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ORIGINAL RESEARCH

ISCHEMIC HEART DISEASE

Psychological Distress and the Risk of Adverse Cardiovascular Outcomes in Patients With Coronary Heart Disease

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ABSTRACT

BACKGROUND Psychological distress is a recognized risk factor in patients with coronary heart disease (CHD), but its clinical significance is unclear.

OBJECTIVES The purpose of this study was to determine if an index of psychological distress is independently associated with adverse outcomes and significantly contributes to risk prediction.

METHODS Pooled analysis of 2 prospective cohort studies of patients with stable CHD (N = 891). A psychological distress score was constructed using measures of depression, anxiety, anger, perceived stress, and post-traumatic stress disorder, measured at baseline. The study endpoint included cardiovascular death or first or recurrent nonfatal myocardial infarction or hospitalization for heart failure at 5.9 years.

RESULTS In both cohorts, first and recurrent events occurred more often among those in the highest tertile of distress score than those in the lowest tertile. After combining the 2 cohorts, compared with the lowest tertile, the hazards ratio for having a distress score in the highest tertile was 2.27 (95% CI: 1.69-3.06), and for the middle tertile, it was 1.52 (95% CI: 1.10-2.08). Adjustment for demographics and clinical risk factors only slightly weakened the associations. When the distress score was added to a traditional clinical risk model, C-statistic, net reclassification index, and integrative discrimination index all significantly improved.

CONCLUSIONS Among patients with CHD, a composite measure of psychological distress was significantly associated with an increased risk of adverse events and significantly improved risk prediction. (JACC Adv 2024;3:100794) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

CHD = coronary heart disease

MI = myocardial infarction

PTSD = post-traumatic stress disorder

Mental health disorders in the U.S. population are a growing concern. In 2020, an estimated 21% of U.S. adults aged 18 years or older had a diagnosed mental illness, with mood and anxiety disorders being especially common.[1] These prevalent mental conditions are often a consequence of exposure to psychological stress or trauma, similar to post-traumatic stress disorder (PTSD), and all tend to be comorbid.[2]

Associations of common mental disorders and of related measures of psychological distress (eg, scales for depression, anxiety, PTSD, and perceived general stress) with cardiac events and mortality have been reported extensively and are especially robust among individuals with pre-existing coronary heart disease (CHD).[3,4] However, whether such measures provide incremental prognostic information beyond traditional risk indicators in patients with CHD has not been rigorously assessed. Furthermore, despite the known inter-relations among these psychological constructs, studies have mostly treated each of these factors as independent exposures. A combined measure of psychological distress may better capture multiple dimensions of maladaptive psychological functioning and therefore may have more face validity and more potential for translation to the clinical setting.

In 2 parallel samples of patients with stable CHD, we sought to investigate whether a composite measure of psychological distress, which incorporates validated brief scales of symptoms of depression, anxiety, anger, perceived general stress, and PTSD, is associated with major adverse cardiovascular events independent of known clinical risk indicators. We also evaluated whether this measure of psychological distress provides additional prognostic information compared with a traditional risk model.

METHODS

STUDY SAMPLE. Between June 2011 and March 2016, we enrolled individuals with stable CHD in 2 parallel studies with similar protocols, the MIPS (Mental Stress Ischemia Prognosis Study)[5] and the MIMS2 (Myocardial Infarction and Mental Stress Study 2).[6] Both studies recruited patients with stable CHD from hospitals and clinics affiliated with Emory University and shared protocols, staff, facilities, and equipment. For MIPS, patients were eligible to participate if they were 30 to 79 years of age, nonhospitalized and hemodynamically stable, with a documented history of CHD, defined as any of the following: an abnormal coronary angiogram demonstrating evidence of atherosclerosis, previous percutaneous or surgical coronary revascularization, a history of myocardial infarction (MI), or a positive nuclear stress test.[5] For MIMS2, patients were included if they were hospitalized for a verified MI within the past 8 months and were 18 to 60 years of age at the time of the MI.[6] MIMS2 also included 50% women by design. Patients were excluded from both studies if they were pregnant, or if they had medical comorbidities expected to shorten life expectancy, such as malignancy or end-stage kidney disease, or severe psychiatric disorders such as schizophrenia likely to interfere with study assessments. Patients were also excluded if they had recent acute events or procedures (within past week).

The research protocol for both studies was approved by the Institutional Review Board of Emory University and all participants provided written informed consent.

