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Posttraumatic Stress Disorder and Incident Fractures in the Danish Population

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Abstract

Summary: Psychological stress may be associated with increased risk of fractures. It is unknown whether posttraumatic stress disorder (PTSD), a marker of chronic severe psychological stress occurring in response to a traumatic event, influences fracture risk. In this nationwide cohort study, persons with PTSD had an increased risk of fractures compared to the general population.

Purpose/Introduction: We conducted a population-based national cohort study in Denmark to examine the association between PTSD and incident fractures.

Methods: We examined the incidence rate of overall and specific fractures among patients with clinician-diagnosed PTSD (n = 4,114), compared with the incidence rate in the general population from 1995–2013, using Danish medical registry data. We further examined differences in associations by gender, age, psychiatric and somatic comorbidity, and follow-up time. We calculated absolute risks, standardized incidence ratios (SIRs), and 95% confidence intervals (95% CIs).

Results: Risk of any fracture among persons with PTSD was 24% (95% CI: 20%, 28%) over the study period. The SIR for any fracture was 1.7 (95% CI: 1.6, 1.9). We found little evidence of effect-measure modification of the association between PTSD and fractures in our stratified analyses.

Conclusions: Our findings suggest that PTSD is associated with increased fracture risk.

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Conflict of Interest

Tammy Jiang, Katalin Veres, Dóra Körmendiné Farkas, Timothy L. Lash, Henrik T. Sørensen, and Jaimie L. Gradus declare that they have no conflict of interest.

Keywords

Stress; Posttraumatic stress disorder; Fracture; Longitudinal; Nationwide

INTRODUCTION

Posttraumatic stress disorder (PTSD) occurs after exposure to a psychological stressor and is characterized by re-experiencing, avoidance, and arousal [1]. PTSD is a common psychiatric disorder that is associated with negative physical health outcomes, premature mortality, and significant costs to society [2,3]. An emerging body of literature suggests that traumatic events and psychological stress may increase the risk of bone fractures [4–6]. Potential mechanisms underlying this association include increased allostatic load due to psychological stress, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, and secretion of glucocorticoids, which may impair the functioning of bone-forming cell osteoblasts and decrease bone mineral density, leading to increased risk of fractures [7–12]. Unhealthy behaviors associated with stress such as smoking, lack of exercise, poor diet, and alcohol consumption [13–16], may also increase the risk of fractures. In animal studies, prolonged stress in mice activates bone resorption, suppresses bone formation, and has long-lasting consequences on skeletal growth [5,17]. Despite these plausible mechanisms linking psychological stress and fractures, we know of no studies investigating the association between PTSD and fracture risk. The current study examines the association between PTSD, a marker of chronic severe psychological stress, and fracture risk using data from a nationwide cohort study in Denmark. Given how common PTSD and fractures are, observed associations could have meaningful public health implications.

Research to date provides inconclusive evidence for the association between psychological stress and fracture risk. In a Danish population-based cohort study, persons who reported high levels of perceived psychological stress, based on the degree to which situations in one's life were appraised as stressful, were at increased risk of osteoporotic fractures compared to persons who reported low levels of perceived psychological stress [4]. In a case-crossover study of elderly people in Sweden, self-reported emotional stress was associated with greater risk of hip and pelvic fractures [6]. However, in a prospective study of older men in the United States, any self-reported stressful life event (*e.g.*, serious illness or accident of wife or partner, death of other close relative or close friend, serious financial trouble, etc.) was not associated with fracture risk [18]. Psychological stress was defined and measured differently across these studies, potentially contributing to heterogeneous results [4,6,18].

Previous studies have been limited by a focus on specific types of psychological stress or a single stressful event and thus, little is known about the association between PTSD and fracture risk. The current study fills this gap in the literature by comparing the incidence rate of fractures in a nationwide cohort of patients with clinician-diagnosed PTSD with the incidence rate of fractures in the general population from 1995–2013. We further examined whether these associations varied by gender, age, depression status, substance abuse/dependence status, somatic comorbidity, and follow-up time.

