JACC: ADVANCES VOL. 3, NO. 1, 2024

ORIGINAL RESEARCH

ISCHEMIC HEART DISEASE

Pathways Linking Post-Traumatic Stress Disorder to Incident Ischemic Heart Disease in Women

Call to Action

Ramin Ebrahimi, MD,[a,b] Paul A. Dennis, PhD, MSA,[c,d] Annie Laurie W. Shroyer, PhD,[e,f] Chi-Hong Tseng, PhD,[a] Carlos A. Alvarez, PharmD,[g,h] Jean C. Beckham, PhD,[c,i] Jennifer A. Sumner, PhD[j]

ABSTRACT

BACKGROUND Post-traumatic stress disorder (PTSD) is associated with increased rates of incident ischemic heart disease (IHD) in women.

OBJECTIVES The purpose of this study was to determine mechanisms of the PTSD-IHD association in women.

METHODS In this retrospective longitudinal cohort study, data were obtained from electronic health records of all U.S. women veterans who were enrolled in Veterans Health Administration care from January 1, 2000 to December 31, 2017. Propensity score matching was used to match women with PTSD to women without PTSD on age, number of prior Veterans Health Administration visits, and presence of various traditional and nontraditional cardiovascular risk factors at index visit. Cox regression was used to model time until incident IHD diagnosis (ie, coronary artery disease, angina, or myocardial infarction) as a function of PTSD and potential mediating risk factors. Diagnoses of IHD, PTSD, and risk factors were defined by International Classification of Diseases-9th or -10th Revision, and/or Current Procedural Terminology codes.

RESULTS PTSD was associated with elevated rates of developing each risk factor. Traditional risk factors (hypertension, hyperlipidemia, smoking, diabetes) accounted for 24.2% of the PTSD-IHD association, psychiatric risk factors (eg, depression, anxiety, substance use disorders) accounted for 33.8% of the association, and all 13 risk factors accounted for 48.5% of the association.

CONCLUSIONS Traditional IHD risk factors explained a quarter of the PTSD-IHD association in women veterans, and over half of the risk of IHD associated with PTSD remained unexplained even when adjusting for a wide range of risk factors. To be actionable, factors underlying the remaining PTSD-IHD association warrant timely investigation.

From the [a]Department of Medicine, University of California, Los Angeles, California, USA; [b]Department of Medicine, Veterans Affairs Greater Los Angeles Healthcare System, Los Angeles, California, USA; [c]Veterans Affairs Durham Health Care System, Durham, North Carolina, USA; [d]Department of Population Health Sciences, Duke University School of Medicine, Durham, North Carolina, USA; [e]Department of Surgery, Northport Veterans Affairs Medical Center, New York, USA; [f]Department of Surgery, Renaissance School of Medicine, Stony Brook University, Stony Brook, New York, USA; [g]Texas Tech University Health Sciences Center, School of Pharmacy, Dallas, Texas, USA; [h]Veterans Affairs North Texas Health Care System, Dallas, Texas, USA; [i]Department of Psychiatry and Behavioral Sciences, Duke University School of Medicine, Durham, North Carolina, USA; and the [j]Department of Psychology, University of California, Los Angeles, California, USA.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received July 26, 2023; revised manuscript received October 16, 2023, accepted October 23, 2023.

ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2023.100744

ABBREVIATIONS AND ACRONYMS

CVD = cardiovascular disease

EHR = electronic health record

FSRF = female-specific risk factor

ICD = International Classification of Disease

IHD = ischemic heart disease

PTSD = post-traumatic stress disorder

VHA = Veterans Health Administration

A sizeable literature has demonstrated that post-traumatic stress disorder (PTSD) precedes and predicts the onset of cardiovascular disease (CVD),[1-11] suggesting that the impact of trauma exposure extends beyond the mind to the heart. Although much research has been conducted in predominantly male veteran samples,[1,4-7] recent studies have documented these associations in women recruited from community and veteran populations.[3,11] Such work in women addresses an important knowledge gap, as sex-based differences have been reported for PTSD and CVD. Lifetime prevalence of PTSD is twice as common in women as in men,[12,13] and PTSD has been found to be more chronic and severe in women than in men.[14,15] Additionally, ischemic heart disease (IHD)—the leading cause of mortality in women in the United States[16]—remains understudied, underdiagnosed, and undertreated in women, despite advances in awareness and prevention.[17]