BASELINE STUDY MEASURES. Demographic information included sex, race, age, and family income. Family income was categorized into 3 groups (<$50,000, $50,000-$100,000, and > $100,000). Body mass index (kg/m^2) was calculated as measured weight (kg) divided by the square of measured height (m). History of cardiovascular risk factors was ascertained by chart review and by standardized questionnaires and included history of smoking, diabetes mellitus, hypertension, and dyslipidemia. Clinical characteristics were abstracted from the medical records and included previous cardiovascular history and medication use (statins, aspirin, clopidogrel, beta-blockers, angiotensin-converting enzyme inhibitors, and antidepressants).

PSYCHOLOGICAL DISTRESS. To assess psychological distress, we constructed a global distress measure integrating scales of psychological characteristics with recognized validity and reliability and known association with cardiovascular disease, with similar methodology previously followed by us and others.[7-9] These were all administered at the baseline visit and included symptoms of depression, anxiety, anger, perceived general stress, and PTSD. Current depressive symptoms were assessed with the Beck Depression Inventory II, a 21-item self-administered scale.[10] PTSD symptoms were assessed using the civilian version of the PTSD Symptom Checklist, a 17-item scale.[11] State anxiety was measured with a 20-item subscale of the State-Trait Anxiety Inventory.[12] State anger was assessed with a 15-item subscale of the Spielberger's State-Trait Anger Expression Inventory[13]; and general perceived stress was assessed with the 10-item Perceived Stress Scale[14]. Within each

study, individuals were ranked on each of the 5 psychological measures; then all ranks were averaged for each participant to obtain a composite psychological distress score.[7,14] Because of this ranking methodology, the psychological distress scores were not comparable in the 2 cohorts given their different sample size. Thus, within each cohort, we computed tertiles of the ranked distress score and used these tertiles as our main exposure variable.

OUTCOMES. Participants were followed prospectively for adverse cardiovascular outcomes for a median time of 5.9 years after the baseline visit. Follow-up information was collected through patient contacts, medical record review, and by querying the Social Security Death Index. MIPS patients were contacted every 6 months for the first 3 years, and then at 5 years. MIMS2 patients were contacted at their approximate 3 and 5-year anniversary from their initial visit. If hospitalizations or procedures were reported, patients' physicians were contacted, and hospital records were obtained. Ascertained cardiovascular events included cardiovascular death, and first and recurrent MI (type 1), and heart failure hospitalizations. All events were adjudicated by consensus by study investigators (A.J.S., A.A.Q., V.V.), who were blinded to other study data. Cardiovascular death was defined as death attributable to an ischemic cardiovascular cause (fatal MI), cardiac arrhythmia (including cardiac resuscitation), or heart failure. The main endpoint of the study was a combined outcome of cardiovascular death or first or recurrent nonfatal MI or hospitalizations for heart failure. A secondary endpoint excluded heart failure and only included cardiovascular death or first/recurrent MI.

STATISTICAL ANALYSIS. Patient characteristics, including demographic, clinical, and psychological factors, were described by tertile of the psychological distress score. Next, we plotted mean cumulative function curves for the study endpoint in each cohort. Given the similarity of results in MIPS and MIMS2, we pooled the 2 cohorts to provide an overall estimate of effect, using an individual patient data meta-analysis approach with random effects to preserve the clustering within the cohorts.[15] We then used the Wei-Lin-Weissfeld model for recurrent events to derive HRs and 95% CIs for the association between psychological distress tertiles and the study endpoint.[16] Patients were censored if lost to follow-up or if they did not experience an adverse event by the end of the study period. Predefined covariates were included in a sequential fashion to the unadjusted model (Model 1) to assess the impact of covariate adjustment on the estimate for psychological distress. First, we added demographic variables, including age, sex, race, and family income (Model 2). Next, we added clinical risk factors, including body mass index, ever smoking, history of hypertension, hyperlipidemia, diabetes mellitus, myocardial infarction, revascularization, and heart failure (Model 3).

In secondary analyses, we examined whether the association of the psychological distress score tertiles with the study outcome varied according to a priori selected patient characteristics, including age ($<$60 vs $\geq$60 years), sex, race (Black vs non-Black), previous MI, history of diabetes, and history of heart failure. Furthermore, we examined the consistency of association across the individual component scales of the global distress index by examining their association with the study endpoint.

The incremental value of the psychological distress score in the prediction of adverse cardiovascular events was tested by adding this variable to a traditional clinical risk model including age, sex, race/ethnicity, body mass index, ever smoking, history of hypertension, diabetes mellitus, hyperlipidemia, and heart failure. The Harrell C statistic (ie, the area under the receiver operating characteristic curve), the category-free net reclassification improvement, and the integrated discrimination improvement were calculated as indices of risk discrimination.[17,18] Significance testing was 2-sided with a significance threshold of $P < 0.05$, and all statistical analyses were performed using Stata software, version 14.0 (StataCorp).

