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Comorbid Conditions Explain the Association Between Posttraumatic Stress Disorder and Incident Cardiovascular Disease

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Background—Posttraumatic stress disorder (PTSD) is associated with risk of cardiovascular disease (CVD). Biopsychosocial factors associated with PTSD likely account for some or all of this association. We determined whether 1, or a combination of comorbid conditions explained the association between PTSD and incident CVD.

Methods and Results—Eligible patients used 1 of 5 Veterans Health Affairs medical centers distributed across the United States. Data were obtained from electronic health records. At index date, 2519 Veterans Health Affairs (VA) patients, 30 to 70 years of age, had PTSD diagnoses and 1659 did not. Patients had no CVD diagnoses for 12 months before index date. Patients could enter the cohort between 2008 and 2012 with follow-up until 2015. Age-adjusted Cox proportional hazard models were computed before and after adjusting for comorbidities. Patients were middle aged (mean=50.1 years, SD±11.0), mostly male (87.0%), and 60% were white. The age-adjusted association between PTSD and incident CVD was significant (hazard ratio=1.41; 95% CI: 1.21–1.63). After adjustment for metabolic conditions, the association between PTSD and incident CVD was attenuated but remained significant (hazard ratio=1.23; 95% CI: 1.06–1.44). After additional adjustment for smoking, sleep disorder, substance use disorder, anxiety disorders, and depression, PTSD was not associated with incident CVD (hazard ratio=0.96; 95% CI: 0.81–1.15).

Conclusions—PTSD is not an independent risk factor for CVD. Physical and psychiatric conditions and smoking that co-occur with PTSD explain why this patient population has an increased risk of CVD. Careful monitoring may limit exposure to CVD risk factors and subsequent incident CVD. (*J Am Heart Assoc.* 2019;8:e011133. DOI: 10.1161/JAHA.118.011133)

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Numerous research studies have shown that posttraumatic stress disorder (PTSD) is a risk factor for incident cardiovascular disease (CVD),[1–9] but it is possible that much

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of this risk is attributable to the higher prevalence of comorbid CVD risk factors in patients with versus without PTSD. Several well-designed studies provide evidence that the association between PTSD and CVD is attenuated but remains significant after controlling for most traditional CVD risk factors such as smoking, hypertension, and diabetes mellitus.[4,6,7,9–11] This extant work has not been presented in the context of the change in the magnitude of the association between PTSD and CVD associated with both individual covariates and blocks of covariates nor has it been determined whether PTSD is associated with incident CVD in patients without comorbid CVD risk factors.

PTSD is associated with a range of biological, psychological, and behavioral correlates that could mediate the association between PTSD and CVD.[12,13] PTSD can result in hypothalamic–pituitary–adrenal axis dysfunction, increased inflammation, and abnormal cortisol regulation, which increases risk of hypertension, diabetes mellitus, and CVD similar to the process observed in patients with depression.[12–14] Poor coping strategies involve heavy smoking, excessive alcohol use, and illicit drug use,[12,14] which in turn can contribute to increased risk of CVD. Depression and

ORIGINAL RESEARCH

Clinical Perspective

What Is New?

- Posttraumatic stress disorder (PTSD) is a risk factor for cardiovascular disease (CVD).
- While no single comorbidity accounts for this association, a combination of physical and psychiatric disorders and smoking, all more prevalent in patients with PTSD, explains the association between PTSD and incident CVD.

What Are the Clinical Implications?

- Longer duration of exposure to CVD risk factors (eg, smoking) among patients with PTSD may increase risk of CVD.
- Early detection and effective management of hypertension, type 2 diabetes mellitus, depression, anxiety, sleep disorders, and other CVD risk factors may be particularly important in mitigating risk of CVD in patients with PTSD.

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other anxiety disorders are frequently comorbid with PTSD, and depression and some anxiety disorders have been identified as CVD risk factors.[9,15,16]

Existing studies of PTSD and incident CVD have not focused on determining which physical, psychiatric, or behavioral factors, either alone or in combination, partly or completely explain the association between PTSD and CVD. For example, recent research has demonstrated that nonobese patients with PTSD have the same risk of type 2 diabetes mellitus (T2DM) as the general population, which indicates the same prevention goals, such as weight management, should reduce the risk of incident T2DM in patients with and without PTSD.[17] To elucidate reasons why patients with PTSD have a higher CVD risk, the present study determined whether 1, or a combination of multiple CVD risk factors common in those with PTSD partly or completely explain the association between PTSD and incident CVD.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request, and appropriate Veterans Administration IRB and data use agreement approvals.

Veterans Health Affairs (VHA) electronic medical record data were obtained from 11 856 patients 18 to 70 years of age (5940 with PTSD and 5916 without PTSD). Electronic medical record data included *International Classification of Diseases, Ninth Revision (ICD-9)* diagnosis codes, vital signs, laboratory results, medications, demographic data, and type of clinic encounter (eg, primary care, mental health clinic, PTSD psychotherapy, etc.).

