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ARTICLE

Military-related risk factors in female veterans and risk of dementia

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Abstract

Objective

To determine whether diagnoses of traumatic brain injury (TBI), posttraumatic stress disorder (PTSD), and depression, alone or in combination, increase dementia risk among older female veterans.

Methods

This cohort study included data from 109,140 female veterans ≥55 years of age receiving care from Veterans Health Administration medical centers in the United States between October 2004 and September 2015 with at least 1 follow-up visit. TBI, PTSD, depression, and medical conditions at study baseline and incident dementia were determined according to ICD-9-CM codes. Fine-Gray proportional hazards models were used to determine the association between military-related risk factors and dementia diagnosis, accounting for the competing risk of death.

Results

During follow-up (mean 4.0 years, SD 2.3), 4% of female veterans (n = 4,125) developed dementia. After adjustment for demographics and medical conditions, women with TBI, PTSD, and depression had a significant increase in risk of developing dementia compared to women without these diagnoses (TBI-adjusted subdistribution hazard ratio [adjusted sHR] 1.49, 95% confidence interval [CI] 1.01–2.20; PTSD adjusted sHR 1.78, 95% CI 1.34–2.36; and depression-adjusted sHR 1.67, 95% CI 1.55–1.80), while women with >1 diagnosis had the highest risk for dementia (adjusted sHR 2.15, 95% CI 1.84–2.51).

Conclusions

We found that women with military-related risk factors had an ≈50% to 80% increase in developing dementia relative to women without these diagnoses, while female veterans with multiple risk factors had a >2-fold risk of developing dementia. These findings highlight the need for increased screening of TBI, PTSD, and depression in older women, especially female veterans.

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Editorial
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From the San Francisco Veterans Affairs Health Care System (K.Y., S.J.L., T.D.H., F.X., D.E.B., S.M., C.B.P.); and Departments of Psychiatry (K.Y., D.E.B., S.M.), Neurology (K.Y.), and Epidemiology & Biostatistics (K.Y.), University of California, San Francisco.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

CI = confidence interval; **ICD-9-CM** = *International Classification of Diseases, 9th Revision, Clinical Modification*; **NPCD** = National Patient Care Databases; **PTSD** = posttraumatic stress disorder; **sHR** = subdistribution hazard ratio; **TBI** = traumatic brain injury; **VHA** = Veterans Health Administration.

Veterans are a population who may be at greater risk for developing dementia due to their high prevalence of traumatic brain injury (TBI), posttraumatic stress disorder (PTSD), and depression.[1–4] While these risk factors are not unique to military service, compared to nonveterans, veterans are 2 to 5 times more likely to have TBI, PTSD, or depression.[5–7] It is estimated that among veterans previously deployed for Operations Enduring Freedom and Iraqi Freedom, almost 1 in 3 have one of these military-related risk factors.[8] Furthermore, the risk of dementia may be further elevated because these conditions often co-occur, particularly with greater frequency, in veterans.[9]

Notably, studies examining military-related and other risk factors for dementia in veterans have been conducted almost exclusively among men. This is a considerable disparity in the field, especially because more women are joining the military[10] and female veterans may be at greater risk for certain psychiatric conditions compared to male veterans.[11,12] In addition, the thresholds for certain risk factors may vary by sex, and studies suggest that biological differences between men and women, possibly as a result of hormonal interactions or sex-divergent signaling pathways, could modify the effect of these factors on dementia risk.[13–15] We sought to address this critical gap by conducting a study of military-related risk factors for dementia in a large cohort of older female veterans. We hypothesized that military-related risk factors would increase the risk of dementia among female veterans.

Methods

Study population

We identified all female Veterans Health Administration (VHA) patients 55 to 110 years of age who were evaluated (inpatient or outpatient visit) between October 1, 2004, and September 30, 2015. Exposure to military-related risk factors was assessed over a 4-year baseline period (starting from the first encounter date). Data were sourced from 2 nationwide VHA system databases: the inpatient and outpatient visits database (National Patient Care Databases [NPCD]) and the Vital Status File database. Women had to have at least 1 visit during the baseline period and at least 1 follow-up visit (n = 112,831), and we excluded those with prevalent dementia (n = 3,691) during the 4-year baseline period. The final sample size was 109,140.

Standard protocol approvals, registrations, and patient consents

All study procedures were approved by institutional review boards at the University of California, San Francisco; San Francisco Veterans Affairs Medical Center; and US Army Medical Research and Materiel Command, Office of Research Protections, Human Research Protection Office. Informed consent was waived because the data were deidentified administrative data.