RESULTS

BASELINE CHARACTERISTICS. Of the total of 949 initial participants (636 in MIPS and 313 in MIMS2), 11 were lost to follow-up (5 in MIPS and 6 in MIMS2), and 47 had missing information on the main exposure, the psychological distress score (20 in MIPS and 27 in MIMS2), leaving an analytical sample size of 891 (611 from MIPS and 280 from MIMS2). Descriptive characteristics of participants by study cohort are shown in Supplemental Table 1. By design, participants in MIMS2 were younger and more often women than those in MIPS.

As expected, the mean composite psychological distress score, based on ranks, was higher in MIPS than in MIMS2 due to difference in sample size. In MIPS, the mean score was 306 $\pm$ 134, and a range of 67 to 605. In MIMS2, the mean score was 142 $\pm$ 66.4, and a range of 27 to 279. **Table 1** shows baseline

TABLE 1 Baseline Characteristics of the Pooled Cohort Stratified Based on Low (<Median) and High (≥Median) Distress Score

	Tertile 1 (Low Psychological Distress) (n = 298)	Tertile 2 (Moderate Psychological Distress) (n = 297)	Tertile 3 (Severe Psychological Distress) (n = 296)
Demographics			
Age, y	61 ± 9	60 ± 10	57 ± 9
Female	79 (26.5)	102 (34.3)	119 (40.2)
Black/African American	92 (30.9)	112 (37.7)	145 (49.0)
Family income			
<$50,000	95 (31.8)	129 (43.4)	184 (62.2)
$50,000-$100,000	191 (64.1)	147 (49.5)	93 (31.4)
>$100,000	12 (4.0)	21 (7.0)	19 (6.4)
Clinical risk factors			
Hyperlipidemia	247 (82.9)	238 (80.1)	241 (81.4)
Hypertension	223 (74.8)	222 (74.7)	239 (80.7)
Diabetes	85 (28.5)	96 (32.3)	105 (35.5)
Ever smoker	158 (53.0)	173 (58.2)	187 (63.2)
Body mass index, kg/m^2	29.2 (4.8)	30.1 (6.0)	30.8 (6.7)
History of myocardial infarction	157 (52.7)	156 (52.5)	162 (54.7)
History of heart failure	26 (8.7)	37 (12.5)	52 (17.6)
History of revascularization procedures	178 (59.7)	181 (60.9)	183 (61.8)
History of major depression	35 (11.7)	77 (25.9)	146 (49.3)
History of post-traumatic stress disorder	8 (2.6)	19 (6.4)	50 (16.8)
Medications			
Statin	258 (86.6)	247 (83.2)	256 (86.5)
Aspirin	257 (86.2)	255 (85.8)	242 (81.7)
Clopidogrel	121 (40.6)	136 (45.8)	132 (44.6)
Beta-blocker	214 (71.8)	232 (78.1)	242 (81.8)
ACEI	139 (46.6)	132 (44.4)	133 (44.9)
Antidepressants	28 (9.4)	66 (22.2)	106 (35.8)
Psychological factors			
Beck Depression Inventory II	2.8 ± 2.6	7.3 ± 4.6	18.2 ± 10.1
PTSD Symptom Checklist	19.5 ± 2.9	25.4 ± 7.2	39.6 ± 13.8
Cohen Perceived Stress Scale	6.5 ± 3.9	12.9 ± 5.2	21.0 ± 6.7
State anxiety	23.0 ± 3.8	30.1 ± 7.3	44.0 ± 10.8
State anger	15.1 ± 0.63	15.9 ± 3.2	20.7 ± 8.2

Values are mean ± SD or n (%).
ACEI = angiotensin-converting enzyme inhibitor; PTSD = post-traumatic stress disorder.

