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Authors

Salas, Joanne
Wang, Wenjin
Schnurr, Paula
et al.

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Severity of Posttraumatic Stress Disorder, Type 2 Diabetes Outcomes and all-cause Mortality: a Retrospective Cohort Study

Joanne Salas, MPH[1,2], **Wenjin Wang, BA**[1], **Paula P. Schnurr, PhD**[3], **Beth E. Cohen, MD**[4], **Kenneth E. Freedland, PhD**[5], **Allan S. Jaffe, MD**[6], **Patrick J. Lustman, PhD**[5], **Matthew Friedman, MD, PhD**[3], **Jeffrey F. Scherrer, PhD**[1,2,7]

[1)]Department of Family and Community Medicine, Saint Louis University School of Medicine. 1402 South Grand Blvd, St. Louis MO. United States

[2)]The Advanced HEAlth Data (AHEAD) Research Institute, Saint Louis University School of Medicine. 1402 South Grand Blvd, St. Louis MO. United States

[3)]National Center for PTSD, White River Junction, VT, and Department of Psychiatry, Geisel School of Medicine at Dartmouth, Hanover, NH, United States

[4)]Department of Medicine, University of California San Francisco School of Medicine and San Francisco VAMC, San Francisco CA, United States

[5)]Department of Psychiatry, Washington University School of Medicine, St. Louis MO, United States

[6)]Department of Cardiovascular Medicine and Department of Laboratory Medicine and Pathology. Mayo Clinic, Rochester, Minnesota, United States

[7)]Department of Psychiatry and Behavioral Neuroscience, School of Medicine, Saint Louis University, St. Louis, MO

Abstract

Background: Some evidence suggests patients with comorbid PTSD and type 2 diabetes (T2D) have worse T2D outcomes than those with T2D alone. However, there is no evidence regarding PTSD severity and risk for starting insulin, hyperglycemia, microvascular complications, and all-cause mortality.

Methods: In this retrospective cohort study, Veterans Health Affairs (VHA) medical record data from fiscal year (FY) 2012 to FY2022 were used to identify eligible patients (n=23,161) who had

Corresponding Author: Jeffrey F. Scherrer, PhD, 1008 S. Spring, SLUCare Academic Pavilion, 3rd Floor, St. Louis, MO 63110, jeffrey.scherrer@health.slu.edu, office:314-977-8486 cell: 314-677-8447.

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a PTSD diagnosis, ≥1 PTSD Checklist score, controlled T2D (HbA1c≤7.5) without microvascular complications at baseline. PTSD Checklist for DSM-5 (PCL-5) scores defined mild, moderate, and severe PTSD. Competing risk and survival models estimated the association between PTSD severity and T2D outcomes before and after controlling for confounding.

Results: Most (70%) patients were ≥ 50 years of age, 88% were male, 64.2% were of white race and 17.1% had mild, 67.4% moderate and 15.5% severe PTSD. After control for confounding, as compared to mild PTSD, moderate (HR=1.05; 95% CI:1.01–1.11) and severe PTSD (HR=1.15; 95%CI:1.07–1.23) were significantly associated with increased risk for microvascular complication. Hyperarousal was associated with a 42% lower risk of starting insulin. Negative mood was associated with a 16% increased risk for any microvascular complication. Severe PTSD was associated with a lower risk for all-cause mortality (HR=0.76; 95%CI:0.63–0.91).

Conclusions: Patients with comorbid PTSD and T2D have an increased risk for microvascular complications. However, they have lower mortality risk perhaps due to more health care use and earlier chronic disease detection. PTSD screening among patients with T2D may be warranted.

Keywords

PTSD; Type 2 diabetes; insulin; microvascular; epidemiology; veterans

INTRODUCTION

Posttraumatic stress disorder (PTSD) affects 6.1% to 9.2% of civilians[1–3] and 13% of primary care patients.[4] The lifetime prevalence of PTSD was 23.1% among users of VA healthcare, versus 7.4% among those who do not use VA care.[5] PTSD has been associated with numerous poor health outcomes, including type 2 diabetes (T2D).[6] In a Veterans Health Administration (VHA) primary care sample, the prevalence of comorbid PTSD and T2D was 8.9%,[7] and among persons with PTSD in the National Epidemiological Survey of Alcohol and Related Conditions (NESARC), 11% had comorbid T2D.[8]

PTSD is associated with increased risk for T2D[9–12] and clinically meaningful PTSD improvement is associated with a 49% decreased risk for incident T2D.[13] The behavioral symptoms of PTSD, such as withdrawal and disengagement in healthy lifestyles, and biological processes associated with PTSD, such as autonomic nervous system dysregulation, may contribute to the increased risk of T2D among persons with PTSD.[14]

Patients with comorbid PTSD and T2D had poorer glycemic control, compared to patients with T2D alone,[15–17] and are more likely to experience hospitalization and low self-rated health status.[18] Yet, the literature on the association between PTSD and T2D outcomes is sparse, and it is not clear if more severe PTSD is associated with increasing risk for adverse events.

