

Posttraumatic Stress Disorder and Risk of Dementia Among US Veterans

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Context: Posttraumatic stress disorder (PTSD) is highly prevalent among US veterans because of combat and may impair cognition.

Objective: To determine whether PTSD is associated with the risk of developing dementia among older US veterans receiving treatment in the Department of Veterans Affairs medical centers.

Design: A stratified, retrospective cohort study conducted using the Department of Veterans Affairs National Patient Care Database.

Setting: Department of Veterans Affairs medical centers in the United States.

Participants: A total of 181 093 veterans 55 years or older without dementia from fiscal years 1997 through 2000 (53 155 veterans with and 127 938 veterans without PTSD).

Main Outcome Measures: During the follow-up period between October 1, 2000, and December 31, 2007, 31 107 (17.2%) veterans were ascertained to have newly

diagnosed dementia according to *International Classification of Diseases, Ninth Revision, Clinical Modification* codes.

Results: The mean baseline age of the veterans was 68.8 years, and 174 806 (96.5%) were men. Veterans with PTSD had a 7-year cumulative incident dementia rate of 10.6%, whereas those without had a rate of 6.6% ($P < .001$). With age as the time scale, Cox proportional hazards models indicated that patients with PTSD were more than twice as likely to develop incident dementia compared with those without PTSD (hazard ratio, 2.31; 95% confidence interval, 2.24-2.39). After multivariable adjustment, patients with PTSD were still more likely to develop dementia (hazard ratio, 1.77; 95% confidence interval, 1.70-1.85). Results were similar when we excluded those with a history of head injury, substance abuse, or clinical depression.

Conclusions: In a predominantly male veteran cohort, those diagnosed as having PTSD were at a nearly 2-fold-higher risk of developing dementia compared with those without PTSD. Mechanisms linking these important disorders need to be identified with the hope of finding ways to reduce the increased risk of dementia associated with PTSD.

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POSTTRAUMATIC STRESS DISORDER (PTSD) is a common psychiatric syndrome associated with high rates of morbidity and mortality and is one of the most common sequelae in veterans returning from combat. Among veterans returning from Iraq and Afghanistan, the prevalence of PTSD has been estimated as 17%.¹ In addition, PTSD can be a chronic condition. Vietnam veterans have been found to have a 20% to 30% lifetime prevalence of combat-related PTSD, and 10% to 15% had the disorder 15 years or longer after returning from Vietnam.^{2,3} A study of older World War II and Korean veterans found that the PTSD prevalence remained as high as 12% even 45 years after combat.⁴

Previous studies⁵⁻⁹ have found that PTSD is associated with greater health care use and an increased risk of developing a wide range of medical conditions in younger and middle-aged veterans. Despite evidence that PTSD may impair cognitive performance^{10,11} and that older individuals with PTSD have greater decline in cognitive performance relative to control patients,¹² little is known about PTSD as a risk factor for developing dementia. Given that PTSD symptoms often continue until late in life and that alterations in the hypothalamic-pituitary-adrenal axis often accompany PTSD¹³ and these in turn may be associated with dementia,¹⁴ there is reason to believe that PTSD might be associated with accelerated brain aging. An-

other possible mechanism that may link PTSD to higher rates of dementia is the co-occurrence of depression, head injury, or medical comorbidities, conditions all associated with both PTSD and dementia.¹⁵⁻¹⁷ No studies to date have determined whether PTSD is independently associated with an increased risk of developing dementia.

The goal of our study was to determine whether PTSD was associated with an increased risk of being diagnosed as having dementia among veterans using Department of Veterans Affairs (VA) health care services in the United States. In addition, we were interested in whether such an association might be explained by medical comorbidities, clinical depression, or head injury.