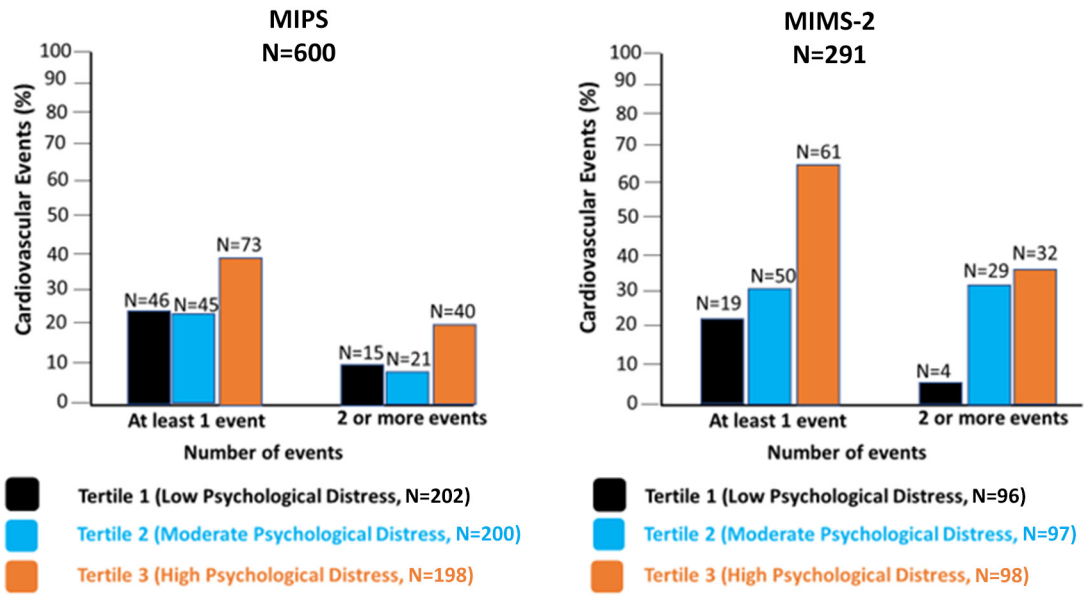
characteristics across tertiles of psychological distress score, calculated separately in the 2 cohorts. Participants in a higher tertile of distress score tertile tended to be older, more often female and Black, to have a history of heart failure, and to be taking antidepressant medications. There were no substantial differences in other clinical risk factors based on distress score category.

PSYCHOLOGICAL DISTRESS AND ADVERSE CARDIOVASCULAR OUTCOMES. The median follow-up time was 6.4 years in MIPS (IQR: 5.5-6.9 years) and 4.6 years in MIMS2 (IQR: 3.8-5.3 years), for a pooled median follow-up time of 5.9 years (IQR: 4.6-6.6 years). In MIPS, there were a total of 164 events and 76 recurrent events, and in MIMS2, 130 and 65, respectively. In both cohorts, the number of at least 1 event and of 2 or more events were highest among those in the highest psychological distress score tertile compared to other tertiles; a dose-response relationship was most prominent in MIMS2 (**Figure 1**). In MIPS, the incidence of at least 1 event was 36.9% among those with the highest psychological distress and 22.8% among those with the lowest psychological distress. Corresponding figures in MIMS2 were 62.2% and 19.8%.

In both study cohorts, as well as in the pooled sample, the cumulative incidence of adverse cardiovascular events was significantly higher in patients in the highest tertile of psychological distress than those with low psychological distress score (**Table 2**, **Figure 2**, **Central Illustration**). The unadjusted HR for the study endpoint in the MIPS cohort was 1.68 (95% CI: 1.16-2.43) comparing highest tertile distress score with lowest tertile distress score, and in the MIMS2 cohort it was 3.65 (95% CI: 1.77-7.52). After combining the 2 cohorts, the unadjusted HR in the overall sample was 2.27 (95% CI: 1.69-3.06) comparing the highest to the lowest tertile of psychological distress, and 1.52 (95% CI: 1.10-2.08) comparing the middle to the lowest tertile of psychological distress. The addition of demographic and clinical variables only slightly attenuated the associations. In the fully adjusted model, the HR for the association was 2.11 (95% CI: 1.47-2.78) and 1.45 (95% CI: 1.02-1.94) comparing the highest and the middle tertile, respectively, to the lowest tertile of psychological distress. Significant results were also obtained when we used a combined outcome of cardiovascular death or first/recurrent nonfatal MI (excluding heart failure hospitalizations). The adjusted HR comparing the highest to the lowest tertile of psychological distress was 1.32 (95% CI: 1.13-2.34, and the adjusted HR comparing the middle to the lowest tertile of psychological distress was 1.23 (95% CI: 1.11-2.03).

In analyses stratified by baseline demographic and clinical characteristics, the association was similar across strata and no significant interactions were found (Supplemental Figure 1). While all of the participants in the MIMS2 cohort had a history of previous MI, and results in the MIMS2 cohort in **Table 2** appeared more robust than in the MIPS cohort, there was no significant interaction between psychological distress score and history of previous MI (Supplemental Figure 1). When examining the individual psychological scales, all scales showed a positive association with a higher risk for the primary outcome, and the association was statistically significant for all scales except for anger (Supplemental Table 2).