Eligibility

Patients with and without PTSD diagnoses were eligible if they had 2 or more visits to 1 of 5 VHA medical centers between fiscal year 2008 to 2012. Because patients <30 years of age have a very low risk of CVD, we restricted the eligible cohort to those 30 to 70 years of age. Patients with PTSD were sampled from 5 VHA clinics distributed across the United States (San Francisco, CA, San Diego, CA, Cincinnati, OH, and Charleston, SC) if they had at least 2 visits to each medical center's PTSD specialty health clinic. Controls were randomly sampled from the same medical centers. The observation period continued until September 30, 2015 to allow all patients at least 3 years of follow-up time (eg, for patients entering the cohort in September 2012), which was sufficient to detect incident CVD.

For patients with PTSD, the index date was the second visit with a PTSD diagnosis (or inpatient discharge date), and for non-PTSD patients the index date was their second visit at 1 of the 5 VHA medical centers. Because duration of PTSD may confound our analysis and to remove prevalent CVD, we included patients who were new PTSD cases by requiring a 1-year "washout" before the index date in which patients with prevalent PTSD and CVD were excluded. All patients were 18 to 70 years of age at index date. We selected the 2959 patients without PTSD diagnosis and 4075 patients with PTSD diagnosis whose index date occurred in fiscal year 2009 to fiscal year 2012. To allow for a biologically plausible relationship between PTSD and incident CVD, we required patients to have >90 days of follow-up after the index date. Inclusion and exclusion criteria resulted in an analytic sample of 4178 patients, of whom 1659 patients had no PTSD diagnosis and 2519 patients had a PTSD diagnosis. The cohort sampling process is shown in Figure.

Variable definitions

Primary exposure

We required 2 separate visits with an *ICD-9* code for PTSD (*ICD-9*: 309.81) within a 12-month period or 1 inpatient stay to classify patients as having PTSD. This algorithm results in positive predictive value = 82%, compared with a standard cutoff for diagnosis on the PTSD Checklist (PCL) score ≥50.[18] This algorithm has 79.4% agreement with lifetime PTSD diagnoses measured by the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition).[19] Patients without PTSD were free of an *ICD-9* code for PTSD in fiscal year 2008 to fiscal year 2012.

In a subset of patients with PCL scores (n=1981), we selected the score closest to and before incident CVD to compute the association between severity of PTSD and incident CVD. PCL scores of 50[20] and 60[21] have been
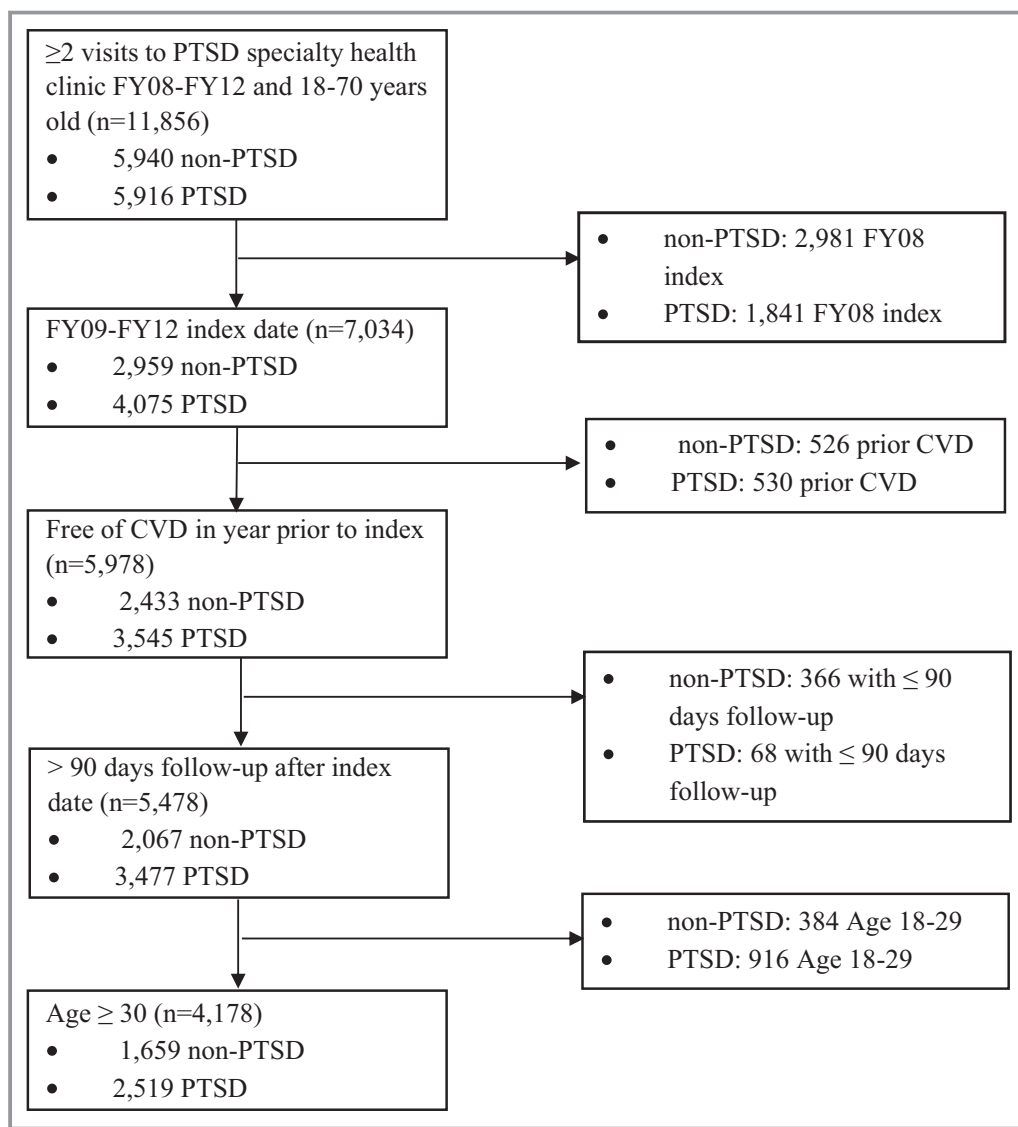
Figure. Eligibility criteria. CVD indicates cardiovascular disease; FY, fiscal year; PTSD, posttraumatic stress disorder.