To address this knowledge gap and inform management of comorbid PTSD and T2D, we examined whether PTSD severity was associated with hyperglycemia, the need to start insulin, microvascular complications, and all-cause mortality. Second, we compared results by age group, race, and presence of comorbid depression and obesity. Third, we

determined if individual PTSD symptoms varied in their association with T2D outcomes. We hypothesized more severe, compared to less severe PTSD, would be associated with worse T2D outcomes and increased risk for mortality.

METHODS

Data source:

This retrospective cohort study utilized VHA administrative medical record data obtained from clinic encounters between 10/1/11 and 9/30/22 (FY12-FY22). Data includes diagnostic codes (ICD-9 and ICD-10), Current Procedural Terminology (CPT) codes, pharmacy records, laboratory results, vital signs, vital status, and demographic information.

All study procedures were reviewed by the Saint Louis University and Veterans Health Affairs IRBs and deemed exempt because data is de-identified.

Eligibility:

The base sample included patients with at least one PTSD diagnostic code from FY12 to FY22. We then selected patients with ≥ 1 PTSD Symptom Checklist score for DSM-IV (PCL-IV) or DSM-5 (PCL-5). PCL-4 total scores were crosswalked to PCL-5 using existing methods.[19] PCL scores were measured between FY14-FY20, so patients could have a 2-year lookback for eligibility and a possible 2 to 9 years of follow-up. T2D was defined by an ICD-9 (250.x0, 250.x2) or ICD-10 code (E11.x) in the year before index.

The index date was the first PCL in FY14-FY20 that met the following eligibility criteria: 1) comorbid PTSD and T2D diagnosis in the year prior; 2) no insulin fills or type 1 diabetes in the two years prior; and 3) no microvascular complications in the two years prior. Patients were required to have controlled diabetes at baseline, i.e., last HbA1c in year before index was < 7.5. Patients were aged 18–80 years at baseline and those with missing demographic data were excluded. This resulted in an eligible cohort of 23,161 patients with comorbid PTSD and T2D with controlled diabetes who were free of microvascular complications at index. The sampling design is shown in figure 1.

Study variables:

Detailed variable definitions are shown in Appendix A, e-table 1.

Outcome variables:

T2D outcomes were starting insulin, poor glycemic control, any microvascular complication, and all-cause mortality. Pharmacy dispensing records documented insulin initiation. Poor glycemic control was defined as an HbAlc ≥ 7.5. Microvascular complications included diabetic nephropathy, retinopathy, or neuropathy. All-cause mortality was obtained from the VA's vital master file, which includes dates of death gathered from VA medical records, the Social Security Administration, the Beneficiary Identification Records Locator Subsystem, and Center for Medicare and Medicaid Services.

Exposure:

PTSD was defined by ICD-9 code 309.81 or ICD-10 code F43.1x on at least 2 separate outpatient visits within a 12-month period or one inpatient stay. Patients must have met this criterion in the year prior to baseline/index. The criterion of two diagnostic codes within four months has an 82% positive predictive value when compared to a gold standard PTSD Checklist (PCL) score ≥50,[20] and the presence of two diagnostic codes has an 88.4% agreement with the Structured Clinical Interview for DSM-IV (SCID) lifetime PTSD diagnosis.[21] This exceeds the accuracy of diagnoses obtained from the World Health Organization Composite International Diagnostic Interview when compared to gold standard diagnosis from the Structured Clinical Interview for DSM Disorders.[22,23]

PCL-5 scores, and crosswalked PCL-4 scores, were used to create a 3-level PTSD severity group. PCL scores <33 were classified as mild PTSD, scores between 33–65 defined moderate PTSD and scores >65 defined severe PTSD. Separate exploratory analyses among the subset of patients whose index PCL was a PCL-5 (n=13,791) treated each PTSD symptom cluster (intrusion, avoidance, negative alternations in cognition and mood, and hyperarousal) as separate exposures. The VHA implemented the PCL-5 in FY2016 (10/1/15). Each individual PCL-5 item was coded as "present" if endorsed as at least moderately (2,3,4 on a scale of 0 to 4).[24] Intrusion and avoidance were positive if at least one out of five items and one out of two items, respectively, were endorsed. Negative alterations of cognition and mood and hyperarousal were counted as present if at least two out of seven items or two out of six items were endorsed, respectively.

Covariates:

All covariates were measured in the 2 years before index date, unless otherwise noted. We controlled for cohort entry year, age, race, gender, marital status, and U.S. census region. Health insurance was defined as VA only vs. VA plus other health coverage. To control for detection bias, we adjusted for the volume of health care utilization defined by computing the average number of outpatient clinic encounters per month. The distribution of the mean was then used to categorize high health care users who were in the top 25th percentile vs. non-high health care users.

We controlled for baseline HbA1c (i.e., last available value in year before index). We controlled for the following psychiatric comorbidities: depression, dysthymia, any anxiety disorders (generalized anxiety, panic disorder, social phobia or anxiety disorder not otherwise specified), obsessive compulsive disorder, bipolar disorder, and schizophrenia. We controlled for any type of substance use disorder and nicotine dependence/smoking status (yes/no).

Because treatment may reduce adverse impacts of PTSD on T2D outcomes, we controlled for minimally adequate duration of PTSD psychotherapies. The minimum adequate duration was at least 9 sessions in any 15-week period. Acute phase antidepressant therapy was defined as a minimum of 12 continuous weeks of fills for an antidepressant. Sustained use of antipsychotics was defined as at least two fills for any antipsychotic medication in a 6-month period.