METHODS

The base population for the study was Danish-born residents of Denmark. Methods for the development of the stress disorder cohort, from which we obtained PTSD diagnoses, have been described elsewhere [19]. We created a national cohort of all persons with any International Classification of Diseases, Tenth Revision (ICD-10) PTSD diagnosis at a psychiatric treatment facility from 1995 through 2013 ($n = 4,040$). For the purposes of the current study, PTSD diagnoses from somatic treatment facilities were added to the cohort as well ($n = 1,636$). There were 662 persons with PTSD diagnoses in both the psychiatric and somatic treatment registries. Figure 1 displays a flow chart of PTSD patients. Additional data included in this study from national medical and social registries are described below.

Data Sources

The Danish Civil Registration System (CRS) contains Danish citizens' date of birth, gender, other demographic data, and central personal registry (CPR) number, which is a unique identifier for each Danish citizen. This identifier can be used to link data across all Danish administrative and medical registries [20]. The CRS, updated daily, contains data on the vital status of each resident.

The Danish Psychiatric Central Research Registry (DPCRR) has recorded all dates of inpatient psychiatric treatment since 1969 and outpatient psychiatric treatment since 1995 and contains up to 20 diagnoses per treatment episode [21,22]. A validation study of stress diagnoses in the DPCRR showed high validity for PTSD diagnoses [23]. This registry was used to obtain data on PTSD for the creation of the initial stress cohort [19].

The Danish National Registry of Patients (DNRP) has covered all inpatient non-psychiatric hospital treatment in Denmark since 1977, and outpatient clinic and emergency room visits since 1995 [24]. We used the DNRP to identify patients with clinician-diagnosed fractures of the neck, spine and pelvis, shoulder and humerus, forearm, hand and wrist, and femur. We also used the DNRP to obtain other physical illness diagnoses and to compute a Charlson Comorbidity Index (CCI) score, a measure of overall physical health status [25]. The diagnoses used to construct the CCI score are listed in Table 1. PTSD and psychiatric comorbidities registered in the DNRP during the study period were also included in the current study.

Analyses

PTSD patients were followed from one year after date of PTSD diagnosis until date of emigration, date of death, or 30 November 2013, whichever came first. We restricted our analyses to fractures diagnosed at least one year after the PTSD diagnosis date to ensure that the PTSD diagnosis did not follow the fracture diagnosis. For the analysis of each fracture type as the outcome, we examined the first diagnosis of that type of fracture. For the analysis of any fracture as the outcome, we randomly chose one fracture diagnosis for patients who had more than one fracture diagnosed on the same day ($n = 201$; 5%). We further restricted our analyses to adults (age 16 years or older).

We calculated absolute risks and associated 95% confidence intervals (CIs) for fractures overall and for each fracture type among persons with PTSD during the study period, treating death as a competing risk. We multiplied person-years of follow-up and Danish national incidence rates of fractures to obtain the number of fractures that would be expected if people with PTSD had the same fracture rate as the general population [26] according to gender, 5-year age groups, and 5-year calendar periods. We also calculated SIRs to measure the association between PTSD and fractures as the ratio of the number of observed cases to the number of expected cases. The CIs were calculated assuming that the observed number of fractures followed a Poisson distribution. Exact confidence limits were calculated when there were fewer than 10 observed fracture diagnoses; otherwise, Byar's approximation was used [26].

Gender, depression status, substance abuse/dependence status, and somatic comorbidities are potentially important confounders of the association between PTSD and fractures. There may also be effect measure modification of the association between PTSD and fractures by these variables, and also by age at PTSD diagnosis and follow-up time. Thus, we conducted stratified analyses by gender, age at PTSD diagnosis (16-39, 40-59, and 60+ years), depression status, substance abuse/dependence status at the start of the study period, somatic comorbidities, and the time interval between first PTSD diagnosis and incident fracture diagnosis (1 to <5, 5 to <10, and 10+ years).