suggested as valid indicators of current PTSD. Because PCL scores were available on a subset of patients, scores were not included in adjusted Cox proportional hazard models.

Outcome

Incident CVD was defined by *ICD-9* codes and Current Procedural Terminology codes for cardiovascular revascularization procedures. When available we followed definitions validated in VHA patient data,[22,23] and methods applied in other administrative data.[24,25] Detailed definitions are provided in Table 1.

Covariates

All variable definitions are shown in Table 1. We required 2 or more visits with the same *ICD-9* code in the same 12 months

or 1 inpatient visit to define mental health conditions because this algorithm improves validity.[18,26] Covariates were measured between 2008 and end of follow-up, (ie, incident CVD or last available encounter).

Metabolic conditions included T2DM, obesity (body mass index used for descriptive analysis), hypertension, and hyperlipidemia. Psychiatric comorbidities included depression, any non-PTSD anxiety disorder, and any substance abuse/dependence (SUD), which included alcohol or any drug abuse/dependence diagnoses. Smoking status was obtained from *ICD-9* code for nicotine dependence and routine VA health screening questionnaires and categorized into never, former, and current smoker. Last, we adjusted for sleep disorders associated with PTSD that may also increase risk of CVD. Demographic variables included age, sex, race (white,

Table 1. Variable Definitions

PTSD (baseline/fixed)—Presence of 309.81 at 1 of 5 VHA PTSD specialty clinics on ≥2 outpatient visits or 1 inpatient in FY2008 to FY2012

Cardiovascular disease—≥1 *ICD-9* diagnosis code or revascularization CPT/*ICD-9* procedure codes
  a *ICD-9* diagnosis codes for any of the following conditions:
    1 hypertensive heart disease: 402x, 403x, 404x, 405x
    2 MI: 410x, 411x
    3 ischemic heart disease: 412x, 413x, 414x
    4 disease of pulm circulation: 415x, 416x, 417x
    5 other heart disease: 420x to 429x
  b CPT codes (outpatient clinic stop files): 35450 to 35459; 35470 to 35475; 35480 to 35495; 92980, 92981, 92984, 92995, 92996; 33510 to 33536; 33572; 37220 to 37235; 92920 to 92944; 0234T to 0238T; G0290, G0291; S2211; S2222; S2204-S2209
  c *ICD-9* procedure codes (inpatient procedure files): 36.0x to 36.3x. All patients with a revascularization code also had an *ICD-9* code for cardiovascular disease

Study end date—Date of cardiovascular disease or last encounter with VHA system
All-cause mortality—Presence of date of death in vital status master file before Sept 30, 2015—observation time for all-cause mortality is days from study index date to either death date or Sept 30, 2015
Depression (time dependent)—(296.2x, 296.3x, 311). Presence of a single inpatient code or ≥2 outpatient codes within a 12-mo period before study end date
Other anxiety (time dependent)—Composite of panic disorder, OCD, social phobia, GAD, anxiety NOS (300.00, 300.01, 300.02, 300.23, 300.3). Presence of a single inpatient code or ≥2 outpatient codes within a 12-mo period before study end date

Substance abuse/dependence (time dependent)—Composite of alcohol and drug abuse/dependence. At least a single code for the following before study end date:
  a Alcohol (303.9x, 305.0x)
  b Drug: sedative (304.1x, 305.4x), cocaine (304.2x, 305.6x), cannabis (304.3x, 305.2x), amphetamine (304.4x, 305.7x), hallucinogens (304.5x, 305.3x), "other" (304.6x, 305.9x), opioid (304.0x, 305.5x), opioid with other SUD (304.7x), other SUD excluding opioid (304.8x), unspecified drug abuse/dependence (304.9x)

Sleep disorder (time dependent)—Primary or secondary diagnosis anywhere in record. At least a single code for 307.4x, 327.x, 780.5x, 333.94

Smoke status (fixed)—This is indicated as Current, Former, Never
  1 Current—"current smoker" in health factors or *ICD-9* code for nicotine dependence (V15.82, 305.1) before study end date
  2 Former—never has a "current smoking" indicator and has an indicator for "former smoker" in health factors before study end date
  3 Never—all else