We controlled for the following physical comorbidities: obesity, hyperlipidemia, atrial fibrillation, angina, heart failure, hypertension, left ventricular hypertrophy, myocardial infarction, peripheral vascular disease, and stroke. Last, we controlled for sustained use, i.e., two fills in any 6-month period, for an antipsychotic and the following antidiabetic medications: metformin, sulfonylurea, dipeptidyl peptidase 4 (DPP-4) inhibitors (DPPs), glucagon-like peptide 1 (GLP-1) agonists (GLPs), Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors (SGLTs) and thiazolidinediones (TZDs)

Analytic approach

We weighted data via entropy balancing (e-balance)[25,26] which removes meaningful differences in the distribution of potential confounding factors by mild, medium and severe PTSD. The *WeightIt* package in Rv4.2.1 was used to calculate e-balance weights.[27] Balance was evaluated using the standardized mean difference percent (SMD% = 100*SMD). Well-balanced covariates have an SMD% < 10%[28].

Analyses were performed with SAS v9.4 (SAS Institute, Cary, NC) at a two-tailed alpha = 0.05. Variable distributions are presented as means (±standard deviation (sd)), frequency and percent. We used intention to treat analyses where PTSD severity was measured at index and assigned as if randomized to mild, moderate, or severe PTSD. Bivariate comparisons between covariates and PTSD severity group were performed using chi-square tests for categorical variables and one-way ANOVA for continuous variables. Maximum SMD% between all pairwise comparisons before and after e-balance assessed covariate balance. Competing risk models,[29] which account for the competing risk of death, were used to estimate the associations between PTSD severity and each T2D outcome. The censor date for starting insulin and for microvascular complications was either death or last visit date in follow-up, while for poor glycemic control, it was death or last HbA1c measurement. Cox proportional hazard models were used to estimate the association between PTSD severity group and all-cause mortality. Censor date for the all-cause mortality models was the end of follow-up (9/30/22). Follow-up time was measured as months from index to either the outcome date or the censor date. All models were computed before and after weighting to calculate hazard ratios and 95% confidence intervals for the association between PTSD severity and T2D outcomes. Weighted models used robust, sandwich-type variance estimators for confidence intervals.[28] The proportional hazard assumption for all models was met ($p>0.10$).

Subgroup analyses were computed by age group (18–49, 50–64 and 65–80 years of age) race (White vs. Black), and depression status (yes/no). E-balance weights balanced confounders for each sub-analysis. Interaction terms of PTSD severity by the stratification variable assessed whether age, race or depression modified the relationship of severity and each outcome ($p<.05$ indicated significant modification). Because obesity is a large risk factor for adverse T2D outcomes, we computed sensitivity analyses limited to patients without obesity.

We explored individual PTSD symptom clusters (intrusion, avoidance, negative alterations in cognition and mood, and hyperarousal) as exposures in Cox and competing risk models for all outcomes. Because symptom level analysis was exploratory and included four

different exposure variables (intrusion, avoidance, negative mood, hyperarousal – all binary yes/no), traditional, fully-adjusted models were computed and included the four exposure variables and all confounders in each outcome model.

Finally, we computed a sensitivity analysis by calculating competing risk and Cox models using continuous PCL score as the exposure. Confounding was controlled using e-balance.

RESULTS

As shown in Table 1, over 70% of the sample was ≥50 years of age, 88% were male, and 30.5% Black race. Mild PTSD was present in 17.1% of the sample, 67.4% had moderate and 15.5% had severe PTSD. During follow-up, approximately 43% of patients developed poor glycemic control and any microvascular complication, 11.4% started insulin and 6.9% died.

Table 2 contains the distribution of patient characteristics by PTSD severity. As indicated by an unweighted SMD%>10, patients 40–59 were more prevalent in severe PTSD (SMD% range = 17.56%−20.85%) while patients ≥60 years of age were more common among mild PTSD (SMD%=36.85). Black race was more prevalent among those with moderate and severe PTSD (SMD%=22.93) and White race was more common in mild and moderate PTSD (SMD%=26.51). Patients with VA health insurance only, compared to VA plus other forms of health insurance, were more prevalent among severe PTSD (SMD%=22.15) as was high health care utilization (SMD%=16.79).

The prevalence of depression increased from 51.5% in mild PTSD to 63.9% in severe PTSD (SMD%=25.19). Anxiety, alcohol, and drug abuse/dependence was more prevalent in severe PTSD (SMD% range: 11.03 – 17.62). Minimally adequate duration of PTSD psychotherapy (SMD%=10.11) and sustained antipsychotic medication fills (SMD%=18.43) increased with worse PTSD severity. Obesity (SMD%=10.41) was more common with increasing PTSD severity. All variables were successfully balanced, SMD% were <10.0.