Given the study design, we were unable to adjust for confounding by behavioral risk factors. Smoking is an important potential unmeasured confounder of the association between PTSD and fractures because smoking is associated with both an increased risk of PTSD and increased risk of fractures [27,28]. We conducted a bias analysis to assess the impact of unmeasured confounding due to smoking using the formula $[RR * P_{z1} + (1 - P_{z2})] / [RR * P_{z0} + (1 - P_{z0})]$, where RR = the association between the unmeasured confounder and the outcome, P_{z1} = the prevalence of the unmeasured confounder among the exposed, and P_{z0} = the prevalence of the unmeasured confounder among the unexposed [29]. The analyses were conducted using SAS version 9.4. The study was approved by the Danish Data Protection Agency (record number 2012-41-0841) and by the Institutional Review Board at Boston University.

RESULTS

From the original PTSD cohort of 5,014 persons, we identified 4,114 persons with an incident PTSD diagnosis who had not been diagnosed with a fracture at the start of the study period and who were still alive one year after PTSD diagnosis. Persons with PTSD were followed for an average of 7.8 years (median follow-up 7.0 years; range 1-18 years). Age at PTSD diagnosis ranged from 16 to 92 years (mean age 40.6 years; median age 40.5 years). Table 1 shows the descriptive characteristics of the cohort at the time of PTSD diagnosis. Cohort members were predominantly female ($n = 2,569$; 62%), younger than age 60 years ($n = 3,840$; 93%), without a depression diagnosis ($n = 3,888$; 95%), without an alcohol abuse/dependence diagnosis ($n = 3,802$; 92%), without a drug abuse/dependence diagnosis ($n = 4,028$; 98%), and with a CCI score of 0 ($n = 3,414$; 83%), indicating little somatic comorbidity.

Overall Associations and Impact of Demographic Factors

Table 2 displays the absolute risks of fractures and the observed and expected numbers of incident fractures in the PTSD cohort, with associated SIRs and 95% CIs. There were 394 fractures among members of the PTSD cohort. Risk of any fracture among persons with PTSD was 24% over the study period (95% CI: 20%, 28%). Fracture of the hand and wrist was the most common type of fracture during the follow-up period (absolute risk: 7.5%, 95% CI: 5.9%, 9.4%). The lowest risk was found for fracture of the neck (absolute risk: 0.19%, 95% CI: 0.08%, 0.44%). The observed incidence rate for any fracture among the PTSD cohort was 1.7 times the expected incidence rate based on the rate in the general population (95% CI: 1.6, 1.9). Table 3 presents the age-specific absolute risks of fractures in the PTSD cohort. There was no effect measure modification of the association between PTSD and fractures by sex and age.

Impact of psychiatric and somatic comorbidity

We conducted stratified analyses by depression status. Depression is a potential strong confounder of the association between PTSD and fractures, as depression is both highly comorbid with PTSD and independently associated with fractures [30,31]. We had too few cases to perform stratified analyses by depression status for fractures of the neck, spine and pelvis, shoulder and humerus, and femur. However, for overall fractures and forearm fractures, the SIRs were generally consistent across depression status. With regard to substance abuse, there was effect modification for fracture of the shoulder and humerus; persons with substance abuse/dependence diagnoses had an SIR of 5.6 (95% CI: 2.8, 10), while persons without these diagnoses had an SIR of 1.2 (95% CI: 0.87, 1.7). There was little effect modification by CCI score.

Follow-up Time

We examined differences in associations between PTSD and fractures by length of time between diagnosis of PTSD and diagnosis of fracture and found that the strength of associations were similar over time (Table 4). For any fracture as the outcome, the SIR was 1.7 (95% CI: 1.5, 2.0) among persons who had a follow-up time between 1 to <5 years, 1.6 (95% CI: 1.4, 2.0) among persons who had a follow-up time between 5 to <10 years, and 2.0 (95% CI: 1.6, 2.4) among persons who were followed for 10+ years.