Obese any (time dependent)—Presence of BMI ≥30 or *ICD-9* (278.00, 278.01) code for obesity before study end date
BMI (fixed—descriptive)—last BMI before study end date
Hypertension (time dependent)—(401.x) At least a single code before study end date
Hyperlipidemia (time dependent)—(272.0, 272.1, 272.2, 272.4). At least a single code before study end date
Type 2 Diabetes mellitus (time dependent)—(250.x0, 250.x2, 357.2, 362.0x, 366.41) Presence of ≥2 codes in any 24-mo period before study end date
Demographic information (all fixed covariates)
Age—age at initial visit to 1 of 5 VHA PTSD specialty clinics
Sex—male vs female
Race—most commonly occurring in record (white vs black vs other)
Marital status—most commonly occurring in record (married vs other)
VHA only insurance—most commonly occurring in record (yes vs no)
Primary healthcare utilization—number of unique primary care clinic stops per total mo in entire VA system. Total mo is calculated from first visit date to any VA facility in FY08 to FY15 to the study end date. Primary Care stop codes: 170, 172, 301, 322, 323, 348, 350. From entire sample of 17- to 80-y-olds, quartiled visits/mo and top quartile=high

BMI indicates body mass index; CPT, Current Procedural Terminology; FY, fiscal year; GAD, generalized anxiety disorder; *ICD9, International Classification of Diseases, Ninth Revision (ICD-9)*; MI, myocardial infarction; NOS, not otherwise specified; OCD, obsessive-compulsive disorder; SUD, substance abuse/dependence; PTSD, posttraumatic stress disorder; VHA, Veterans Health Affairs.

Table 2. Sample Characteristics, Veterans Age 30 to 70 Years and Free of CVD (n=4178)

Variable, n (%) or Mean (±SD)	Overall (n=4178)	No PTSD (n=1659)	PTSD (n=2519)	P Value
Outcome				
Median (IQR) follow-up (d)	1547.5 (1112.0–1967.0)	1577.0 (1028.0–2019.0)	1530.0 (1137.0–1927.0)	0.459
Cumulative incidence				
Crude, n (%)	782 (18.7)	268 (16.1)	514 (20.4)	0.001
Age-adjusted, %	16.9	13.6	19.0	<0.0001
Incidence rate, PY				
Crude	46.1/1000 PY	40.0/1000 PY	50.1/1000 PY	0.003
Age-adjusted	41.4/1000 PY	33.3/1000 PY	46.7/1000 PY	<0.0001
Age, mean (±SD) (y)	50.1 (±11.0)	51.6 (±10.8)	49.1 (±11.0)	<0.0001
Age category, n (%) (y)				
30–39	909 (21.8)	301 (18.1)	608 (24.1)	<0.0001
40–49	1018 (24.4)	354 (21.3)	664 (26.4)	
50–59	1127 (27.0)	508 (30.6)	619 (24.6)	
60–70	1124 (26.9)	496 (29.9)	628 (24.9)	
Male sex, n (%)	3635 (87.0)	1442 (86.9)	2193 (87.1)	0.896
Race, n (%)				
White	2554 (61.1)	1048 (63.2)	1506 (59.8)	<0.0001
Black	1092 (26.1)	325 (19.6)	767 (30.5)	
Other	284 (6.8)	109 (6.6)	175 (6.9)	
Missing	248 (5.9)	177 (10.7)	71 (2.8)	
Marital status, n (%)				
Not married	2048 (49.0)	758 (45.7)	1290 (51.2)	<0.0001*
Married	2013 (48.2)	787 (47.4)	1226 (48.7)	
Missing	117 (2.8)	114 (6.9)	<5	
VHA only insurance, n (%)	2515 (60.2)	1071 (64.6)	1444 (57.3)	<0.0001
High primary HCU, n (%)	1185 (28.4)	293 (17.7)	892 (35.4)	<0.0001
Comorbidities[†]				
PTSD severity[‡]	…	…	(n=1981)	
Mean PCL score (±SD)			57.2 (±15.7)	
PCL 17–35	…	…	214 (10.8)	
PCL 36–70	…	…	1349 (68.1)	…
PCL 71–85	…	…	418 (21.1)	
Depression, n (%)	2153 (51.5)	308 (18.6)	1845 (73.2)	<0.0001
Other anxiety, n (%)	939 (22.5)	165 (9.9)	774 (30.7)	<0.0001
Sleep disorder, n (%)	1950 (46.7)	456 (27.5)	1494 (59.3)	<0.0001
SUD, n (%)	1547 (37.0)	315 (19.0)	1232 (48.9)	<0.0001
Hypertension, n (%)	2299 (55.0)	796 (48.0)	1503 (59.7)	<0.0001
Hyperlipidemia, n (%)	2293 (54.9)	749 (45.2)	1544 (61.3)	<0.0001
Type 2 diabetes mellitus	755 (18.1)	247 (14.9)	508 (20.2)	<0.0001
Obesity, n (%)[§]	2361 (56.5)	776 (46.8)	1585 (62.9)	<0.0001
BMI, mean (±SD)[‖]	29.9 (±5.9)	29.3 (±5.9)	30.2 (±5.9)	<0.0001

Table 2. Continued

Variable, n (%) or Mean (±SD)	Overall (n=4178)	No PTSD (n=1659)	PTSD (n=2519)	P Value
BMI category||				
<25	762 (18.2)	323 (19.5)	439 (17.4)	<0.0001
25 to <30	1407 (33.7)	520 (31.3)	887 (35.2)	
≥30	1749 (41.9)	592 (35.7)	1157 (45.9)	
Missing	260 (6.2)	224 (13.5)	36 (1.4)	
Smoking, n (%)				
Never	1571 (37.6)	732 (44.1)	839 (33.3)	<0.0001
Former	642 (15.4)	272 (16.4)	370 (14.7)	
Current	1965 (47.0)	655 (39.5)	1310 (52.0)	

BMI indicates body mass index; CVD, cardiovascular disease; HCU, healthcare utilization; IQR, interquartile range; PCL, PTSD checklist; PTSD, posttraumatic stress disorder; PY, person-years; SUD, substance abuse/dependence; VHA, Veterans Health Affairs.

