braunwald's heart disease - a textbook of cardiovascular medicine, 11th ed*. Philadelphia, PA: Elsevier-Saunders; 2019:1879–1889.
- Rooks CR, Ibeanu I, Shah A, Pimple P, Murrah N, Shallenberger L, Pace T, Douglas Bremner J, Raggi P, Vaccarino V. Young women post-MI have higher

- plasma concentrations of interleukin-6 before and after stress testing. *Brain Behav Immun*. 2016;51:92–98.
33. Samad Z, Boyle S, Ersboll M, Vora AN, Zhang Y, Becker RC, Williams R, Kuhn C, Ortel TL, Rogers JG, O'Connor CM, Velazquez EJ, Jiang W. Sex differences in platelet reactivity and cardiovascular and psychological response to mental stress in patients with stable ischemic heart disease: insights from the REMIT study. *J Am Coll Cardiol*. 2014;64:1669–1678.
 34. Ohira T, Diez Roux AV, Prineas RJ, Kizilbash MA, Carnethon MR, Folsom AR. Associations of psychosocial factors with heart rate and its short-term variability: Multi-Ethnic Study of Atherosclerosis. *Psychosom Med*. 2008;70:141–146.
 35. Sigmon ST, Pells JJ, Boulard NE, Whitcomb-Smith S, Edenfield TM, Hermann BA, LaMattina SM, Scharrel JG, Kubik E. Gender differences in self-reports of depression: the response bias hypothesis revisited. *Sex Roles*. 2005;53:401–411.
 36. Flanders WD, Eldridge RC, McClellan W. A nearly unavoidable mechanism for collider bias with index-event studies. *Epidemiology*. 2014;25:762–764.
 37. Gok Metin Z, Ejem D, Dionne-Odom JN, Turkman Y, Salvador C, Pamboukian S, Bakitas M. Mind-body interventions for individuals with heart failure: a systematic review of randomized trials. *J Card Fail*. 2018;24:186–201.