Bias Analysis to Assess the Impact of Unmeasured Confounding due to Smoking

We conducted a bias analysis to assess the potential impact of unmeasured confounding due to smoking on our results. The prevalence of smoking among people with and without PTSD is approximately 58% and 38%, respectively [32]. A meta-analysis of smoking and fracture risk found that smokers had 1.13 times the risk of any fracture compared to nonsmokers [27]. Using these parameters, we estimated the potential bias in the associations between PTSD and fractures due to uncontrolled confounding by smoking. The ratio of the unadjusted to adjusted PTSD and overall fracture rate ratios was 1.02, indicating that uncontrolled confounding due to smoking does not completely account for our observed associations between PTSD and fractures, assuming a valid bias model.

DISCUSSION

PTSD is associated with an increased incidence rate of fractures of the neck, spine and pelvis, shoulder and humerus, forearm, hand and wrist, and femur. The incidence rate for any fracture among persons with PTSD was 1.7 times the incidence rate that would be expected based on the fracture rate in the general population during the same time period (95% CI: 1.6, 1.9).

Our results are consistent with the results from a study of elderly Swedes which found that there was an increased risk of hip and pelvic fracture after emotional stress [6]. The current study found that PTSD was associated with an increased incidence rate of spine and pelvis fractures among participants who were age 60 years and older. Similarly, a previous population-based study in Denmark found that persons with a high level of perceived psychological stress were at increased risk of hip fractures compared to persons with a low level of perceived psychological stress [4]. PTSD may influence fractures through various biological and behavioral mechanisms. Psychological stress may have negative effects on bone tissue through increases in allostatic load and the secretion of glucocorticoids, which reduces the rate of absorption of calcium and inhibits bone growth [33,34]. PTSD is associated with smoking, and nicotine has been shown to decrease bone mineral content and bone mineral density in animal studies and contribute to increased risk of fractures in humans [27,35–38].

Several limitations should be kept in mind when interpreting our results. Follow-up of fractures started 1 year after PTSD diagnosis to ensure that the PTSD diagnosis did not result from the fracture. Thus, our study did not include the time period during which increased associations between psychological stress and fractures have been found previously [4]. Furthermore, our sample had few cases of some types of fractures (*e.g.*, neck fractures), which limited our ability to conduct stratified analyses for these fracture types. Another limitation is that in stratified analyses each SIR is standardized to a different population. Comparisons of SIRs across strata may therefore reflect heterogeneous effects, differential influence of chance or bias, and differences arising from standardization to different populations. These three cannot be easily separated and thus our comparisons of SIRs across strata should be interpreted with caution. We were also unable to adjust for medication use, behavioral risk factors, and other potential confounders. However, our stratified analyses showed that an association between PTSD and fractures is present even in the absence of depression, substance use, comorbid somatic diagnoses, and across various demographic characteristics. We further assessed the impact of unmeasured confounding due to smoking, a potentially critical unmeasured behavioral confounder, and found that unmeasured confounding due to smoking would not completely account for our observed associations, assuming a valid bias model. However, if smoking is a mediator of the association between PTSD and fractures, then our bias analysis would not apply.

Our study has many strengths including the use of a large clinician-diagnosed cohort of persons diagnosed with PTSD, enabling us to examine various types of fractures. We reduced the potential for selection bias through the use of nationwide registries to identify subjects with few exclusion criteria and little loss to follow-up. Classification of PTSD in the

DPCRR, the registry from which we identified the majority of the PTSD cohort, was strong when validated against medical records, with a positive predictive value of 83% [23]. The DNRP, the registry from which we ascertained fracture outcomes, consistently registers fractures and should contain all fractures since all cases should result in hospital admissions [24]. We expect specificity of fracture diagnoses in this population to be 100% (i.e., individuals without fractures are correctly classified as such) and any imperfect sensitivity of fracture diagnoses to be nondifferential and independent with respect to PTSD diagnosis. This form of outcome misclassification is expected to result in unbiased ratio measures.

In summary, we found that PTSD is associated with an increased rate of fractures. There was little evidence of effect modification by gender, depression status, and substance abuse/dependence status. Though this study was conducted among Danes, our findings may be generalizable to other populations if the mechanisms underlying the association between PTSD and fractures are the same. PTSD is a complex psychiatric disorder and there are many combinations of symptoms that may result in a PTSD diagnosis [39]. It is unknown whether different combinations of PTSD symptoms would have the same effect on fracture risk. This is an interesting etiologic question that warrants further investigation in future studies. Other important directions for future studies include corroborating these findings while controlling for additional potential confounders and further elucidating the mechanisms that underlie the observed associations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Flowchart of PTSD cohort

Table 1.