FIGURE 1 Distribution of First and Recurrent Events for the Study Endpoints in Each Study Cohort by Tertiles of Psychological Distress Score



MIMS2 = Myocardial Infarction and Mental Stress Study 2; MIPS = Mental Stress Ischemia Prognosis Study.

TABLE 2 Association Between Psychological Distress Score Tertiles and the Study Endpoint (an Aggregate of Cardiovascular Death or First or Recurrent Nonfatal Myocardial Infarction or Heart Failure Hospitalization), in Each Cohort

	Tertile 1 (Low Psychological Distress)	Tertile 2 (Moderate Psychological Distress)	Tertile 3 (Severe Psychological Distress)
MIPS cohort			
Model 1	Ref	0.98 (0.57-1.68)	**1.68 (1.16-2.43)**
Model 2	Ref	0.95 (0.55-1.63)	**1.50 (1.07-2.29)**
Model 3	Ref	0.94 (0.55-1.63)	**1.47 (1.06-2.23)**
MIMS2 cohort			
Model 1	Ref	**2.80 (1.22-6.43)**	**3.65 (1.77-7.52)**
Model 2	Ref	**2.65 (1.11-6.29)**	**3.30 (1.58-6.92)**
Model 3	Ref	**2.19 (1.06-4.99)**	**2.38 (1.11-5.07)**

Values are HR (95% CI). Model 1: Unadjusted. Model 2: Adjusted for age, sex, race (Black vs non-Black), and family income. Model 3: Adjusted for Model 2 variables plus clinical risk factors, including body mass index, ever smoking, history of hypertension, hyperlipidemia, diabetes mellitus, prior myocardial infarction, prior revascularization, and heart failure. **Bold** values are statistically significant at $P < 0.05$.

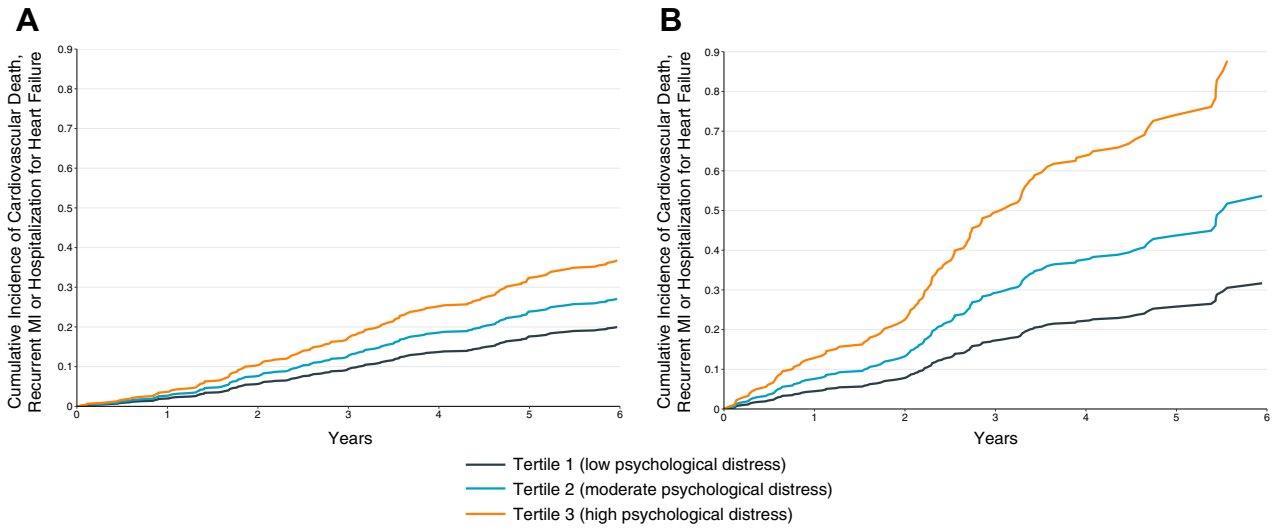
MIMS2 = Myocardial Infarction and Mental Stress Study 2; MIPS = Mental Stress Ischemia Prognosis Study.