METHODS

DATA AND STUDY PARTICIPANTS

Data for this retrospective cohort study were obtained from the VA National Patient Care Database, which captures all inpatient and outpatient services within the VA each fiscal year (October 1 through September 30). Records were extracted for veterans 55 years and older who had been treated at a VA health care facility and did not have a diagnosis of dementia during our baseline period, fiscal years 1997 through 2000, and who also had at least 1 visit during our follow-up period from fiscal year 2001 (October 1, 2000) to the end of the calendar year 2007.

There were 3 120 213 veterans seen at a VA facility at least once during the 1997 through 2000 fiscal years who were 55 to 100 years of age at the time of their first encounter. We excluded the 170 378 (5.5%) who had received a dementia diagnosis at the VA during this period. Among the remaining 2 949 835 veterans, we identified 59 633 (2.0%) as having received a PTSD diagnosis at least twice during the baseline period, all of whom were included in our potential cohort. The rest of the potential cohort was a group of 178 899 randomly selected veterans (3 per patient with PTSD) without a PTSD diagnosis.

Among the 238 532 patients with and without PTSD selected as potential participants, we excluded 26 311 (11.0%) who died during the baseline period and 31 128 (13.1%) who were not seen at a VA health care facility during the follow-up period because we did not have the ability to determine whether they had developed incident dementia. Thus, our final cohort of 181 093 veterans consisted of 53 155 patients with and 127 938 without PTSD.

OUTCOME MEASURES

Posttraumatic Stress Disorder

Veterans with PTSD were identified using *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*¹⁸ codes recorded in the VA database. To be conservative, those with a diagnosis code of 309.81 (PTSD) on at least 2 different visits during the baseline period were classified as having PTSD. Veterans with 1 diagnosis of PTSD were not included in our primary analyses (combined total=88 568 veterans).

Dementia

Veterans with dementia were identified using *ICD-9-CM* codes during the baseline period to exclude prevalent cases and during the follow-up to identify incident cases. Patients with diagnosis codes 290.0, 290.2, 290.3, 331.2 (senile dementias, n=3450), 290.4 (vascular dementia, n=2698), 294.8 (demen-

tia not otherwise specified, n=10 291), 331.0 (Alzheimer disease, n=3882), 331.1 (frontotemporal dementia, n=139), and 331.82 (Lewy body dementia, n=356) were considered to have dementia diagnoses.

Evaluation of incident dementia diagnosis occurred from October 1, 2000, through December 31, 2007. If dementia was not diagnosed before the patient's death or the end of the follow-up period, the patient's data was censored at whichever event occurred first. Dates of death were obtained through the VA Vital Status File, which combines death data from the VA, the Center for Medicare and Medicaid Services, and the Social Security Administration.¹⁹

Baseline Characteristics

Baseline age (in years) was calculated on October 1, 2000. Sex and race/ethnicity information was also determined based on VA database records. We classified veterans as living in broad educational and income strata according to zip code tabulation areas by linking our data to 2000 US Census data. For educational level, veterans were categorized according to whether they were living in a zip code tabulation area where 25% or less vs greater than 25% of the adult population had completed a college education (bachelor's degree or higher). This cutoff was chosen because the average zip code tabulation area in 2000 had a 24.4% college-educated adult population.²⁰ For income, veterans were categorized in tertiles of median zip code tabulation area income for adults younger than 75 years or 75 years or older.

Indicators of prevalent medical comorbidity during the baseline period were obtained using *ICD-9-CM* diagnosis codes for hypertension, diabetes mellitus, myocardial infarction, cancer, and cerebrovascular disease. Psychiatric comorbidities were also determined using *ICD-9-CM* codes, including history of tobacco use, alcohol abuse, other substance abuse, major clinical depression, and head injury, including concussion, contusion, skull fracture, and other head injury (*ICD-9-CM* codes 310.2, 800-804.xx, 850.x, 851.x, 854.0, 854.1, and 959.01). The Committee on Human Research at the University of California, San Francisco, the Committee for Research and Development at the San Francisco VA, and the Human Research Protection Office of the US Army Medical Research and Material Command approved the study.