Numerous behavioral and biological pathways may contribute to the link between PTSD and IHD and shed light on potential targets for screening and intervention to offset IHD risk. PTSD has been associated with greater prevalence of smoking, physical inactivity, sleep disturbance, unhealthy diet, obesity, and substance abuse.[18,19] Additionally, PTSD is characterized by dysregulation of the biological stress response, including the hypothalamic-pituitary-adrenal axis and autonomic nervous system, which may contribute to various processes and conditions that increase IHD risk, including chronic inflammation, hypercoagulability, oxidative stress, hypertension, hyperlipidemia, and diabetes.[20-22] Furthermore, PTSD is frequently comorbid with—and can trigger the onset of—psychiatric disorders (eg, depression, anxiety, substance dependence)[12] that have also been linked to the development of IHD.[23-25]

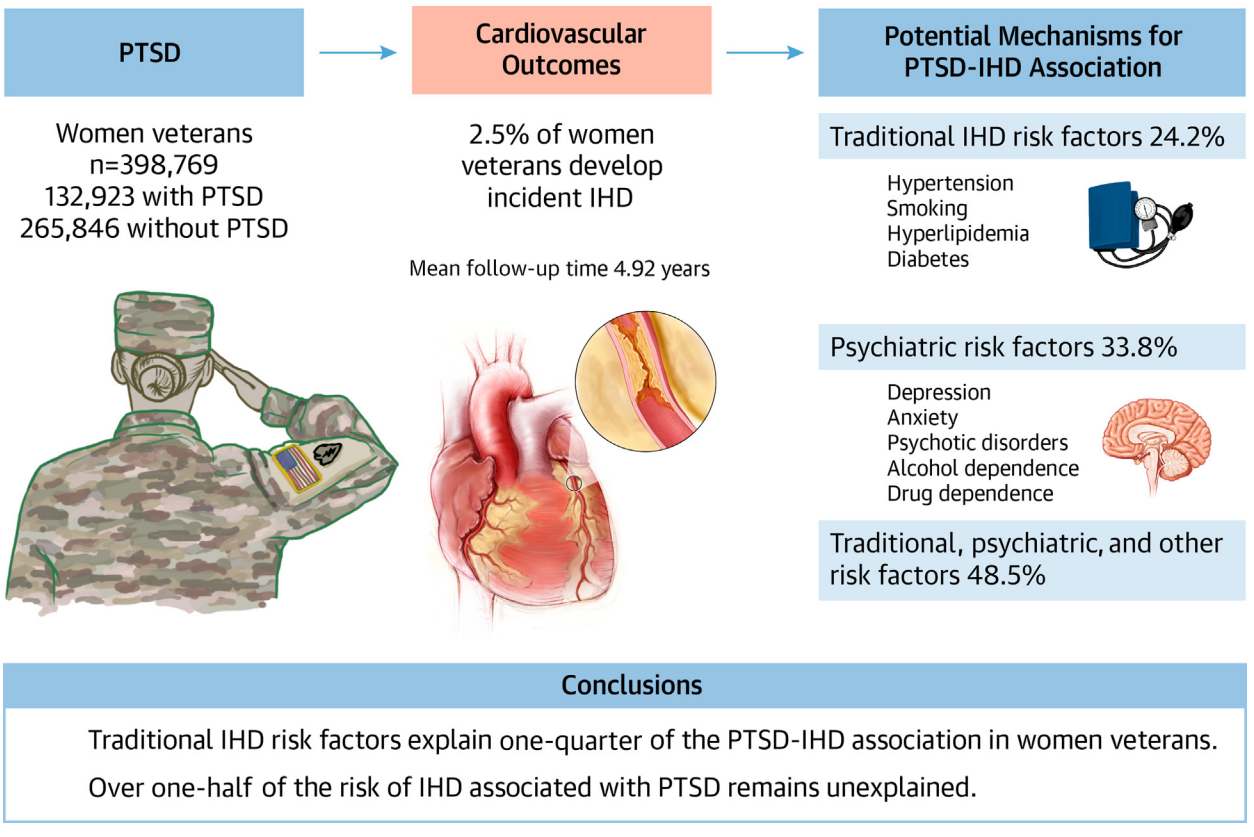
Only a few studies have examined mechanisms underlying the association of PTSD with incident cardiovascular events. For example, in a predominantly male veteran sample, the PTSD-incident CVD relationship was attenuated, albeit still significant, after accounting for several traditional cardiovascular risk factors (eg, hypertension, hyperlipidemia, type 2 diabetes).[7] However, this association was no longer significant in the fully adjusted model that also included obesity, smoking, substance use, and sleep, anxiety, and depressive disorders. Additionally, in a large community-based sample of women, nearly 50% of the association of elevated PTSD symptoms with incident CVD was accounted for by a range of health behaviors and medical risk factors, including smoking, body mass index, alcohol use, physical activity, diet quality, hypertension, and type 2 diabetes.[3] However, despite a recent call to action highlighting the unique cardiovascular risk profile of women veterans,[26] understanding of mechanisms linking PTSD with cardiovascular events in this population is lacking.