We tested the incremental prognostic value of adding psychological distress score tertiles to a traditional clinical risk model that included baseline demographic characteristics and clinical risk indicators. With the addition of distress score tertiles, the C-statistic, the category-free net reclassification index, and the integrative discrimination index all denoted a significantly improved risk prediction of adverse cardiovascular events in comparison with the traditional risk model (Table 3). The C-statistic increased by 5% ($P < 0.01$) with the addition of the psychological distress score to the model, while the category-free net reclassification metric showed a 46% improvement in reclassification of participant risk.

DISCUSSION

In adults with stable CHD who participated in 2 parallel prospective studies, those with higher psychological distress, defined with a composite measure of scales of depression, anxiety, anger, perceived general stress, and PTSD, had a significantly higher risk of adverse cardiovascular events over a follow-up period

FIGURE 2 Cumulative Incidence of Adverse Cardiovascular Events by Tertile of Psychological Distress and Study Cohort



Cumulative incidence of the main study endpoint (an aggregate of cardiovascular death or first or recurrent nonfatal myocardial infarction or heart failure hospitalization) in the 2 study populations, MIPS (A) and MIMS2 (B), by tertiles of psychological distress score. Because of the repeated events analysis, patients were removed from the risk set at each time point only if they died or were censored. MIMS2 = Myocardial Infarction and Mental Stress Study 2; MIPS = Mental Stress Ischemia Prognosis Study.

of 5.9 years. The findings were consistent in each of the 2 cohorts, although appeared more robust in the post-MI cohort (MIMS2 study). They also applied to both first and subsequent events. In the pooled sample, those with a distress score in the highest tertile, compared with those with distress score in the lowest tertile, exhibited over 2-fold higher risk for cardiovascular events, and the risk was over 50% higher for those in the middle tertile. Demographic and clinical factors did not explain the associations, and the inclusion of psychological distress in a traditional risk model significantly improved risk prediction. Our results suggest that an evaluation of patients' psychological status with a self-reported composite measure could be of value for risk stratification and risk assessment in CHD patients.

For quite some time, psychological health has come to the fore as an important determinant of cardiovascular health.[3,4,19,20] Numerous investigations have described a link between various dimension of psychological distress, including elevated symptoms of depression, anxiety, PTSD, or perceived psychosocial stress, and cardiovascular events, both in individuals with cardiovascular disease,[3,21-24] and those without,[3,4,25-30] with effect sizes similar to traditional cardiovascular risk factors. In parallel, many mechanisms have been demonstrated through which psychological distress may affect cardiovascular outcomes in patients with CHD. These include behavioral and self-care factors (increased smoking, unhealthy eating behaviors, sedentary lifestyle, and medication nonadherence) as well as multiple biological pathways involving chronic, acute, or repeated effects of psychological stress on the autonomic nervous system, the immune and inflammatory response, endothelial function, platelet activity, and myocardial ischemia.[21,31,32]

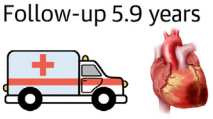
Consistent with this accumulating evidence, professional societies have issued statements and recommendations acknowledging the importance of the psychosocial sphere in cardiovascular health,[19,33] and some have advocated surveillance, especially for depression, in routine care settings.[34,35] Despite this growing attention, psychological factors, broadly defined, remain minimally appreciated in the routine assessment of CHD patients, and cardiovascular professional associations in the United States have been cautious about incorporating psychological aspects in guideline recommendations.[36] As a recent example, the American Heart Association updated their

CENTRAL ILLUSTRATION **Psychological Distress Is Associated With Adverse Cardiovascular Outcomes in Patients With Coronary Heart Disease**

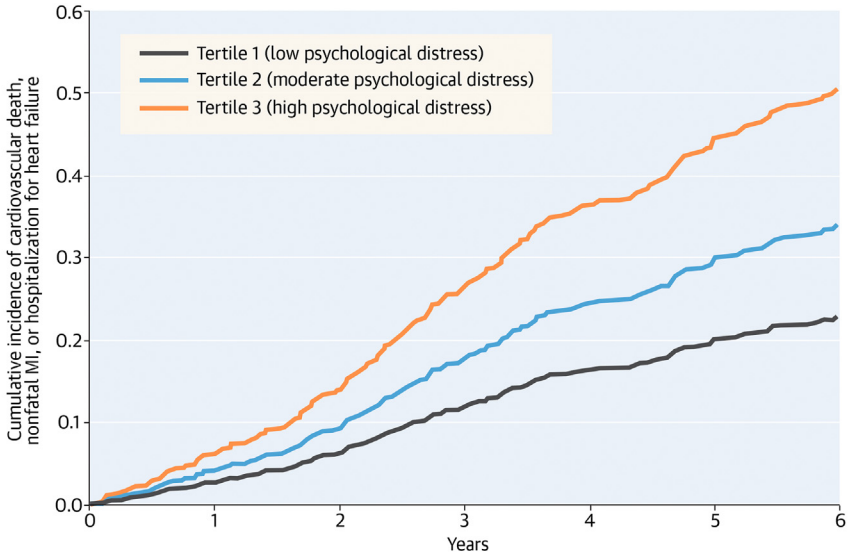
Pooled analyses of 2 prospective cohort studies of patients with stable coronary heart disease (N = 891)