*Exact *P* value.

†Comorbidities occur anytime before either CVD or last visit date.

‡Last PTSD Checklist (PCL) before CVD or last visit date, limited to n=1981 patients with PTSD who had ≥1 PCL score.

§BMI≥30 or *ICD-9, International Classification of Diseases, Ninth Revision, Clinical Modification* code.

||Last BMI before CVD or last visit date. There were 3918 overall: 2483 patients with PTSD and 1435 without PTSD.

black, "other"), marital status, access to health insurance other than VHA, and volume of primary care utilization. The latter 2 variables are used to control for detection bias.[17,27,28]

Analytic approach

Analyses were performed with SAS v9.4 (SAS Institute, Cary, NC) at an alpha level of 0.05. With the exception of smoking status and demographic variables, all covariates were modeled as time dependent, which means patients can contribute time to both exposed and nonexposed status. For example, a patient contributes to nonhypertension status until a diagnosis of hypertension.

Bivariate analyses estimated the association between covariates and PTSD using χ^2 tests for categorical variables or independent samples *t* tests for continuous variables. Unadjusted and adjusted Cox proportional hazard models were computed to obtain hazard ratios (HR) and 95% CI. Bivariate, unadjusted models assessed the crude association of PTSD and each covariate with CVD. Adjusted Cox proportional hazard models for the relationship of PTSD and CVD were expanded by first including age, then adding physical comorbidities, then psychiatric disorders, SUD, sleep disorders, and smoking and last adding demographics. Individual variables were added to separate Cox proportional hazard models to determine the effect of each physical, psychiatric, and behavioral covariate on the age-adjusted association between PTSD and incident CVD. Follow-up time was measured as days since index date to study end date, which was the date of CVD diagnosis or last clinic encounter for those who did not develop CVD. The proportional hazard assumption was tested by examining a time-dependent interaction term of PTSD and log (follow-up time), where a

significant (*P*<0.05) test indicates assumption violation and different hazard trends over time.

Secondary outcome

Separate age-adjusted and fully adjusted Cox proportional hazard models were computed to measure the association between PTSD and risk for all-cause mortality.

Post hoc sensitivity analysis

We stratified analysis on the block of variables that explained the association between PTSD and incident CVD by comparing the association between PTSD and CVD in patients with none versus 1 or more explanatory variable(s).

Subgroup analysis

Because age, sex, and race are associated with PTSD and risk of CVD, we modeled interaction terms for PTSD by age, sex, and race. Stratified Cox proportional hazard models were computed for significant interactions.

This study was approved by the Institutional Review Board of participating institutions with a waiver of informed consent.

Results

The cohort characteristics and distribution of covariates by PTSD are shown in Table 2 as well as the median follow-up time and CVD incidence rates. Overall, patients were middle aged (mean = 50.1 years, SD, ±11.0), mostly male (87.0%), ≈60% were white, and about half were married. PTSD was associated with an age-adjusted CVD incidence rate of 46.7/ 1000 person years (PY), which was significantly (*P*<0.0001)

greater than that observed in patients without PTSD (33.3/ 1000 PY).

The mean PCL closest to and before CVD was 57.2 (SD±15.7). Younger patients were more likely to have PTSD (*P*<0.0001). White race was less common and black race was more common among patients with PTSD (*P*<0.0001). Patients with only VHA health insurance were less prevalent among those with PTSD (*P*<0.0001) and high healthcare users were more prevalent among those with PTSD versus without PTSD (*P*<0.0001).

Depression, other anxiety disorder, sleep disorders, and SUD were each significantly more common among patients with versus without PTSD (*P*<0.0001). Similarly, T2DM, obesity, hypertension, and hyperlipidemia were significantly more prevalent among patients with PTSD compared with those without PTSD (*P*<0.0001). Significantly higher average body mass index was observed in patients with PTSD (*P*<0.0001), and the percent of patients with a body mass index ≥30 was significantly higher in those with versus without PTSD (*P*<0.0001). Current smokers were significantly more prevalent in patients with PTSD compared with those without PTSD (*P*<0.0001).

During follow-up, 782 patients developed CVD. Of these cases, 10.5% were incident hypertensive heart disease diagnoses, 6.8% myocardial infarction, 29.8% ischemic heart disease, 4.2% diseases of pulmonary circulation, and 56.0% "other" heart disease diagnoses. These were not mutually exclusive and 6.4% had multiple components of incident CVD.

Results of unadjusted, bivariate Cox proportional hazard models are shown in Table 3. In an unadjusted model, PTSD was significantly (*P*=0.003) associated with increased risk of CVD (HR=1.25; 95% CI: 1.08−1.45); however, higher versus lower PCL scores closest to and before incident CVD were not significantly associated with incident CVD. Age, male sex, and high primary care health services use were all significantly and positively associated with incident CVD. All psychiatric and physical comorbidities were significantly associated with increased risk of CVD. Both current and former smokers were significantly more likely to develop CVD compared with never smokers.