Military-related risk factors for dementia: TBI, depression, and PTSD

TBI, depression, and PTSD diagnoses were determined with ICD-9-CM codes at all inpatient and outpatient visits during baseline. TBI was defined by a comprehensive list of ICD-9-CM codes used by the Defense and Veterans Brain Injury Center and the Armed Forces Health Surveillance Branch for TBI surveillance (2012 criteria).[16] Diagnosis codes 296.2, 296.3, and 311 were used for depression, and code 309.81 was used for PTSD.

Dementia

Prevalent dementia during baseline and incident dementia over follow-up were identified with the comprehensive list of ICD-9-CM codes provided by the VA Dementia Steering Committee (2016 version).[17]

Other measures

Demographic information and medical and psychiatric comorbid conditions were obtained from the NPCD. Demographic data, including age and race/ethnicity (categorized as non-Hispanic white, non-Hispanic black, Hispanic, or other/unknown), were based on self-report from the first encounter visit. In addition, we used ZIP code and 2016 American Community Survey data to classify veterans as living in broad educational and income strata. Education was defined as a 2-level variable categorized according to whether veterans were living in a ZIP code tabulation area where ≤25% vs >25% of the adult population had completed a college education (bachelor's degree or higher). Income was defined as a 3-level variable categorized by tertile of median ZIP code tabulation area income for adults.

Comorbid conditions were assessed during the 4-year baseline with standard ICD-9-CM codes from the NPCD. Comorbid conditions potentially associated with dementia included diabetes mellitus, hypertension, myocardial infarction, TIA/stroke, alcohol abuse, and tobacco use.

Analyses

Baseline characteristics of female veterans were grouped on the basis of the following: no military-related risk factors, TBI only, PTSD only, depression only, and >1 military-related risk factor. We compared these groups using analysis of variance for continuous variables and χ^2 analysis for categorical variables.

Fine-Gray proportional hazards models were used to examine time to dementia diagnosis, accounting for the competing risk of death, with censoring at the date of the last medical encounter and age as the time scale.[18] Models that included all military-related risk factors—TBI only, PTSD only, depression only, and >1 military-related risk factor—were unadjusted and then adjusted for confounding factors selected a priori in steps for demographics (age, race, education, and income) and demographics and comorbid conditions and reported as subdistribution hazard ratios (sHRs) with 95% confidence intervals (CIs). We also performed several sensitivity analyses: 1) requiring 2 diagnoses for each risk factor; 2) imposing a 2-year lag between military-related risk factor exposure and dementia diagnosis; and 3) adjusting for the number of health care follow-up visits (defined as the number of inpatient or outpatient visits per person per year). Proportional hazards model assumptions were checked for all final models. Values of p were 2 sided with statistical significance defined as $p < 0.05$. All analyses were performed with SAS version 9.4.

Data availability

The study data are derived from VHA electronic health records and contain protected health information; therefore, the data cannot be placed it in a public repository. Please contact the authors for additional details regarding the process of accessing this data.

Results

Of the 109,140 female veterans without dementia at baseline, the average age was 68.5 (SD 9.4) years, and the average follow-up time was 4.0 (SD 2.3) years. Most women (74%) were non-Hispanic white; 12% were non-Hispanic black; and the remaining were Hispanic (1%), Asian (1%), or other/unknown (12%).

Baseline characteristics of the veterans (separated into nonoverlapping groups determined by depression, PTSD, and TBI diagnoses) are shown in table 1. Women with diagnoses of depression or PTSD were younger than women with no diagnoses or those with TBI. Race, education, and income also differed significantly between the groups, such that relative to women without diagnoses, women with depression were more likely to be white, women with TBI and depression were located in areas with less education, and women with TBI lived in less wealthy ZIP codes. Women with TBI, depression, or PTSD were also more likely to have medical comorbid conditions than women with no diagnoses ($p < 0.05$ for all).

Overall, 4,125 women (4%) developed dementia during follow-up. Compared to women with no military-related risk factors (3.4%), those with diagnoses of TBI, depression, or PTSD had higher rates of incident dementia (with incident rates ranging from 3.9% for PTSD to 5.7% for TBI, $p < 0.001$). Table 2 shows the unadjusted and adjusted risks for the association between TBI, depression, and PTSD and dementia. TBI, depression, and PTSD alone increased the risk of dementia in models fully adjusted for demographics and comorbid conditions (TBI-adjusted sHR 1.49, 95% CI 1.01–2.20; depression-adjusted sHR 1.67, 95% CI 1.55–1.80; PTSD-adjusted sHR 1.78, 95% CI 1.34–2.36). Women with >1 military-related risk factor had the highest risk of dementia (adjusted sHR 2.15, 95% CI 1.84–2.51). Cumulative incidence of dementia adjusted for demographics and comorbid conditions in the 5 groups is shown in the figure.