In a propensity score-matched sample of nearly 400,000 women veterans, we recently demonstrated that PTSD was associated with a 44% greater rate of developing IHD.[11] In the current study, we extended this investigation by examining potential mechanisms underlying this association. In addition to considering traditional IHD risk factors, we comprehensively examined female-specific risk factors (FSRFs) relevant to pregnancy (ie, gestational diabetes, gestational hypertension, placental abruption, pre-eclampsia) and other mental and physical health conditions in order to capture more nontraditional potential IHD risk factors that may be particularly relevant for women veterans (**Central Illustration**).[26] In examining these various pathway variables, we estimated the percentages of the PTSD-IHD association explained by the potential risk factors.

METHODS

STUDY COHORT AND KEY VARIABLES. This mechanism-focused project extended our prior study demonstrating that PTSD predicted incident IHD in women veterans; the complete methodology for deriving the cohort examined is described in Ebrahimi et al.[11] Briefly, national Veterans Health Administration (VHA) administrative data were used to collect electronic health records (EHRs) for women veterans aged ≥18 years who were enrolled in VHA care between January 1, 2000, and December 31, 2017, as approved by the University of California-Los Angeles and the Veterans Affairs Greater Los Angeles Healthcare System Institutional Review Board. Diagnostic data and health codes from inpatient, outpatient, and emergency department visits were used to identify the presence or absence of various conditions. For diagnoses based on International Classification of Diseases-9th and -10th Revision (ICD-9, ICD-10) codes, we required ≥1 inpatient and ≥2 outpatient documentations to increase the precision of detecting events, especially in outpatient records. This method has been used extensively in analyses of VHA data and has been found to be valid and have enhanced accuracy.[7,27-29] For example, this approach has been found to be a valid measure of PTSD, with a recent study demonstrating high sensitivity (0.99)

CENTRAL ILLUSTRATION **Potential Mechanisms Linking PTSD With Adverse Cardiovascular Outcomes in Women Veterans**



Ebrahimi R, et al. JACC Adv. 2024;3(1):100744.

IHD = ischemic heart disease; PTSD = post-traumatic stress disorder.

and specificity (0.96) using ICD-9 and ICD-10 codes.[27] Health factor data and weight measurements taken during health care visits were additionally used to identify the presence of smoking and obesity.

The study sample consisted of 398,769 women veterans without a history of IHD at the start of follow-up; there were 132,923 women with PTSD and 265,846 without PTSD. Using propensity score matching, women veterans with and without PTSD were comprehensively matched for a wide range of potential risk factors, including traditional IHD risk factors (diabetes, hypertension, hyperlipidemia, smoking), obesity, chronic kidney disease, neuroendocrine disorders, psychiatric disorders (anxiety, depression, schizophrenia, alcohol dependence, non-alcohol drug dependence), and FSRF relevant to pregnancy (gestational diabetes, gestational hypertension, placental abruption, pre-eclampsia), as well as age and number of prior VHA visits. The outcome examined was incident IHD, defined as new-onset coronary artery disease, angina (stable or unstable), and myocardial infarction (non-ST-segment elevation or ST-segment elevation). Women veterans who were and were not diagnosed with PTSD during the observation period were matched on index visit date, which indicated the start of follow-up. Specifically, propensity score matching was used to match the date of PTSD diagnosis for women veterans with a date of a VHA health care encounter for women veterans without PTSD; these matched dates were defined as the index visit for each women veteran.