STATISTICAL ANALYSES

Baseline characteristics were summarized with means and standard deviations or percentages for the veterans with and without PTSD. The characteristics of the 2 groups were compared using *t* tests for continuous variables and χ^2 tests for categorical variables.

Cumulative incidence of dementia was plotted by patient age (in years) for each group. These curves show estimates of the cumulative incidence by age in the presence of death as a competing risk; with complete follow-up, this could be estimated by the simple proportion with a dementia diagnosis by any given age. This is in contrast to Kaplan-Meier curves, which estimate the incidence that would be observed if the competing risk could be "removed." To determine whether the relative rates of incident dementia over time would be different for those without other major neuropsychiatric diagnoses, we also constructed cumulative incidence curves excluding those with diagnoses of major clinical depression, substance abuse, or head injury during the baseline period.

Cox proportional hazards models were used to compare the age of incident dementia in patients with and without PTSD. With age as the time scale, the effects of age on incidence are flexibly modeled by the baseline hazard, which is nonparametric in the

Table 1. Baseline Characteristics of the Veterans With and Without PTSD

Characteristic	Study Group ^a	
	Without PTSD (n=127 938)	With PTSD (n=53 155)
Age, mean (SD) [range], y	69.9 (8.2) [55.0-100.0]	66.2 (9.0) [55.0-100.0]
Female sex	5118 (4.0)	1169 (2.2)
>25% College-educated ZCTA ^b	37 358 (29.2)	16 319 (30.7)
Median annual income of ZCTA ^c		
Low tertile (<\$24 000)	41 708 (32.6)	15 574 (29.3)
Middle tertile (\$24 000 to \$31 800)	41 836 (32.7)	17 275 (32.5)
High tertile (>\$31 800)	39 661 (31.0)	17 807 (33.5)
Hypertension	74 460 (58.2)	34 710 (65.3)
Diabetes mellitus	30 321 (23.7)	14 511 (27.3)
Myocardial infarction	7037 (5.5)	4146 (7.8)
Cerebrovascular disease	11 898 (9.3)	6379 (12.0)
Cancer	20 726 (16.2)	10 897 (20.5)
Alcohol abuse	4606 (3.6)	8345 (15.7)
Other substance abuse	14 841 (11.6)	13 927 (26.2)
History of tobacco use	3710 (2.9)	1860 (3.5)
Major clinical depression	4222 (3.3)	20 199 (38.0)
Head injury	384 (0.3)	478 (0.9)

Abbreviations: PTSD, posttraumatic stress disorder; ZCTA, zip code tabulation area.

^aData are presented as number (percentage) of veterans unless otherwise indicated. *P* value by *t* test for continuous variables and χ^2 test for categorical variables was <.001 for all variables.

^bZip code tabulation area from the 2000 US Census. College-educated indicates completion of a bachelor's degree or higher.

^cMedian income levels are age specific (<75 years and \geq 75 years, calculated separately).

Cox model and need not even be estimated to obtain estimates of covariate effects. Several different adjusted Cox models were run to assess the influence of confounding by different types of baseline characteristics. First, models were adjusted for the demographic characteristics of race/ethnicity, sex, and educational and income strata. Second, the models were adjusted for indicators of medical comorbidity at baseline, including hypertension, diabetes, myocardial infarction, and cerebrovascular disease, followed by adjustments for neuropsychiatric comorbidities, such as clinical depression, substance abuse, and head injury. To assess the impact of differential opportunity for receiving dementia diagnoses by presence or absence of PTSD, we also ran models adjusting for a time-varying covariate for the number of inpatient or outpatient visits to a VA clinic per month. Proportional hazards assumptions were tested graphically and statistically and were met for all models. All analyses were conducted with Stata statistical software, version 10.1 (StataCorp LP, College Station, Texas), and SAS statistical software, version 9.1 (SAS Institute Inc, Cary, North Carolina).