The incidence rate per 1,000 person years (PY) for each T2D outcome is shown in Table 3. PTSD severity was significantly associated with incidence of starting insulin (p=.002). The incidence rate for insulin starts was 23.8/1,000PY in mild PTSD, 22.6/1,000PY in moderate and 27.3/1,000PY in severe PTSD. PTSD severity was significantly associated with all-cause mortality rate (p<.001). The mortality incidence rate was 15.7/1000PY among patients with mild PTSD, 13.0/1000PY in moderate PTSD and 9.9/1000PY among those with severe PTSD. PTSD severity was not significantly associated with the incidence rate for poor glycemic control and microvascular complication.

Median follow-up time from index to outcome or censor date increased with severity of PTSD. Median follow-up time to insulin initiation was 53 (Interquartile range (IQR):37–80) months in mild PTSD, 55 (IQR:38–79) months in moderate and 57 (IQR:39–81) months in severe PTSD. Median time to poor glycemic control was 36 months in mild (IQR: 19–59) and moderate (IQR: 9–58) PTSD and 37 (IQR: 18–60) months in severe PTSD. Follow-up time to any microvascular complication was 40 (IQR: 24–63), 41 (IQR: 25–62) and 43 (IQR: 25–64) months for mild, moderate and severe PTSD, respectively. Last, follow-up

time to all-cause mortality was 60 (IQR: 42–88), 61 (IQR: 43–87) and 63 (IQR: 45–89) months for mild, moderate and severe PTSD, respectively.

After weighting data to control for confounding (see Table 4), there was no significant association between PTSD severity and risk of starting insulin or risk of poor glycemic control. Compared to mild PTSD, moderate (HR=1.05; 95% CI:1.01–1.11) and severe PTSD (HR=1.15; 95%CI:1.07–1.23) were significantly associated with increased risk for microvascular complication. Patients with severe PTSD had a significantly lower risk for all-cause mortality compared to those with mild PTSD (HR=0.76; 95%CI:0.63–0.91).

The associations between PTSD severity and risk for T2D outcomes, stratified by age groups, are shown in e-Table 2. Only the relationship between PTSD severity and starting insulin was significantly modified by age. Among those 18 to 49 years of age, severe PTSD compared to mild PTSD was associated with increased risk of starting insulin (HR=1.24; 95%CI:1.01–1.52). Among patients 65 to 80 years of age, moderate vs. mild PTSD was associated with lower risk of starting insulin (HR=0.70; 95%CI:0.58–0.85).

As shown in e-Table 3, associations between PTSD severity and outcomes did not differ by race. In e-Table 4, comorbid depression modified the relationship between PTSD severity and all-cause mortality. No relationship was observed among patients without depression. Among those with depression, severe vs. mild PTSD was associated with lower risk of all-cause mortality (HR=0.63; 95%CI: 0.50–0.80).

Among patients without obesity, moderately severe vs. mild PTSD was significantly associated with a lower risk for starting insulin (HR=0.81; 95%CI:0.67–0.97), see e-Table 5. Among non-obese patients, severe and moderate PTSD, compared to mild PTSD, was significantly associated with risk for any microvascular complication (HR=1.18; 95%CI:1.05–1.33; and HR=1.09; 95%CI:1.01–1.09, respectively).

As shown in Table 5, after controlling for confounding and other symptom clusters, hyperarousal was significantly associated with a lower risk of starting insulin (HR=0.58;95%CI:0.43–0.80). Negative alterations of cognition and mood was significantly associated with an increased risk for any microvascular complication (HR=1.16; 95%CI:1.01–1.33). Other PTSD symptoms were not associated with T2D outcomes and all-cause mortality.

As shown in e-Table 6, among non-obese patients, negative alterations of cognition and mood were significantly associated with any microvascular complication (HR=1.41; 95%CI:1.11–1.78) and hyperarousal was associated with a lower risk for mortality (HR=0.52; 95%CI:0.31–0.85).

As shown in e-Table 7, using the PCL score as a continuous exposure variable in models did not change results or conclusions. Unit increases in PCL score were unrelated to starting insulin and poor glycemic control. However, there was a small but significant increase in the risk for any microvascular complication (HR=1.002; 95%CI: 1.001–1.004) and a small significant decrease in the risk for all-cause mortality (HR=0.995; 95%CI: 0.992–0.998).

DISCUSSION

In a large cohort of VHA patients with comorbid PTSD and T2D, we observed that compared to mild PTSD, moderate and severe PTSD were linked to a 5% and 15% increased risk, respectively, of T2D microvascular complications, despite no evidence for a relationship between PTSD severity and glycemic control. Overall, only the PTSD symptom cluster, negative alterations in cognition and mood, was associated with an increased microvascular complication risk. In contrast, hyperarousal was associated with a 42% lower risk of starting insulin. These associations remained when the sample was limited to patients without obesity.