The data set used for these analyses was structured such that each row represented an interval of time between health care encounters, with the index visit date marking the beginning of the first interval. As such, each patient was represented by multiple rows.

TABLE 1 Patient Characteristics

	Full Analytic Sample (N = 398,769)	Women Veterans With PTSD (n = 132,923)	Women Veterans Without PTSD (n = 265,846)
Age, y			
18-29	104,727 (26.26%)	32,016 (24.09%)	72,711 (27.35%)
30-39	103,749 (26.02%)	35,200 (26.48%)	68,549 (25.79%)
40-49	99,433 (24.93%)	36,546 (27.49%)	62,887 (23.66%)
50-59	67,415 (16.91%)	23,235 (17.48%)	44,180 (16.62%)
60+	23,445 (5.88%)	5,926 (4.46%)	17,519 (6.59%)
Race/ethnicity			
Black	112,229 (28.14%)	39,984 (32.34%)	72,245 (30.89%)
White	200,685 (50.33%)	67,655 (54.73%)	133,030 (56.88%)
Latina	30,081 (7.54%)	10,746 (8.69%)	19,335 (8.27%)
Asian, Pacific Islander	9,419 (2.36%)	3,081 (2.49%)	6,338 (2.71%)
American Indian, Native Alaskan	5,066 (1.27%)	2,152 (1.62%)	2,914 (1.10%)
Other/unknown	41,289 (10.35%)	9,305 (7.00%)	31,984 (12.03%)

Values are n (%).
PTSD = post-traumatic stress disorder.

Risk factors and IHD status were dichotomously coded. Once a risk factor was identified, it was coded as present until diagnosis of IHD or censoring due to death or end of observation. Risk factors identified prior to the index visit date (and thus balanced by PTSD status via propensity score matching) were coded as absent in the analytic data set so that only those factors identified after the index date could count as potential mediators of the PTSD-IHD association.

DATA ANALYSIS. To test mediation of the PTSD-IHD association, Cox regression with time-varying covariates was used to model time to development of IHD as a function of PTSD and the above 13 risk factors as time-varying predictors, with separate models for each risk factor. Age group at index visit, categorized as <30 years, 30 to 39, 40 to 49, 50 to 59, and 60+, was covaried due to its potentially confounding relationship with the risk factors and IHD. This model structure—that is, inclusion of PTSD and potential mediators in the same model—permitted a single-model significance test of mediation using Saunders and Blume's[30] essential mediation components approach. Thus, using common mediation nomenclature, the effect of PTSD on IHD represents path C'; the covariance between PTSD and the risk factor, path A; and the effect of a given risk factor on IHD, path B; with the indirect effect estimated as the product of paths A and B. Using this approach, we also examined the indirect effect of PTSD on IHD via all 4 traditional risk factors in a single model, as well as via all 5 psychiatric risk factors in a second model and all 13 risk factors jointly in a third model.

All tests were 2-sided; $P < 0.05$ was used to determine significance. Analyses were conducted using SAS 9.4. HRs and 95% CIs are reported for the effects of PTSD and risk factors on IHD. Coefficients and corresponding confidence intervals are reported for the covariances between PTSD and risk factors. Percentages of the PTSD-IHD association explained by risk factors are reported for the indirect effects. Furthermore, we followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines in preparing this manuscript.[31]

RESULTS

Demographic characteristics for the analytic sample are reported in Table 1. The sample was relatively young (over half of the sample was younger than 40 at index visit) and racially/ethnically diverse. The mean length of follow-up was 4.92 ± 4.87 years during which 9,940 (2.5%) women were diagnosed with incident IHD. As reported previously,[11] PTSD patients and controls were similar on demographic and baseline clinical features due to propensity score matching (see also Table 1).

According to the first set of models examining the indirect effect of PTSD on IHD via the 13 risk factors separately, PTSD was associated with elevated rates of developing each risk factor (Table 2). In particular, PTSD was most strongly associated with elevated rates of psychiatric risk factors, obesity, smoking, and hyperlipidemia. In turn, all risk factors except FSRF relevant to pregnancy were, independent of PTSD, significantly associated with elevated rates of IHD, most notably chronic kidney disease, diabetes, and hyperlipidemia. Results of the mediation analyses examining risk factors individually indicated that the association of PTSD with IHD was significantly mediated by all risk factors except FSRF relevant to pregnancy. Depression explained the most covariance in the PTSD-IHD association (17.2%), followed by anxiety (12.7%) and hyperlipidemia (10.9%).