RESULTS

PARTICIPANT CHARACTERISTICS

The mean (SD) baseline age of the 181 093 veterans in our cohort was 68.8 (8.6) years; 174 806 (96.5%) were men. Baseline characteristics of veterans are presented in **Table 1**. Compared with the patients without PTSD, those with PTSD were younger, had greater comorbidities, and lived in zip codes with more college-educated and higher-

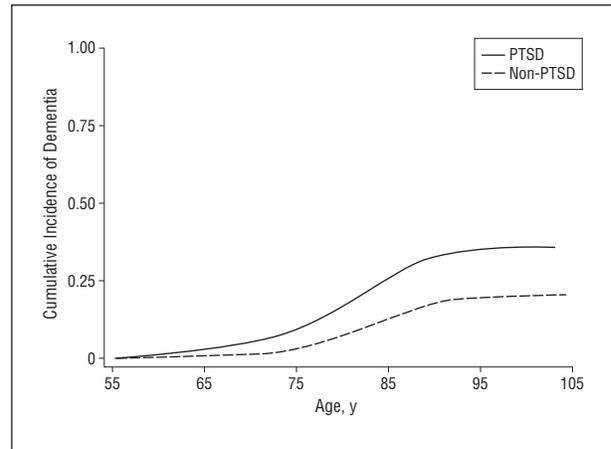


Figure. Cumulative incidence of dementia by age for all veterans. PTSD indicates posttraumatic stress disorder.

income individuals, although the absolute differences were small. Substance abuse ($P=.004$), tobacco use ($P=.009$), major clinical depression ($P=.001$), and head injury ($P=.009$) were also statistically significantly more common among patients with than in those without PTSD.

INCIDENT DEMENTIA

The median follow-up time for veterans with and without PTSD was 7.2 (range, 0.1-7.4) years. Cumulative incidence rates of dementia were significantly higher for veterans with than those without PTSD. Those with PTSD had a 7-year cumulative incidence rate of 10.6% with incident dementia, whereas veterans without PTSD had a 7-year rate of 6.6% ($P<.001$). Incident dementia rates were higher for patients with PTSD throughout the follow-up period (**Figure**).

Cox proportional hazards models using age as the time scale also show that patients with PTSD were more than twice as likely to develop incident dementia compared with those without PTSD (hazard ratio [HR], 2.31; 95% confidence interval [CI], 2.24-2.39) (**Table 2**). After adjusting for the demographic variables of sex, race/ethnicity, educational level, and income, results were similar (HR, 2.28; 95% CI, 2.21-2.36). Adjustment for medical comorbidities at baseline also was not greatly influential but reduced the risk slightly (HR, 2.21; 95% CI, 2.13-2.28). Adjustment for other neuropsychiatric diagnoses reduced the strength of the association between PTSD and dementia, although those with PTSD were still more likely to develop incident dementia than those without (HR, 1.84; 95% CI, 1.76-1.91). In the final multivariable-adjusted model adjusting for demographics and medical and neuropsychiatric comorbidities, patients with PTSD were still nearly twice as likely to develop incident dementia as those without (HR, 1.77; 95% CI, 1.70-1.85).

We next determined whether the association between PTSD and risk of dementia differed by dementia diagnosis subtype. The unadjusted HR ranged from 1.94 to 3.13, and the multivariable-adjusted HR ranged from 1.71 to 2.19 (**Table 3**). There was no consistent pattern other than

that PTSD was associated with a higher risk of dementia among all dementia subtypes.