Results from age-adjusted Cox proportional hazard models are shown in Table 4. After adjusting for age, PTSD was significantly (*P*<0.0001) associated with incident CVD (HR=1.41; 95% CI: 1.21−1.63). PTSD remained significantly (*P*<0.007) associated with incident CVD after adjusting for physical conditions in model 2; however, there was a 44% reduction in the magnitude of the association (HR=1.23; 95% CI: 1.06−1.44). As shown in model 3, PTSD was no longer associated with incident CVD after additional adjustment for smoking, SUD, sleep disorders, other anxiety disorders, and depression diagnoses (HR=0.96; 95% CI: 0.81−1.15). Results from model 3 remained largely unchanged after adding demographic variables.

Table 3. Crude HRs—Bivariate Relationship of Each Individual Covariate* With Incident CVD, Veterans Age 30 to 70 Years of Age and Free of CVD (n=4178)

Covariate	Crude HR (95% CI)	*P* Value
PTSD case	1.25 (1.08–1.45)	0.003
PTSD severity[†]	(n=1981)	
PCL score 17–35	1.00	
PCL score 36–70	1.03 (0.72–1.46)	0.886
PCL score 71–85	0.87 (0.58–1.31)	0.503
Age (y)	1.05 (1.04–1.06)	<0.0001
Male sex	1.90 (1.46–2.48)	<0.0001
Race		
White	1.00	
Black	1.09 (0.93–1.27)	0.291
Other	0.67 (0.48–0.93)	0.015
Marital status		
Not married	1.00	
Married	0.96 (0.84–1.11)	0.603
VHA only insurance	0.77 (0.67–0.88)	0.0002
High primary HCU	2.29 (1.99–2.63)	<0.0001
Comorbidities		
Depression	1.30 (1.13–1.49)	0.0003
Other anxiety	1.30 (1.10–1.53)	0.002
Sleep disorder	1.42 (1.23–1.64)	<0.0001
Substance abuse/dependence	1.38 (1.20–1.59)	<0.0001
Hypertension	2.47 (2.12–2.88)	<0.0001
Hyperlipidemia	1.80 (1.55–2.08)	<0.0001
Type 2 diabetes mellitus	1.86 (1.58–2.19)	<0.0001
Obesity[‡,§]	1.43 (1.24–1.66)	<0.00001
Smoking		
Never	1.00	
Former	1.26 (1.02–1.55)	0.034
Current	1.24 (1.06–1.45)	0.008

BMI indicates body mass index; CVD, cardiovascular disease; FY, fiscal year; HR, hazard ratio; HCU, healthcare utilization; IQR, interquartile range; PCL, PTSD Checklist; PY, person-years; PTSD, posttraumatic stress disorder; VHA, Veterans Health Affairs.
*Comorbidities occur anytime before either CVD or last visit date.
[†]Last PCL before CVD or last visit date, limited to n=1981 patients with PTSD who had ≥1 PCL score.
[‡]BMI≥30 or *ICD-9-CM* code.
[§]Last BMI before CVD or last visit date. Total of 3918 overall: 2483 patients with PTSD and 1435 without PTSD.

The age-adjusted incidence rate per 1000 PY for all-cause mortality did not significantly differ between patients with and without PTSD (8.3/1000 PY versus 6.9/1000 PY; *P*=0.198). As shown in Table 5, PTSD was not associated with all-cause mortality in fully adjusted survival models (HR=0.83; 95% CI: 0.59−1.28).

Table 4. Results From Cox Proportional Hazards Models Estimating the Association of PTSD Status on Incident CVD (n=4178)

Model no.	Nested Models	Overall (n=4178)*	
		PTSD vs No PTSD HR (95% CI)	P Value
Model 1	Age-adjusted	1.41 (1.21–1.63)	<0.0001
Model 2	Model 1+T2DM, obese, hypertension, hyperlipidemia	1.23 (1.06–1.44)	0.007
Model 3	Model 2+smoke, SUD, sleep, other anxiety, depression	0.96 (0.81–1.15)	0.691
Model 4	Model 3+demographic (full)	0.90 (0.75–1.08)	0.258

CVD indicates cardiovascular disease; HR, hazard ratio; PTSD, posttraumatic stress disorder; SUD, substance abuse/dependence; T2DM, type 2 diabetes mellitus.
*Proportional hazards assumption, P=0.80.

PTSD remained significantly associated with incident CVD in each survival model that adjusted for individual comorbid conditions (Table 6). Adjusting for T2DM alone, obesity alone, and hyperlipidemia alone had a modest attenuating effect on the association between PTSD and incident CVD; however, adjusting for hypertension reduced the strength of association by 32% (HR=1.28; 95% CI: 1.10–1.49). Individual adjustment for SUD, sleep disorder, and depression also substantially attenuated the association. Adjusting for SUD reduced the magnitude of the association between PTSD and incident CVD by 32%, sleep disorder reduced the association by 40%, and depression reduced the association by 51%. Adjusting for sex, race, marital status, and access to only VHA insurance has little effect on association between PTSD and CVD. However, controlling higher volume of healthcare use reduced the association by 51%.