According to the second set of models in which the summed effect of multiple risk factors was assessed, the 4 traditional risk factors together accounted for 24.2% of the association of PTSD with IHD, whereas the 5 psychiatric risk factors together accounted for 33.8% of the association. All 13 risk factors together accounted for 48.5% of the association.

DISCUSSION

In a recent retrospective cohort study of nearly 400,000 women veterans,[11] we found that PTSD was associated with a 44% greater rate of incident IHD

TABLE 2 Indirect Effects of PTSD on Ischemic Heart Disease via Traditional and Nontraditional Risk Factors

	Controls (n = 265,846)	PTSD (n = 132,923)	Mediation Path A[a] PTSD→Risk Factor	Mediation Path B Risk Factor→IHD	Indirect Effect[b]
Hyperlipidemia	34,449 (13.0%)	24,125 (18.1%)	0.07 (0.07-0.07) <0.001	1.86 (1.78-1.94) <0.001	10.9% <0.001
Hypertension	27,230 (10.2%)	18,425 (13.9%)	0.05 (0.05-0.05) <0.001	1.78 (1.70-1.87) <0.001	7.4% <0.001
Diabetes	14,178 (5.3%)	10,029 (7.5%)	0.03 (0.03-0.03) <0.001	2.07 (1.95-2.18) <0.001	6.3% <0.001
Smoking	24,415 (9.2%)	19,902 (15.0%)	0.07 (0.07-0.07) <0.001	1.61 (1.52-1.69) <0.001	8.3% <0.001
Obesity	40,567 (15.3%)	29,650 (22.3%)	0.08 (0.08-0.08) <0.001	1.11 (1.05-1.17) <0.001	2.2% <0.001
Chronic kidney disease	3,904 (1.5%)	2,487 (1.9%)	0.01 (0.01-0.01) <0.001	3.13 (2.89-3.40) <0.001	2.7% <0.001
Neuroendocrine disease	12,276 (4.6%)	9,134 (6.9%)	0.03 (0.03-0.03) <0.001	1.30 (1.21-1.39) <0.001	2.0% <0.001
Female-specific risk factors	3,008 (1.1%)	1,773 (1.3%)	0.00 (0.00-0.00) <0.001	1.30 (0.92-1.85) 0.14	0.0% 0.14
Depression	38,263 (14.4%)	46,770 (35.2%)	0.20 (0.20-0.20) <0.001	1.40 (1.33-1.47) <0.001	17.2% <0.001
Anxiety	29,508 (11.1%)	28,476 (21.4%)	0.11 (0.11-0.11) <0.001	1.55 (1.46-1.64) <0.001	12.7% <0.001
Psychotic disorders	1,481 (0.6%)	2,204 (1.7%)	0.02 (0.02-0.02) <0.001	1.54 (1.35-1.75) <0.001	2.4% <0.001
Alcohol dependence	4,460 (1.7%)	9,859 (7.4%)	0.07 (0.07-0.07) <0.001	1.53 (1.40-1.67) <0.001	7.7% <0.001
Drug dependence	4,019 (1.5%)	7,670 (5.8%)	0.06 (0.06-0.06) <0.001	1.80 (1.64-1.97) <0.001	8.9% <0.001

Values are n (%) or HR (95% CI). Note: Age group was covaried in models summarized in the indicated columns. [a]Mediation path A was estimated using the model covariances. Given that both risk factors were scored 0 and 1, the corresponding coefficients are analogous to standardized betas. [b]Percentages represent the proportion of the PTSD-IHD association explained by the risk factors listed along the left column. *P* values correspond to the statistical significance of the indirect (mediation) effect.

IHD = ischemic heart disease; PTSD = post-traumatic stress disorder.

compared to a propensity score-matched control group. The present study extended this finding by investigating specific mechanisms that underlie the link between PTSD and IHD in women veterans and their level of contribution. By using EHR data for health care encounters after the matched index visit date for women veterans with and without PTSD, we were able to investigate the role played by a wide range of risk factors that developed after a PTSD diagnosis in linking PTSD to IHD longitudinally.