We conducted several sensitivity analyses. To determine whether those with PTSD were more likely to receive a diagnosis of dementia because of more frequent care at the VA (inpatient or outpatient), we adjusted for the number of visits to inpatient and outpatient clinics. The addition of adjustment for clinic visits did not appreciably change the model results, but those with PTSD had more clinic visits ($P < .001$). To determine whether veterans with PTSD remained at an increased risk of developing dementia even in the absence of psychiatric comorbidities, we excluded veterans with a diagnosis of major clinical depression, substance abuse, or head injury ($n = 48\,241$) during the baseline period and found almost identical results. We also repeated our analyses excluding women veterans and including veterans with a diagnosis of PTSD at 1 or more visits ($n = 88\,568$), and our results were similar in both analyses. Finally, we determined whether veterans with PTSD had a greater risk of developing dementia compared with veterans without PTSD psychiatric disorders and found an increased risk (adjusted HR, 1.47; 95% CI, 1.37-1.56).

Table 2. Association Between PTSD and Risk of Dementia in Multivariable-Adjusted Models

Study Group	HR (95% CI) ^a
Unadjusted	
No PTSD	1.00 [Reference]
PTSD	2.31 (2.24-2.39)
Demographics	
No PTSD	1.00 [Reference]
PTSD	2.28 (2.21-2.36)
Medical comorbidities	
No PTSD	1.00 [Reference]
PTSD	2.21 (2.13-2.28)
Neuropsychiatric comorbidities	
No PTSD	1.00 [Reference]
PTSD	1.84 (1.76-1.91)
All	
No PTSD	1.00 [Reference]
PTSD	1.77 (1.70-1.85)

Abbreviations: CI, confidence interval; HR, hazard ratio; PTSD, posttraumatic stress disorder.

^aThe HRs and 95% CIs were determined using age as the time scale.

We found that among primarily male veterans, those diagnosed as having PTSD had nearly a 2-fold increased risk of dementia compared with those without PTSD. This association remained after adjustment for important differences between those with and without PTSD, such as demographics and medical and neuropsychiatric comorbidities.

There are several reasons why patients with PTSD may have an increased risk of developing dementia. One possibility is that PTSD is causally related to the development of dementia. There is some evidence, albeit controversial, that veterans with PTSD perform more poorly on cognitive tests.^{10-12,21} This poorer performance on cognitive testing compared with those without PTSD could be a risk factor for development of dementia because those with worse function may have less cognitive reserve and be at higher risk for cognitive impairment.²²

Another mechanism possibly linking PTSD to dementia is chronic stress. Stress may damage the hippocampus, a brain structure crucial for memory and learning. Indeed, others, including some of us,²³ have previously found that PTSD is associated with decreased concentrations of the neuronal marker, *N*-acetyl aspartate, in the hippocampus. Others²⁴ have found that veterans with PTSD have smaller hippocampal volumes, which are correlated with deficits in short-term memory performance. Smaller hippocampal volumes have been associated with poor cognitive function and increased risk of dementia in healthy elderly people.²⁵ It is possible then that PTSD leads to hippocampal atrophy, which in turn increases risk of cognitive deficits and dementia, especially during short-term follow-up, or that a smaller hippocampus is a predisposition factor for both PTSD and dementia.

As a stress-related disorder, PTSD also is associated with alterations in the hypothalamic-pituitary-adrenal axis and proinflammatory cytokines. Acute stress produces increases in cortisol levels, and a study²⁶ has found that hypercortisolemia is associated with increased risk of dementia. Veterans with chronic PTSD typically have reduced cortisol levels, which may reflect an allostatic down-regulation of the glucocorticoid system and may facilitate chronic inflammation.¹³ Several studies have demonstrated that PTSD is associated with proinflammatory immune alterations, including increased levels of cyto-

Table 3. Association Between PTSD and Risk of Subtypes of Dementia^a

Study Group	HR (95% CI) ^b					
	Alzheimer Disease (n=3882)	Frontotemporal Dementia (n=139)	Senile Dementia (n=3450)	Vascular Dementia (n=2698)	Lewy Body Dementia (n=356)	Dementia NOS (n=10 291)
Unadjusted						
No PTSD	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
PTSD	1.94 (1.82-2.08)	3.13 (2.25-4.37)	2.57 (2.40-2.75)	2.40 (2.22-2.59)	2.41 (1.95-2.98)	2.36 (2.27-2.46)
Fully adjusted						
No PTSD	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
PTSD	1.71 (1.58-1.85)	2.19 (1.43-3.34)	2.03 (1.87-2.20)	1.69 (1.54-1.85)	2.05 (1.59-2.62)	1.80 (1.72-1.89)

Abbreviations: CI, confidence interval; HR, hazard ratio; NOS, not otherwise specified; PTSD, posttraumatic stress disorder.