We performed a sensitivity analysis that required women to have at least 2 diagnoses for military-related risk factors of interest. The results of this analysis were similar in magnitude and significance to our main findings. We also conducted an additional sensitivity analysis imposing a 2-year lag between military-related risk factors diagnosis and dementia diagnosis, and the estimated effect sizes and significance were nearly identical to our primary models. Because of the concern that diagnoses (PTSD, depression, TBI) would lead to increased follow-up visits, which in turn could lead to earlier detection of dementia, we conducted a final sensitivity analysis in which we adjusted for the number of follow-up visits per person per year for each group. The number of visits varied significantly between the groups; women with TBI, depression, or PTSD had more than twice the number of medical visits per year than the women with no diagnoses. Results were similar to the original findings but attenuated, particularly for women with TBI and those with >1 military risk factor (TBI-adjusted sHR 1.16, 95% CI 0.77–1.77, depression-adjusted sHR 1.52, 95% CI 1.41–1.64, PTSD-adjusted sHR 1.56, 95% CI 1.18–2.07, >1 risk factor–adjusted sHR 1.57, 95% CI 1.33–1.86).

Discussion

Our study of >100,000 older women investigated the relationship between military-related risk factors and dementia risk in female veterans. We found that women with TBI, depression, or PTSD had an ≈50% to 80% increase in risk of developing dementia relative to women without these diagnoses, while women with multiple conditions (e.g., TBI with depression or PTSD) had a >2-fold increase in dementia risk even after adjustment for demographics, common medical comorbid conditions, alcohol abuse, and tobacco use.

In our study, having a TBI increased dementia risk in female veterans by 50%. A few prior studies reported nonsignificant relationships between TBI and dementia,[19–21] possibly as a result of variations in the definition of TBI or other methodologic differences.[22] The association observed in our study is consistent with recent research in veteran and civilian populations indicating that TBI increases the risk of developing dementia.[3,23,24] In addition, these findings parallel estimates from our prior study of male veterans in which TBI was similarly associated with a 60% increase in the risk of dementia.[3] It has been hypothesized that the link between TBI and dementia risk may be due to axonal damage,[25] an injury that reduces cognitive reserve, thereby increasing vulnerability to dementia neuropathology or accelerating

Table 1 Baseline characteristics of 109,140 older female veterans by diagnosis of TBI, depression, and PTSD

Characteristics	None (n = 81,835)	TBI only (n = 488)	Depression only (n = 20,410)	PTSD only (n = 1,363)	>1 Military-related risk factor (n = 5,044)	*p* Value
Demographics						
Age, y	69.2 (9.8)	69.4 (10.1)	66.9 (8.4)	65.1 (6.7)	63.8 (5.2)	<0.001
Race, n (%)						<0.001
Non-Hispanic white	59,565 (72.8)	339 (69.5)	16,115 (79.0)	1,034 (75.9)	3,674 (72.8)	
Non-Hispanic black	9,988 (12.2)	64 (13.1)	2,046 (10.0)	185 (13.6)	761 (15.1)	
Hispanic	472 (0.6)	7 (1.4)	147 (0.7)	6 (0.4)	48 (1.0)	
Asian	1,346 (1.6)	18 (3.7)	98 (0.5)	17 (1.3)	23 (0.5)	
Others/unknown	10,464 (12.8)	60 (12.3)	2,004 (9.8)	121 (8.9)	538 (10.7)	
>25% College educated in ZIP code, n (%)[a]	38,145 (48.4)	203 (43.0)	8,540 (43.0)	615 (47.1)	2,279 (46.8)	<0.001
Median income in ZIP code in the lowest tertile (<$43,477)[a]	25,425 (33.1)	165 (36.6)	6,822 (34.4)	413 (31.8)	1,556 (32.1)	<0.001
Comorbid conditions, n (%)						
Diabetes mellitus	13,030 (15.9)	97 (19.9)	5,723 (28.0)	324 (23.8)	1,399 (27.7)	<0.001
Hypertension	38,948 (47.6)	266 (54.5)	14,680 (71.9)	792 (58.1)	3,407 (67.6)	<0.001
Myocardial infarction	1,531 (1.9)	17 (3.5)	669 (3.3)	34 (2.5)	151 (3.0)	<0.001
TIA/stroke	5,320 (6.5)	78 (16.0)	2,359 (11.6)	121 (8.9)	628 (12.5)	<0.001
Alcohol abuse	745 (0.9)	13 (2.7)	1,061 (5.2)	120 (8.8)	669 (13.3)	<0.001
Tobacco use or smoking	9,047 (11.1)	70 (14.3)	5,305 (26.0)	293 (21.5)	1,489 (29.5)	<0.001
Medical visits per year, n						
Inpatient	19.1 (16.5)	25.0 (22.1)	24.3 (19.6)	28.0 (19.5)	34.3 (26.9)	<0.001
Outpatient	9.3 (15.7)	16.6 (20.2)	17.2 (17.8)	20.7 (23.5)	27.2 (24.3)	<0.001