Characteristics of patients one year after PTSD diagnosis. Denmark, 1995-2013.

Characteristic	PTSD (n, %) (n=4114)
Gender	
Female	2569 (62%)
Male	1545 (38%)
Age (years)	
16-39	2006 (49%)
40-59	1834 (45%)
60+	274 (6.7%)
Depression diagnosis	226 (5.5%)
Alcohol abuse/dependence diagnosis	312 (7.6%)
Drug abuse/dependence diagnosis	86 (2.1%)
CCI score	
0	3414 (83%)
1 +	700 (17%)
Trauma/accident diagnosis	22 (0.53%)
Myocardial infarction diagnosis	63 (1.5%)
Congestive heart failure diagnosis	27 (0.66%)
Peripheral vascular disease diagnosis	42 (1.0%)
Cerebrovascular disease diagnosis	95 (2.3%)
Dementia diagnosis	9 (0.22%)
Chronic pulmonary disease diagnosis	227 (5.5%)
Connective tissue disease diagnosis	65 (1.6%)
Ulcer disease diagnosis	87 (2.1%)
Mild liver disease diagnosis	43 (1.1%)
Diabetes types I and II diagnosis	81 (2.0%)
Hemiplegia diagnosis	3 (0.07%)
Moderate to severe renal disease diagnosis	26 (0.63%)
Diabetes with end organ diagnosis	27 (0.66%)
Any tumor diagnosis	92 (2.2%)
Leukemia diagnosis	2 (0.05%)
Lymphoma diagnosis	5 (0.12%)
Moderate to severe liver disease diagnosis	8 (0.19%)
Metastatic solid tumor diagnosis	6 (0.15%)
AIDS diagnosis	1 (0.02%)

Table 2.

Associations between PTSD and fracture types. Denmark, 1995-2013.

Fracture type	Risk (95% CI)	Association with PTSD		
		Observed	Expected	SIR (95% CI)
Any fracture	24% (20%, 28%)	394	227.4	1.7 (1.6, 1.9)
Neck	0.19% (0.08%, 0.44%)	6	2.8	2.2 (0.79, 4.7)
Spine and pelvis	2.6% (1.7%, 3.9%)	42	20.2	2.1 (1.5, 2.8)
Shoulder and humerus	2.2% (1.5%, 3.0%)	48	31.8	1.5 (1.1, 2.0)
Forearm	6.6% (5.3%, 8.1%)	125	90.4	1.4 (1.2, 1.7)
Hand and wrist	7.5% (5.9%, 9.4%)	155	97.2	1.6 (1.4, 1.9)
Femur	3.5% (2.0%, 5.7%)	47	29.5	1.6 (1.2, 2.1)

Table 3.

Age-specific absolute risks of fractures.

Fracture type	16–39 years	40–59 years	60+ years
	Absolute risk (95% CI)	Absolute risk (95% CI)	Absolute risk (95% CI)
Any fracture	17% (14%, 20%)	30% (21%, 40%)	37% (24%, 51%)
Neck	0.08% (0.01%, 0.43%)	0.28% (0.08%, 0.79%)	0.49% (0.05%, 2.5%)
Spine and pelvis	1.2% (0.60%, 2.2%)	4.4% (2.3%, 7.6%)	3.8% (1.8%, 7.1%)
Shoulder and humerus	1.8% (0.98%, 3.1%)	2.3% (1.4%, 3.5%)	3.4% (1.2%, 7.5%)
Forearm	3.3% (2.2%, 4.9%)	11% (8.3%, 14%)	4.7% (2.3%, 8.4%)
Hand and wrist	8.0% (6.3%, 10.0%)	7.7% (4.5%, 12%)	4.2% (2.0%, 7.8%)
Femur	1.6% (0.34%, 5.1%)	3.6% (1.1%, 8.9%)	16% (9.6%, 23%)

Table 4.