This approach led to several important findings. First, PTSD was associated with elevated rates of each of the investigated risk factors. Second, except for FSRF relevant to pregnancy, which was very low in prevalence, each of the risk factors investigated significantly mediated the association of PTSD with IHD in separate models. Third, psychiatric disorders accounted for a greater proportion of the PTSD-IHD association than the traditional risk factors (33.8% vs 24.2%, respectively).

This latter finding suggests that, in patients with PTSD, it will be critical to take into consideration both PTSD and its common psychiatric comorbidities when addressing risk for IHD and other cardiovascular adverse outcomes. Indeed, the majority of individuals with PTSD meet criteria for at least 1 other psychiatric disorder, and a substantial percentage have 3 or more other psychiatric diagnoses.[32] Furthermore, it is not surprising that other psychiatric disorders coexisting with PTSD also confer IHD risk, given established links between depression, anxiety, and substance abuse with CVD.[23,25] Nevertheless, more research is needed to better understand factors that may contribute to this pattern of results. For example, the presence of psychiatric comorbidity may reflect more severe manifestations of PTSD[33] and, as such, a higher IHD risk. Alternatively, psychiatric comorbidity may reflect shared diagnostic criteria (eg, anhedonia, negative affect, and sleep and concentration difficulties are symptoms of both PTSD and depression)

rather than the presence of multiple distinct disorders. Research that compares diagnosis-based approaches with methods that consider dimensions of psychopathology that cut across diagnostic entities (eg, akin to the National Institute of Mental Health Research Domain Criteria)[34] may help to elucidate key mental health manifestations driving elevated IHD risk in women veterans. Additional research is also needed to investigate whether treatments used for these psychiatric conditions may impact cardiovascular risk. For example, treating PTSD with evidence-based psychotherapies (eg, Cognitive Processing Therapy) may alleviate not only symptoms of PTSD but also those of comorbid conditions (eg, depression, anxiety),[35] which may, in turn, reduce cardiovascular risk. It is also of interest to investigate whether transdiagnostic treatments (eg, Transdiagnostic Behavior Therapy)[36] and/or interventions designed for particular comorbid presentations (eg, Concurrent Treatment of PTSD and Substance Use Disorders Using Prolonged Exposure)[37] may effectively offset elevated cardiovascular risk by addressing not only PTSD but also downstream psychological processes in targeted ways. Finally, considering cardio-relevant effects of commonly used pharmacotherapy for psychiatric conditions is important. For example, antidepressants are commonly prescribed for PTSD, depression, and anxiety, and some research has linked their use to heightened risk of developing CVD.[38] Additionally, in a large sample of community-dwelling women, antidepressant use accounted for an estimated 21% of the association between elevated PTSD symptoms and incident hypertension, with medication use predicting elevated rates of hypertension.[39] Thus, considering potential cardiovascular consequences of psychotherapy and pharmacotherapy interventions for individuals with PTSD is an important future direction.

These findings also add to a growing body of work[3,7] suggesting that a range of mental, behavioral, and medical factors play a role in linking PTSD to CVD events. In the study by Scherrer et al[7] examining mediators of the association of PTSD with incident CVD in over 4,000 veterans—87% of whom were male—hyperlipidemia, hypertension, diabetes, and obesity together accounted for 40% of the elevated risk associated with PTSD. Adding smoking, depression, anxiety disorders, substance use disorders, and sleep disorders to the model accounted for 100% of that elevated risk. By contrast, in our study, traditional risk factors accounted for just 24% of the association of PTSD with IHD, and all 13 investigated risk factors together accounted for <50% of that association. This finding parallels previous research in community-dwelling women demonstrating that a range of health behavior and medical risk factors accounted for nearly half of the PTSD-CVD relation.[3] These results not only suggest that mechanisms by which PTSD leads to cardiovascular risk may differ between sexes, they highlight the importance of future research to better understand such sex differences, and other novel conditions that may further account for the elevated cardiovascular risk posed by PTSD.