To our knowledge, this is the first report on the relationships between PTSD severity and T2D outcomes. We found no evidence that PTSD severity was followed by poor glycemic control. Comparing this finding with existing literature is difficult because most studies have compared PTSD vs. no PTSD. One exception, consistent with our results, indicated that total PTSD symptom score was not associated with HbA1c values.[30] Although absolute differences in HbA1c values were small[7] significantly higher mean HbA1c values have been reported among those with PTSD and depression, as compared to patients without both conditions, but no difference was found when comparing PTSD vs. no PTSD. Following the Fukushima nuclear disaster, probable PTSD was associated with suboptimal glycemic control (i.e.HbA1c ≥7.0)[17] which is consistent with a study of PTSD and hyperglycemia among low-income Black women.[15] Among women treated for T2D in primary care, those with avoidance and hyperarousal symptoms had higher HbA1c scores compared to those without each symptom,[31] while intrusion was the only symptom positively correlated with higher HbA1c symptoms in a civilian sample.[30] We observed hyperarousal was inversely associated with insulin initiation suggesting better overall T2D control and negative mood was followed by greater risk for complications. The existing studies of specific PTSD symptoms and T2D outcomes are inconsistent which may be due to different cohort characteristics with one study of women,[31] a second in civilians[30] and the present study among VHA patients. We observed that severe PTSD was associated with a 15% increased risk for microvascular complications. Complications are typically related to hyperglycemia and the absence of an association between PTSD severity and glycemic control in the present study may be explained by the VHA's superior T2D care compared to the private sector.[32]

We did not expect an inverse relationship between more severe PTSD and mortality. Some evidence suggests persons with PTSD have an increased mortality risk due to chronic disease, suicide and substance abuse.[33,34] Yet the risk associated with having PTSD likely differs from the association between PTSD severity and mortality. A recent meta-analyses and a study of the World Trade Center Health Registry found PTSD was significantly associated with a 32% to 91% increased risk for mortality.[35,36] However, 8 out of 30 studies included in the meta-analyses found a null relationship between PTSD and all-cause mortality[36] and another found a lower risk for mortality.[37] We balanced the year of cohort enrollment which indicates differences in follow-up time by PTSD severity or age group do not explain mortality results. More severe PTSD may lead to frequent interaction with the healthcare system which may lead to earlier detection and treatment of chronic

conditions and life-threatening illness. VHA patients with PTSD had more visits to primary care, specialty mental health, other specialty care and were more likely to use integrated behavioral health, all of which may improve health outcomes.[37] Another possibility is the healthy soldier effect related to high military fitness requirements.[38] However, this would only apply to older Veterans because the effect was not observed in Veterans of the Afghanistan and Iraq wars.[38] We also observed no increased risk for mortality among patients with both PTSD and depression which is not consistent with evidence that persons with both conditions have a greater risk for some causes of death, e.g., suicide, relative to having either condition alone.[33] However, a study of internalizing vs. externalizing disorders and all-cause mortality among veterans with T2D suggest substance use disorders, but not depression and anxiety, are significantly associated with a 22% increased risk of death. This association was no longer significant after controlling for adherence to anti-diabetic medications.[39] These authors note prior work indicating medication non-adherence among patients with diabetes is associated with mortality.[40] Although speculative, another potential explanation is that the high prevalence of comorbidities in patients with PTSD and T2D results in more medical encounters, as compared to those without these conditions. These additional medical encounters may lead to early identification and treatment of life-threatening conditions. Given the mix of evidence, further research on PTSD and mortality is needed. Some groups may have a greater risk for mortality based on specific comorbidities or because of different sources of vulnerability related to genetic or environmental risks. For patients with comorbid PTSD and T2D, adding psychosocial factors and genetic information to medical record data could identify subgroups who do vs. do not have elevated risk of death. Efforts to obtain data to conduct this type of research are currently underway in the form of the Million Veteran Program[41] and the All of Us Study.[42]

Limitations:

The duration of PTSD and T2D prior to index was unknown. Heterogeneity in duration of illness may contribute to less precise point estimates. There is a risk of misclassification and unmeasured confounding. For example, it is possible that patients had undiagnosed microvascular complications and were misclassified as unaffected. This would bias hazard ratios toward the null. Unmeasured confounding is a risk but we believe we have measured a large number of potential confounding factors and are unaware of any key confounding factor not included in this study or uncorrelated with measured confounding variables. Last, the study was based on VHA data and may not generalize to civilians. Nonetheless, we have largely replicated results in VHA and civilian cohorts across a wide range of conditions.[43–47]

Conclusions:

Patients with severe as compared to mild PTSD have an elevated risk for microvascular complications. This may be due to the negative cognitive and mood symptoms of PTSD. Further research with other cohorts is needed to understand mixed findings regarding PTSD severity and glycemic burden and mortality. Patients and providers should be aware of the risk for microvascular complications in comorbid severe PTSD and T2D. Enhanced T2D monitoring in patients with severe PTSD is appropriate.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data sharing statement:

Data will be made available after completion of funding period and via direct request to the corresponding author.