SIRs for PTSD and incident fractures, stratified by gender, age at first PTSD diagnosis, depression status, substance abuse/dependence status, somatic comorbidity status, and follow-up time.

	Any fracture SIR (95% CI)	Neck SIR (95% CI)	Spine and pelvis SIR (95% CI)	Shoulder and humerus SIR (95% CI)	Forearm SIR (95% CI)	Hand and wrist SIR (95% CI)	Femur SIR (95% CI)
Gender							
Female	1.6 (1.4, 1.8)	-	2.4 (1.7, 3.4)	1.4 (0.96, 2.0)	1.3 (1.0, 1.6)	1.5 (1.2, 1.9)	1.6 (1.1, 2.3)
Male	1.9 (1.6, 2.3)	3.4 (1.1, 7.8)	1.4 (0.68, 2.6)	1.8 (1.0, 3.0)	1.7 (1.2, 2.3)	1.8 (1.4, 2.2)	1.5 (0.8, 2.6)
Age at first PTSD diagnosis(years)							
16-39	1.8 (1.5, 2.1)	-	2.0 (1.0, 3.4)	2.8 (1.6, 4.4)	1.1 (0.79, 1.6)	1.7 (1.3, 2.1)	2.4 (0.9, 5.3)
40-59	1.7 (1.5, 2.0)	-	2.3 (1.4, 3.6)	1.4 (0.88, 2.0)	1.7 (1.4, 2.1)	1.5 (1.1, 1.9)	1.2 (0.65, 2.0)
60+	1.6 (1.2, 2.1)	-	1.8 (0.81, 3.4)	0.8 (0.3, 1.8)	0.7 (0.36, 1.4)	1.8 (0.84, 3.5)	1.8 (1.2, 2.6)
Depression							
Yes	1.8 (1.2, 2.8)	-	-	-	1.2 (0.44, 2.6)	2.3 (1.0, 4.3)	-
No	1.7 (1.6, 1.9)	2.3 (0.83, 5.0)	2.2 (1.6, 2.9)	1.5 (1.1, 2.1)	1.4 (1.2, 1.7)	1.6 (1.3, 1.9)	1.6 (1.2, 2.2)
Substance abuse/dependence							
Yes	2.9 (2.1, 3.9)	-	3.8 (1.2, 8.8)	5.6 (2.8, 10.0)	2.3 (1.2, 3.9)	2.1 (1.2, 3.4)	-
No	1.6 (1.5, 1.8)	2.0 (0.64, 4.6)	2.0 (1.4, 2.7)	1.2 (0.87, 1.7)	1.3 (1.1, 1.6)	1.6 (1.3, 1.8)	1.5 (1.1, 2.1)
CCI score							
0	1.7 (1.5, 1.9)	-	1.8 (1.2, 2.6)	1.3 (0.93, 1.9)	1.4 (1.1, 1.7)	1.6 (1.4, 1.9)	1.3 (0.89, 1.9)
1+	2.1 (1.6, 2.6)	-	3.2 (1.7, 5.5)	2.2 (1.2, 3.6)	1.5 (0.92, 2.2)	1.6 (0.97, 2.4)	2.2 (1.3, 3.4)
Follow-up time (years)							
1 to <5	1.7 (1.5, 2.0)	-	1.3 (0.64, 2.3)	2.1 (1.4, 3.1)	1.4 (1.1, 1.9)	1.5 (1.2, 1.9)	2.1 (1.4, 3.1)
5 to <10	1.6 (1.4, 2.0)	5.2 (1.7, 12.0)	2.4 (1.4, 3.9)	1.3 (0.74, 2.2)	1.2 (0.88, 1.7)	1.7 (1.3, 2.2)	0.8 (0.34, 1.6)
10+	2.0 (1.6, 2.4)	-	3.0 (1.6, 5.0)	0.9 (0.34, 1.8)	1.5 (1.0, 2.1)	1.8 (1.2, 2.6)	1.9 (1.0, 3.1)

Results not presented when fewer than five incident fracture cases were identified in a stratification subgroup.