Psychological distress score constructed using measures of depression, anxiety, anger, perceived stress, and PTSD

Composite endpoint including cardiovascular death or first or recurrent nonfatal myocardial infarction or hospitalization for heart failure
Follow-up 5.9 years



Cumulative Incidence of Adverse Cardiovascular Events by Tertiles of the Psychological Distress Score



No. at risk:	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Tertile 1	298	287	277	260	234	201	190
Tertile 2	297	282	267	248	217	182	172
Tertile 3	296	276	256	230	204	169	155

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Cumulative incidence of the main study endpoint (an aggregate of cardiovascular death or first or recurrent nonfatal myocardial infarction or heart failure hospitalization) in the pooled cohort, by tertiles of psychological distress score. Because of the repeated events analysis, patients were removed from the risk set at each time point only if they died or were censored. Tertile 3 vs. Tertile 1: HR, 2.27, 95% CI, 1.69, 3.06. Tertile 2 vs Tertile 1: HR, 1.52, 95% CI, 1.10, 2.08. MI = myocardial infarction; PTSD = post-traumatic stress disorder.

cardiovascular health metric to "the Essential 8" to include sleep.[37] While the critical importance of psychological health for cardiovascular health was acknowledged, it was considered mainly as a foundation for other health factors (such as sleep and weight) and was not included as a formal metric on its own, even though more routine assessment and intervention in this area was encouraged.[37]

One issue behind the hesitation of including psychological evaluation in the clinical assessment of patients with CHD is the lack of agreement on which psychological factors are the most robust predictors of cardiovascular health.[19] It has been argued that psychological status is multidimensional, and that it is not clear how to best combine various measures, or which indicators are the most important to target.[37]

TABLE 3 Risk Discrimination Testing for the Prediction of the Study Endpoint (an Aggregate of Cardiovascular Death or First or Recurrent Nonfatal Myocardial Infarction or Heart Failure Hospitalization) in the Pooled Sample, After Adding Psychological Distress Score Tertiles to a Traditional Clinical Model

	C-Statistics (95% CI)	ΔC-Statistic (95% CI)	Continuous NRI (95% CI)	IDI (95% CI)
Base model	0.72 (0.63-0.81)	-		
Base model + psychological distress	0.77 (0.68-0.94)	0.05 (0.01-0.11)	0.46 (0.17-0.86)	0.05 (0.02-0.09)

Base model includes demographic factors (age, sex, and race/ethnicity), and clinical risk factors (body mass index, ever smoking, history of hypertension, hyperlipidemia, diabetes, and heart failure).

IDI = integrative discrimination index; NRI = net reclassification index.

Psychological conditions are also highly comorbid and symptoms may reflect different manifestations of shared psychological states.[24] However, the majority of previous studies have assessed each psychological condition in isolation.[24,26-30] Another potential barrier is that a comprehensive psychosocial assessment can be burdensome for incorporation in routine clinical care. It has been suggested that brief, self-report measures may be more efficient for assessing psychological health in busy medical clinics than lengthy psychological evaluations or psychiatric interviews.[4] Furthermore, such assessments would not carry the potential stigma and nocebo consequences of a psychiatric diagnosis received outside of a psychiatric clinic.[38] Yet, few investigations have examined the prognostic value of a combination of brief self-report measures of psychological distress in CHD patients. Furthermore, no previous studies have tested whether this assessment would add prognostic information above and beyond traditional risk factors and lifestyle behaviors.

In order to address these gaps, we examined a composite measure of psychological distress that combined validated short scales of depression, anxiety, anger, perceived general stress, and PTSD, representing psychological disturbances that have previously been related, separately, to cardiovascular risk and prognosis.[3,4,21-23,25] We found that this measure improved risk discrimination of patients with CHD. This finding has important clinical implications as it suggests that routine assessment of psychological status using a composite, self-reported distress score could benefit the management of individual patients in the clinical setting, by improving risk stratification. In addition to aiding in risk assessment, this measure may facilitate monitoring of patient psychological status during behavioral interventions.