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Highlights

- PTSD is a risk factor for type 2 diabetes
- Uncertain if PTSD severity is associated with comorbid diabetes outcomes
- Severe PTSD associated with increased risk of microvascular complications
- PTSD severity inversely associated with all-cause mortality

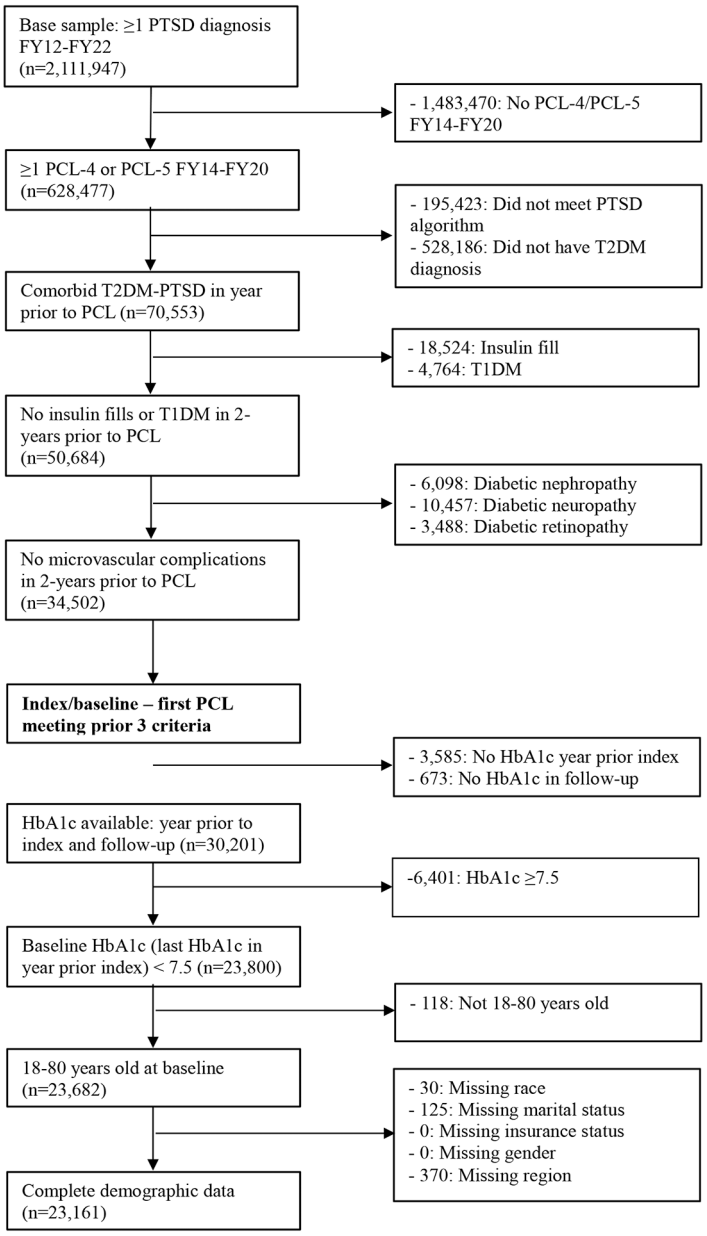

Figure 1.
Veterans Health Administration eligibility criteria

Table 1.

Baseline characteristics and outcomes for comorbid PTSD-T2D veterans (n=23,161)

	n(%) or mean(±sd)
Index fiscal year	
2014	4224 (18.2)
2015	2766 (11.9)
2016	2311 (10.0)
2017	2999 (12.9)
2018	3784 (16.3)
2019	4167 (18.0)
2020	2910 (12.6)
Demographics	
Age	
18–39	2293 (9.9)
40–49	4555 (19.7)
50–59	5881 (25.4)
≥60	10432 (45.0)
Male gender	20377 (88.0)
Race	
Black	7057 (30.5)
Other	1224 (5.3)
White	14880 (64.2)
Married	14060 (60.7)
Region	
Northeast	2540 (11.0)
Midwest (North central)	4236 (18.3)
South	11648 (50.3)
West	4737 (20.5)
VA only insurance	8461 (36.5)
High healthcare utilization	5791 (25.0)
PTSD-T2D	
PCL-5 score, mean(±sd)	48.7 (±16.4)
PCL severity	
Mild	3959 (17.1)
Moderate	15612 (67.4)
Severe	3590 (15.5)
HbA1c, mean(±sd)	6.3 (±0.6)
Psychiatric comorbidities	
Depression	13178 (56.9)
Dysthymia	901 (3.9)

	n(%) or mean(±sd)
Anxiety	6215 (26.8)
OCD	192 (0.8)
Bipolar Disorder	2020 (8.7)
Schizophrenia	617 (2.7)
Alcohol abuse/dependence	6057 (26.2)
Drug abuse/dependence	3821 (16.5)
Smoking	10640 (45.9)
Adequate PTSD treatment	2410 (10.4)
Antidepressant medication≥ 12 weeks	15332 (66.2)
Atypical antipsychotic (sustained use)	4239 (18.3)
Physical comorbidities	
Obesity	15565 (67.2)
Hyperlipidemia	17748 (76.6)
Atrial Fibrillation	1143 (4.9)
Angina	387 (1.7)
Congestive heart failure	1086 (4.7)
Hypertension	17382 (75.1)
Left ventricular hypertrophy	641 (2.8)
MI	359 (1.6)
Peripheral vascular disease	986 (4.3)
Stroke	805 (3.5)
Diabetes drugs (sustained use)	
Metformin	10584 (45.7)
Sulfonylurea	2637 (11.4)
DPP[1]	361 (1.6)
GLP[2]	112 (0.5)
SGLT[3]	107 (0.5)
TZD[4]	176 (0.8)
Outcomes	
Start insulin	2637 (11.4)
Poor glycemic control	9802 (42.3)
Diabetic nephropathy	3934 (17.0)
Diabetic neuropathy	6452 (27.9)
Diabetic Retinopathy	3102 (13.4)
Any microvascular outcome	9889 (42.7)
All-cause Mortality	1606 (6.9)

[1] dipeptidyl peptidase 4 (DPP-4) inhibitors (DPPs),

[2] glucagon-like peptide 1 (GLP-1) agonists (GLPs),

3) Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors (SGLTs),

4) thiazolidinediones (TZDs)

Table 2.