STUDY LIMITATIONS. As a retrospective large-scale administrative database analysis, there are several inherent data-related study limitations, including selection bias and misclassification. Although we examined a broad range of potential mechanisms underlying the PTSD-IHD association, there were important FSRF variables unavailable for extraction in the EHR, including menopausal status and birth control medications, as well as other relevant risk factors (eg, diet, exercise, sleep).[3] Further research that considers a wider range of potential cardiovascular risk factors that are unique to women, as well as additional behavioral risk factors, is thus needed. Moreover, although PTSD diagnostic codes have been extensively used and validated via EHR reviews,[7,11,27-29,40,41] trauma type, time of exposure, and PTSD severity could not be determined from diagnostic data. Similarly, the duration for all risk factors, once detected, could not be ascertained. Consistent with prior published literature, absent reliable indicators of abatement, all risk factors were assumed to be persistent following initial detection.[3,7,11] Furthermore, our work was conducted as part of a project examining the links between traumatic stress and CVD specifically in women veterans; more research is needed in nonveteran samples and to test for sex differences in these associations. Also, while patients who died were censored at the time of death, death poses a competing risk to diagnosis of IHD. Modeling death as a competing risk was unfortunately impossible due to memory limitations imposed by national Veterans Administration computing resources. Realistically, the most likely outcome of this limitation is that we underestimated the association of PTSD with IHD. However, what impact that might have had on our analysis of mediating pathways is difficult to know.

Preventive IHD-related and PTSD-related care received by the veterans may have also impacted their likelihood of developing a subsequent IHD diagnosis. These were unaccounted for in the present analyses given the measurement complexities involved. Consequently, our results generalize to the full population of women veterans with PTSD, both

treated and untreated. For reference, a synthesis of research on rates of veterans' access to PTSD treatment estimated that 58% of veterans with PTSD receive VHA PTSD care,[42] although that figure is likely much lower for women veterans, with 1 study indicating that just 31% of women veterans with PTSD received treatment.[43] As such, research specific to PTSD and IHD treatments is warranted to understand their potential for offsetting downstream effects and sex differences.

However, our study also had many strengths. This was the largest analysis of the potential mechanisms linking PTSD with IHD in women veterans. In addition, we evaluated a comprehensive list of potential risk factors besides the traditional risk factors. These included neuroendocrine disorders, never studied before, and FSRF relevant to pregnancy, rarely studied. Furthermore, this is the first study to describe the relative contribution of the increased risk for each risk factor, and specific risk factor categories, thus highlighting the importance of expanding identification and appropriate treatment of other modifiable risk factors beyond the traditional cardiovascular risk factors. Finally, the findings presented here extend the literature on mechanisms linking PTSD with cardiovascular risk.

CONCLUSIONS

A vast range of conditions can develop after PTSD and contribute to incident IHD. In this study, psychiatric risk factors in particular accounted for a large share of the incident IHD risk associated with PTSD in women veterans. This study adds to a growing body of work highlighting the burden of PTSD with respect to poor heart health. Our results reinforce the findings and recommendations of a recent American Heart Association Scientific Statement highlighting the need to attend to the interplay between psychiatric and cardiovascular conditions,[44] and they serve as a call to action to better understand and address the mechanisms by which PTSD may increase the risk of IHD. Subsequent research is also needed to determine whether treating PTSD, such as with the evidence-based psychotherapies being implemented widely in VHA care, can offset this excess cardiovascular risk.

ACKNOWLEDGMENT The authors would like to thank Arthur Mayeno, PhD, for his contribution in the preparation of this grant.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This research was funded through a grant from the Department of Defense U.S. Army Medical Research and Material Command Congressionally Directed Medical Research Programs (Ebrahimi; PR171210). The project was also supported by VA North Texas Health Care system, the VA Greater Los Angeles Healthcare System, and Northport and Durham VA Medical Centers. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Ramin Ebrahimi, Veterans Affairs Greater Los Angeles Healthcare System (VAGLAHS), 11301 Wilshire Blvd, Los Angeles, California 90073, USA. E-mail: Ebrahimi@ucla.edu OR Ramin.Ebrahimi@va.gov. @RaminEbrahimiMD.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: A variety of traditional and nontraditional risk factors underlie the PTSD-IHD relation in women veterans.

COMPETENCY IN PATIENT CARE: Patients with PTSD should be educated about their increased risk of IHD and the fact that besides traditional CVD risk factors, other risk factors such as psychiatric disorders, obesity, and neuroendocrine disorders also increase their risk, thus highlighting the importance of the management of such disorders.

TRANSLATIONAL OUTLOOK: As PTSD is a common disorder with a lifetime prevalence of ~10% in women, future research investigating the >50% of unexplained risk of IHD associated with PTSD in women veterans is warranted.

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KEY WORDS cardiovascular, IHD, longitudinal, mechanisms, PTSD, risk