^a*International Classification of Diseases, Ninth Revision, Clinical Modification* codes: 290.0, 290.2, 290.3, and 331.2 (senile dementias); 290.4 (vascular dementia); 294.8 (dementia not otherwise specified); 331.0 (Alzheimer disease); 331.1 (frontotemporal dementia); and 331.82 (Lewy body dementia).

^bThe HRs and 95% CIs were determined using age as the time scale.

kines,²⁷ enhanced cellular immune responses,²⁸ and increased levels of C-reactive protein.^{29,30} It was found previously that inflammation is associated with increased risk of cognitive decline.³¹ Several other related possible mechanisms include alterations in homocysteine level and other vascular risk factors, possibly because of medications, in the setting of PTSD.^{32,33}

Another explanation for the association is that dementia and PTSD co-occur more frequently together or that one condition may “unmask” the other. Indeed, there have been several case series and case reports that PTSD symptoms may worsen in veterans as they develop dementia or cognitive impairment.³⁴⁻³⁶ We doubt this explains our findings because we excluded those veterans with PTSD and a diagnosis of dementia at baseline. In addition, we required a documented PTSD diagnosis on at least 2 visits to ensure a robust clinical diagnosis. Finally, it may be that having PTSD, or other chronic brain disorders, may predispose patients to developing dementia because of an increased nonspecific vulnerability, for example, genetic vulnerabilities shared by both disorders or childhood environmental factors.³⁷ It is possible that having PTSD, especially in patients followed up by mental health care professionals, may bring more attention to other neuropsychiatric diagnoses, such as dementia. We attempted to control for this possible detection bias by adjusting for the number of VA visits, and our results were not appreciably different.

We believe our study has several important strengths, including a large number of veterans with and without PTSD who received care at a VA facility, allowing for documentation of dementia diagnosis for several years. In addition, we have attempted to carefully adjust for possible confounding from medical and neuropsychiatric comorbidities. Finally, this study is the first, to our knowledge, to report that PTSD may increase the risk of developing dementia. Several limitations of our study are also important to mention. The diagnoses of PTSD, dementia, and medical and neuropsychiatric comorbidities were made on the basis of clinician ICD-9-CM codes, an insensitive assessment of symptoms compared with structured research diagnostic interviews and with some differences compared with *Diagnostic and Statistical Manual of Mental Disorders*-based criteria. Because of this, we were also unable to assess the possibility of any subclinical cases of PTSD or dementia, and our data cannot be used to estimate the prevalence of PTSD in the older veteran population. In addition, our population included primarily male veterans followed up by the VA system; therefore, we need to determine whether our findings generalize to women and to those patients not cared for at VA medical centers.

The finding that PTSD is associated with a near doubling of the risk of dementia has important public health, policy, and biological implications. Posttraumatic stress disorder has emerged as a common sequela of combat and other trauma exposure, and its course is often chronic, leading to increased mortality and morbidity. As patients with PTSD age, these adverse health conditions usually increase in frequency, and some have suggested that PTSD may accelerate the “aging process” in general.³⁸ It is important that those with PTSD are treated, and further investigation is needed to see whether successful treat-

ment of PTSD may reduce the risk of adverse health outcomes, including dementia. In addition, it is critical to follow up patients with PTSD, especially if they are of an advanced age, to screen for cognitive impairment. Finally, mechanisms linking PTSD and dementia must be identified in hope of finding ways to improve the care and outcomes of patients with PTSD.

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