Baseline characteristics for comorbid PTSD-T2D veterans, by PCL severity (n=23,161)

	Mild PTSD (n=3,959)	Moderate PTSD (n=15,612)	Severe PTSD (n=3,590)	p-value	Max Unweighted SMD%	Max weighted SMD%
Index fiscal year				<.001		
2014	684 (17.3)	2847 (18.2)	693 (19.3)		5.25	0.01
2015	537 (13.6)	1803 (11.6)	426 (11.9)		6.13	0.01
2016	440 (11.1)	1528 (9.8)	343 (9.6)		5.17	0.02
2017	427 (10.8)	2048 (13.1)	524 (14.6)		11.41	0.02
2018	613 (15.5)	2562 (16.4)	609 (17.0)		4.01	0.01
2019	708 (17.9)	2857 (18.3)	602 (16.8)		4.02	0.02
2020	550 (13.9)	1967 (12.6)	393 (11.0)		8.92	0.02
Demographics						
Age				<.001		
18–39	365 (9.2)	1522 (9.8)	406 (11.3)		6.94	0.01
40–49	653 (16.5)	3059 (19.6)	843 (23.5)		17.56	0.01
50–59	821 (20.7)	3991 (25.6)	1069 (29.8)		20.85	0.01
≥60	2120 (53.6)	7040 (45.1)	1272 (35.4)		36.85	0.00
Male gender	3507 (88.6)	13788 (88.3)	3082 (85.6)	<.001	8.29	0.01
Race				<.001		
Black	1025 (25.9)	4724 (30.3)	1308 (36.4		22.93	0.01
Other	191 (4.8)	783 (5.0)	250 (7.0)		9.31	0.02
White	2743 (69.3)	10105 (64.7)	2032 (56.6)		26.51	0.02
Married	2479 (62.6)	9474 (60.7)	2107 (58.7)	.002	8.04	0.01
Region				<.001		
Northeast	526 (13.3)	1690 (10.8)	324 (9.0)		13.62	0.01
Midwest (North central)	747 (18.9)	2909 (18.6)	580 (16.2)		7.08	0.01
South	1848 (46.7)	7858 (50.3)	1942 (54.1)		14.86	0.03
West	838 (21.2)	3155 (20.2)	744 (20.7)		2.36	0.02
VA only insurance	1255 (31.7)	5686 (36.4)	1520 (42.3)	<.001	22.15	0.01
High healthcare utilization	858 (21.7)	3894 (24.9)	1039 (28.9)	<.001	16.79	0.00
PTSD-T2D						
HbA1c, mean(±sd)	6.3 (±0.6)	6.3 (±0.6)	6.3 (±0.6)	.902	0.93	0.00
Psychiatric comorbidities						
Depression	2038 (51.5)	8847 (56.7)	2293 (63.9)	<.001	25.19	0.01
Dysthymia	154 (3.9)	603 (3.9)	144 (4.0)	.917	7.7	0.02
Anxiety	1000 (25.3)	4132 (26.5)	1083 (30.2)	<.001	11.03	0.02
OCD	31 (0.8)	125 (0.8)	36 (1.0)	.455	2.38	0.02
Bipolar Disorder	342 (8.6)	1297 (8.3)	381 (10.6)	<.001	7.99	0.01
Schizophrenia	99 (2.5)	380 (2.4)	138 (3.8)	<.001	8.37	0.05