Table 5. Results From Cox Proportional Hazards Models Estimating the Association of PTSD and All-Cause Mortality (n=4178)

Model No.	Nested Models	Overall (n=4178)*	
		PTSD vs No PTSD HR (95% CI)	P Value
Model 1	Age-adjusted	1.23 (0.93–1.64)	0.152
Model 2	Model 1+CVD, T2DM, obesity, hypertension, hyperlipidemia, smoking, SUD, sleep disorder, other anxiety disorders, depression, and demographics	0.83 (0.59–1.28)	0.300

CVD indicates cardiovascular disease; HR, hazard ratio; PTSD, posttraumatic stress disorder; SUD, substance abuse/dependence; T2DM, type 2 diabetes mellitus.
*Proportional hazards assumption, P=0.26.

Table 6. Cox Proportional Hazard Models—Association of PTSD and Incident CVD, Controlling for Individual, Specific Covariates (n=4178)

Covariates in model	PTSD vs No PTSD HR (95% CI)	P Value
Age-adjusted	1.41 (1.21–1.63)	<0.0001
Age+T2DM	1.37 (1.18–1.59)	<0.0001
Age+obese	1.34 (1.15–1.56)	0.0001
Age+hypertension	1.28 (1.10–1.49)	0.001
Age+hyperlipidemia	1.34 (1.15–1.56)	0.0001
Age+smoke	1.39 (1.19–1.61)	<0.0001
Age+SUD	1.28 (1.10–1.50)	0.002
Age+sleep disorder	1.25 (1.07–1.46)	0.005
Age+other anxiety	1.32 (1.13–1.54)	0.0004
Age+depression	1.20 (1.01–1.43)	0.042
Age+sex	1.40 (1.21–1.62)	<0.0001
Age+race	1.34 (1.16–1.56)	0.0001
Age+marital status	1.35 (1.16–1.57)	<0.0001
Age+VHA insurance	1.40 (1.21–1.62)	<0.0001
Age+primary HCU	1.20 (1.03–1.40)	0.020

CVD indicates cardiovascular disease; HCU, healthcare utilization; HR, hazard ratio; PTSD, posttraumatic stress disorder; SUD, substance abuse/dependence; T2DM, type 2 diabetes mellitus; VHA, Veterans Health Affairs.

Results of survival models stratified on patients having none versus 1 or more of the following conditions: depression, anxiety disorder, substance use disorder, sleep disorder, or current smoking (versus past/never) are shown in Table 7. The prevalence of 1 or more of these conditions among patients with PTSD was significantly greater than those without PTSD (95.2% versus 61.8%, P<0.0001). Having 1 or more of these conditions was slightly greater among those with incident CVD versus those who did not develop CVD (85.4% versus 81.1%, P=0.005).

Among patients without depression, anxiety disorders, SUD, sleep disorder, and current smoking, PTSD was not significantly associated with incident CVD in age-adjusted and fully adjusted models. In both patients with 1 or more of these comorbidities, PTSD was significantly associated with incident CVD in age-adjusted models but not significantly associated with incident CVD in fully adjusted models. However, the stratum-specific HR were not significantly different.

There was no significant interaction of PTSD by sex or by race on risk of CVD (Table 8). We observed a significant (P=0.029) interaction of PTSD by age group (30–39, 40–49, 50–59, and 60–70 years of age). Fully adjusted Cox proportional hazard models computed for each age group indicated the magnitude of association between PTSD and incident CVD was largest for 50- to 59-year-olds (HR=1.36; 95% CI: 0.96–1.92). PTSD was not significantly associated with incident

Table 7. Cox Proportional Hazard Models Estimating the Association Between PTSD and Incident CVD Stratified on Presence of Comorbid Depression, Anxiety Disorder, SUD, Sleep Disorder, and Smoking (current vs past/never) (n=4178)

| Model No. | Nested Models | No Comorbid Condition* (n=756) | One or More Comorbid Condition (n=3422) | P Value[†] |
		PTSD vs No PTSD HR (95% CI)	PTSD vs No PTSD HR (95% CI)	
Model 1	Age-adjusted	0.99 (0.64–1.55), P=0.979	1.28 (1.08–1.53), P=0.006	0.296
Model 2	Model 1+T2DM, obesity, hypertension, hyperlipidemia, and demographics	0.73 (0.46–1.26), P=0.179	1.09 (0.91–1.31), P=0.343	0.110

CVD indicates cardiovascular disease; HR, hazard ratio; PTSD, posttraumatic stress disorder; SUD, substance abuse/dependence; T2DM, type 2 diabetes mellitus.
*Comorbid conditions: comorbid depression, anxiety disorder, SUD, sleep disorder, and smoking (current vs past/never).
[†]Wald χ^2 P value comparing stratum HRs for PTSD vs no PTSD.

CVD among patients 30 to 39 years of age (HR=0.87; 95% CI: 0.47−1.61) and 40 to 49 years of age (HR=0.68; 95% CI: 0.45−1.04). Among patients 60 to 70 years of age, patients with PTSD were significantly less likely to develop CVD compared with those without PTSD (HR=0.74; 95% CI: 0.56−0.98).

In all models, the proportional hazard assumption was met.