In an earlier analysis of the MIPS study that was based on a shorter follow-up and a different formulation of the distress score (including hostility and constructed with Z-transformation rather than ranks), we previously reported that psychosocial distress was associated with adverse outcomes in women but not in men.[9] Using a larger sample that also includes MIMS2, a longer follow-up, and a more robust construction of the score based on ranks, we now demonstrate that psychosocial distress is associated with adverse outcomes in both women and men. The current construction of the score is more consistent with previous literature. In the ENHANCED (Enhancing Cardiac Rehabilitation With Stress Management Training) randomized trial in CHD patients, a global stress measure constructed in a similar fashion as ours was responsive to a stress management intervention added to standard cardiac rehabilitation and including education, group support, and cognitive-behavior therapy.[7] Furthermore, a reduction in this stress measure, regardless of the baseline level of stress, was associated with a lower risk of adverse clinical events, with almost a 50% reduction in event rate compared to cardiac rehab without stress management.[7] Other recent trials have supported the value of cognitive behavioral interventions in the setting of cardiac rehab in improving anxiety and depression,[39,40] as well as improving adherence to cardiac rehab and quality of life and reducing hospital admissions.[40] Other modalities, especially mindfulness-based interventions, have also shown beneficial effects on psychological and physiological outcomes in adults with cardiovascular disease.[41]

Our results, together with evidence from randomized trials of behavioral interventions and data from mechanistic research, suggest that the incorporation of assessments of psychological distress in routine cardiology care could be helpful. However, before recommending routine screening for psychological distress, additional data from randomized controlled trials are needed to inform the development of screening guidelines that can improve patient management and outcomes.[38] More research is needed also on best practices for the implementation of such screening in cardiovascular care, and on optimal clinical decision support systems. Such trials should consider broad inclusion of outcomes to inform policy, such as patients' quality of life and health care

expenditures. For the individual patient, however, alleviating psychological distress remains a priority in patient-centered cardiovascular care. Treatment modalities may include holistic behavioral approaches in addition to traditional medical therapy when indicated, and should capitalize on extensive data supporting psychosocial care in cardiovascular rehabilitation[7,39,40] and on established models of integrated care delivery with team-based approaches.[42]

STUDY LIMITATIONS. Our study has several strengths. The study population was well characterized for psychosocial exposures across multiple domains as well as for clinical risk factors and had excellent representation of Black/African American and female participants. Also, cardiovascular events and causes of death were systematically adjudicated by experienced cardiologists using an established protocol. Our study, however, is not without limitations. Psychological distress measures were self-reported, thus recall bias and reverse causation is possible, as people with more severe disease may report more stress. Even though we adjusted for clinical risk indicators, this bias is still possible. However, it was our goal to use a self-reported distress score since this approach may have more applicability in the clinical setting. Potential measurement error in study covariates may have affected our ability to fully account for confounding factors. Residual confounding, if present, could have biased the results either toward the null or away from the null. Lastly, we studied a sample from a single university center in Atlanta, Georgia, which may limit generalizability, thus our results require replication in different locations. However, we replicated the findings in 2 independent cohorts. Furthermore, the high proportion of Black/African-American participants in our study, reflective of the diversity of the Atlanta area, is a strength and sets our study apart from many other studies of cardiovascular disease where this patient group has been under-represented.

CONCLUSIONS

Among patients with stable CHD, a composite measure of psychological distress was associated with an increased risk of adverse events and its inclusion in a traditional risk model significantly improved risk prediction. Our results suggest that the value of assessing patients' psychological status with a self-reported composite measure should be rigorously evaluated for its incorporation in the risk stratification and risk assessment of this patient population.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Among patients with stable CHD, psychological distress is associated with worse outcomes.

COMPETENCY IN PATIENT CARE: Our study suggests that the incorporation of assessments of psychological distress in routine cardiology care could be a helpful tool in risk stratification and risk assessment of this patient population.

COMPETENCY IN SYSTEMS-BASED PRACTICE: Addressing psychological distress in patients with CHD may be achieved through a multidisciplinary approach of health care professionals, including cardiologists, psychologists, and psychiatrists. Psychological interventions, such as cognitive-behavioral therapy and stress management techniques, may help in reducing distress and improving overall well-being in these patients.

TRANSLATIONAL OUTLOOK: Further research is needed to understand the underlying mechanisms linking psychological distress to adverse outcomes in patients with stable CHD and explore effective interventions.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.