	Mild PTSD (n=3,959)	Moderate PTSD (n=15,612)	Severe PTSD (n=3,590)	p-value	Max Unweighted SMD%	Max weighted SMD%
Alcohol abuse/dependence	925 (23.4)	4014 (25.7)	1118 (31.1)	<.001	17.62	0.00
Drug abuse/dependence	606 (15.3)	2512 (16.1)	703 (19.6)	<.001	11.40	0.02
Smoking	1855 (46.9)	7117 (45.6)	1668 (46.5)	.284	2.54	0.02
Adequate PTSD treatment	352 (8.9)	1628 (10.4)	430 (12.0)	<.001	10.11	0.01
Antidepressant medication ≥ 12 weeks	2600 (65.7)	10264 (65.7)	2468 (68.8)	.002	6.53	0.01
Atypical antipsychotic (sustained use)	655 (16.5)	2730 (17.5)	854 (23.8)	<.001	18.43	0.00
Physical comorbidities						
Obesity	2567 (64.8)	10495 (67.2)	2503 (69.7)	<.001	10.41	0.01
Hyperlipidemia	3127 (79.0)	11924 (76.4)	2697 (75.2)	<.001	9.15	0.01
Atrial Fibrillation	230 (5.8)	768 (4.9)	145 (4.0)	.002	8.19	0.01
Angina	80 (2.0)	261 (1.7)	46 (1.3)	.044	5.79	0.05
Congestive heart failure	223 (5.6)	710 (4.6)	153 (4.3)	.007	6.41	0.03
Hypertension	3029 (76.5)	11705 (75.0)	2648 (73.8)	.021	6.36	0.01
Left ventricular hypertrophy	132 (3.3)	412 (2.6)	97 (2.7)	.057	4.15	0.02
MI	81 (2.1)	236 (1.5)	42 (1.2)	.007	7.04	0.02
Peripheral vascular disease	224 (5.7)	662 (4.2)	100 (2.8)	<.001	14.30	0.03
Stroke	145 (3.7)	547 (3.5)	113 (3.2)	.449	2.83	0.00
Diabetes drugs (sustained use)						
Metformin	1893 (47.8)	7037 (45.1)	1654 (46.1)	.007	5.50	0.02
Sulfonylurea	472 (11.9)	1767 (11.3)	398 (11.1)	.468	2.63	0.01
DPP[1]	78 (2.0)	240 (1.5)	43 (1.2)	.024	6.22	0.02
GLP[2]	18 (0.5)	79 (0.5)	15 (0.4)	.758	1.30	0.15
SGLT[3]	20 (0.5)	72 (0.5)	15 (0.4)	.855	1.29	0.13
TZD[4]	32 (0.8)	120 (0.8)	24 (0.7)	.765	1.62	0.05

[1] dipeptidyl peptidase 4 (DPP-4) inhibitors (DPPs),

[2] glucagon-like peptide 1 (GLP-1) agonists (GLPs),

[3] Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors (SGLTs),

[4] thiazolidinediones (TZDs)

Table 3.

Outcomes: cumulative incidence percent and incidence rate, by PCL-5 severity (n=23,161)

Outcome	Mild PTSD (n=3959)	Moderate PTSD (n=15612)	Severe PTSD (n=3590)	p-value
Starting insulin				
#events (%)	450 (11.4)	1705 (10.9)	482 (13.4)	<.001
Incidence rate per 1,000PY	23.8/1000PY	22.6/1000PY	27.3/1000PY	.002
Poor glycemic control				
#events (%)	1630 (41.2)	6590 (42.2)	1582 (44.1)	.035
Incidence rate per 1,000PY	122.5/1000PY	125.5/1000PY	128.8/1000PY	.364
Any microvascular complication				
#events (%)	1690 (42.7)	6628 (42.5)	1571 (43.8)	.362
Incidence rate per 1,000PY	116.7/1000PY	114.9/1000PY	116.0/1000PY	.827
Mortality				
#events (%)	329 (8.3)	1083 (6.9)	194 (5.4)	<.001
Incidence rate per 1,000PY	15.7/1000PY	13.0/1000PY	9.9/1000PY	<.001

Table 4.

Outcomes: Competing risk survival and Cox proportional hazard models, before and after entropy balancing. (n=23,161)

Outcome	Mild PTSD HR (95% CI)	Moderate PTSD HR (95% CI)	Severe PTSD HR (95% CI)
Starting insulin [a]			
Unweighted	1.00	0.95 (0.86–1.06)	1.17 (1.03–1.33)
Weighted	1.00	0.93 (0.84–1.03)	1.06 (0.93–1.21)
Poor glycemic control [a]			
Unweighted	1.00	1.03 (0.98–1.09)	1.07 (1.01–1.15)
Weighted	1.00	1.01 (0.96–1.07)	1.04 (0.97–1.11)
Any microvascular complication [a]			
Unweighted	1.00	0.99 (0.94–1.04)	1.01 (0.94–1.08)
Weighted	1.00	1.05 (1.01–1.11)	1.15 (1.07–1.23)
Mortality [b]			
Unweighted	1.00	0.83 (0.73–0.94)	0.62 (0.52–0.74)
Weighted	1.00	0.92 (0.81–1.04)	0.76 (0.63–0.91)

[a]Competing risk survival models

[b]Cox proportional hazard model

Table 5.

Exploratory analysis of presence vs. absence of PCL-5 symptom cluster. Fully adjusted models among patients whose index PCL is a PCL-5. (n=13,791)[a]

Symptom class	***Starting insulin*** [b]	***Poor glycemic control*** [b]	***Microvascular complication*** [b]	***Mortality*** [c]
	HR (95% CI)	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Intrusion	0.83 (0.60–1.14)	0.97 (0.83–1.15)	1.07 (0.90–1.26)	0.94 (0.64–1.38)
Avoidance	1.08 (0.83–1.41)	0.98 (0.87–1.11)	0.89 (0.80–1.01)	0.98 (0.73–1.33)
Negative cognitive and mood symptoms	1.09 (0.80–1.49)	0.96 (0.83–1.10)	1.16 (1.01–1.33)	0.87 (0.63–1.20)
Hyperarousal	0.58 (0.43–0.80)	0.89 (0.77–1.04)	0.91 (0.78–1.06)	0.94 (0.67–1.33)

[a]Fully adjusted model controls for all confounders, PCL severity, and the presence/absence of the other 3 symptom clusters.

[b]Competing risk survival models

[c]Cox proportional hazard model