Discussion

In a large sample of VHA patients, we observed that patients diagnosed with PTSD from September 30, 2008 to October 1, 2012, and followed up through 2015, were 41% more likely

Table 8. Fully Adjusted Cox Proportional Hazard Models, Stratified by Age Category, Race, and Sex (n=4178)

Demographic Stratum	Sample Size, n	PTSD vs No PTSD HR (95% CI)
Age category (y)		
30−39	909	0.87 (0.47–1.61)
40−49	1018	0.68 (0.45–1.04)
50−59	1127	1.36 (0.96–1.92)
60−70	1124	0.74 (0.56–0.98)
Age×PTSD, P=0.029		
Race		
White	2554	0.85 (0.68–1.06)
Black	1092	1.09 (0.76–1.58)
Other	284	0.97 (0.44–2.16)
Race×PTSD, P=0.792		
Sex		
Female	543	1.42 (0.66–3.08)
Male	3635	0.88 (0.73–1.06)
Sex×PTSD, P=0.474		

HR, hazard ratio; PTSD, posttraumatic stress disorder.

than those without PTSD to develop CVD. Physical comorbidities partially explained this association. After adjusting for these conditions, the magnitude of the association between PTSD and incident CVD was reduced by 44% but remained statistically significant (HR=1.23; 95% CI: 1.06−1.44). PTSD was not associated with incident CVD after controlling for a combination of physical, psychiatric, and behavioral conditions (HR=0.96; 95% CI: 0.81−1.15). In a subsample of patients without smoking, sleep disorders, anxiety disorders, and depression, PTSD was not associated with CVD. However, PTSD remained significantly associated with CVD after adjusting for age and each individual covariate, which suggests there is no single comorbidity or behavior that explains this association. Instead, a combination of comorbid conditions that are more prevalent in patients with versus without PTSD appears to explain the association between PTSD and incident CVD. This is consistent with the model of PTSD and health outcomes proposed by Schnurr and Green,[12,13] which emphasizes multiple biological, psychological, and behavioral correlates as mechanisms thorough which PTSD leads to poor health. Lastly, allostatic load has been proposed as a mechanism through which multiple risk factors, even those not present at clinically significant levels, could lead to disease.[12,13,29]

Existing studies differ in the selection or availability of covariates adjusted for when measuring the association between PTSD and incident CVD. Thus, it is difficult to make direct comparisons of our findings with several large studies of PTSD and incident CVD. Analysis of the Nurses' Health Study data indicated the magnitude of the association between PTSD and incident cardiovascular events was reduced by >50% after adjusting for hypertension, T2DM, hormone therapy, and antidepressant use.[5] In contrast, in the Veterans Affairs Normative Aging Study, very little change in the association between PTSD and CVD was observed after controlling for smoking, blood pressure, cholesterol, body mass index, self-reported family history of CVD, education, depression, and alcohol consumption.[7] There was little

change in the magnitude of association between severe PTSD compared with no PTSD symptoms and incident CVD over a 14-year follow-up of the Baltimore cohort from the Epidemiologic Catchment Area study.[6]

While our study adjusted for a similar set of variables as prior publications did, we modeled them as time dependent, which could allow the confounder to have a stronger effect on the PTSD–incident CVD association. Though speculative, it is possible that longer duration of exposure to comorbid conditions, not just the lifetime presence of comorbid diagnoses, is the reason we observed no significant association between PTSD and incident CVD in multivariate models.

We found some evidence that PTSD was most strongly associated with incident CVD among patients 50 to 59 years of age. This is logical given the lower risk of CVD in patients <50 years of age, and the increasing risk of CVD in older patients may limit detecting a contribution from PTSD.

Limitations

We did not have data about family history of CVD; however, others have reported that family history is not a confounder because it is unrelated to PTSD diagnosis[2] and Sumner et al[5] reported no change in HR after controlling for family history of myocardial infarction or stroke. Our results may not generalize to patients older than 70 years of age. Patients had follow-up time ranging from 3 to 8 years, which is not sufficient for measuring lifetime CVD risk. About 75% of our sample was <60 years of age; therefore, our study may represent the association between PTSD and risk of early-onset CVD. Findings may not generalize to nonveteran patient populations. Misclassification is always possible in retrospective cohort studies. If we misclassified patients with undiagnosed PTSD as noncases, this would result in underestimating the association between PTSD and CVD. We did not use propensity score matching or weighting to control for confounding by demographic variables. However, our experience using both propensity score matching and weighting indicates results are most often replicated with traditional multivariate adjustment. We did not adjust for multiple testing; however, all hypotheses tests were planned.

Conclusions

Our findings suggest that exposure to smoking, and physical and psychiatric disorders explain the increased risk of CVD in patients with PTSD. Because these conditions are more common in patients with PTSD, closer monitoring for comorbidities may be warranted. Early detection and effective management may reduce the burden of CVD associated with PTSD. Additionally, PTSD itself can be effectively treated and further research is needed to determine whether PTSD remission is associated with fewer comorbidities and lower CVD risk. Recognizing that PTSD does not preordain CVD may empower patients to seek care to prevent and/or manage CVD risk factors. Patients *without* PTSD are also at risk of CVD if they smoke, have a sleep disorder, depression, or metabolic disease. In both patient populations, the risk of CVD can be mitigated with health behavior change and effective chronic disease management.

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