Abbreviations: PTSD = posttraumatic stress disorder; TBI = traumatic brain injury.
Values are mean (SD) when appropriate.
[a] Education had 3,790 (3.47%) missing values, and income has 5,973 (5.47%) missing values.

production of dementia-related proteins such as β-amyloid and tau.[26,27] In addition, other neuropathologic changes have been linked to both TBI and dementia, including white matter degeneration and neuroinflammation.[28,29] Evidence from humans and animal models suggests that the inflammatory cascade triggered after a TBI may be distinct for men and women[30] and that estrogen and progesterone could have neuroprotective effects after brain injury.[15,31] While the extent to which TBI outcomes differ between men and women is unclear,[32,33] these results demonstrate that women are also vulnerable to the long-term neurologic effects of TBI. Female veterans are an especially critical population because they may acquire a TBI from injuries, falls, or intimate partner violence, similar to women in the general population, but also through their military service and increasing involvement in combat.[34]

Our findings indicate that PTSD and depression independently increase dementia risk in older female veterans. There is a robust body of evidence to support depression as a risk factor for developing dementia with studies in both community-based populations of women[35,36] and (mostly male) veterans,[2] but there is very little information pertaining to risk among female veterans, who reportedly have higher rates of depression compared to male veterans.[12,37,38] In our cohort, risk of dementia increased by almost 70% for female veterans with depression. While the observed association was slightly lower than the risk reported in a comparable study of older male veterans (hazard ratio 2.18, 95% CI 2.08–2.28),[2] it supports a risk relationship between depression and dementia in older women.

Rates of PTSD are also high among female veterans,[38,39] and in our study, risk of dementia increased by almost 80% for female veterans with PTSD. This is consistent with other investigations in male veterans that report an increase in risk of 80% to 100%.[1,40] Mechanisms linking PTSD and depression to dementia are less well defined but may include inflammation,

Table 2 Association between TBI, depression, and PTSD and risk of dementia among 109,140 female veterans

Military-related risk factor	No.	Dementia, n (%)	Person-time (SD), y	sHR (95% CI)		
				Unadjusted	Model 1	Model 2
None	81,135	2,792 (3.4)	3.83 (2.29)	Referent	Referent	Referent
TBI only	488	28 (5.7)	3.70 (2.36)	1.64 (1.12–2.39)	1.58 (1.07–2.32)	1.49 (1.01–2.20)
Depression only	20,410	1,055 (5.2)	4.22 (2.36)	1.78 (1.66–1.91)	1.75 (1.63–1.88)	1.67 (1.55–1.80)
PTSD only	1,363	53 (3.9)	4.81 (2.35)	1.81 (1.37–2.39)	1.84 (1.39–2.43)	1.78 (1.34–2.36)
>1 Military-related risk factor	5,044	197 (3.9)	4.61 (2.43)	2.41 (2.07–2.80)	2.32 (1.99–2.71)	2.15 (1.84–2.51)

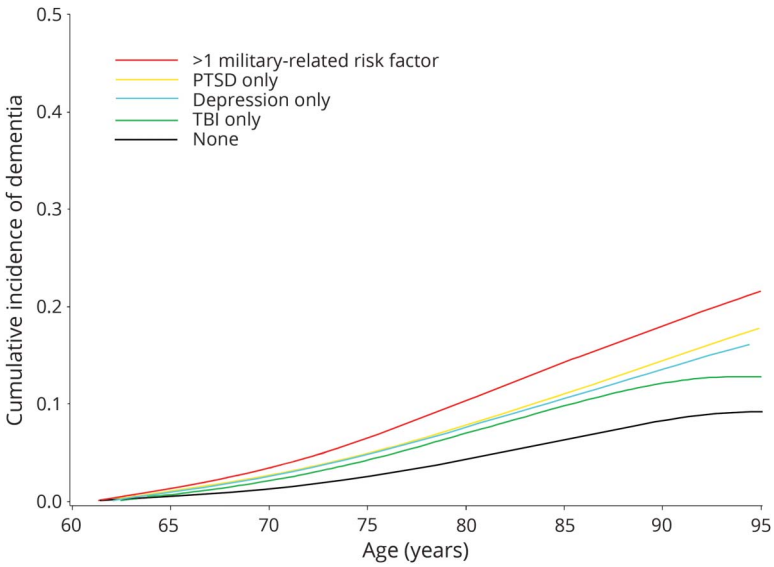
Abbreviations: CI = confidence interval; PTSD = posttraumatic stress disorder; sHR = subdistribution hazard ratio; TBI = traumatic brain injury.
Model 1: adjusted for demographics (age, race, education, income). Model 2: Model 1 plus adjusted for comorbid conditions (diabetes mellitus, hypertension, myocardial infarction, TIA/stroke, alcohol abuse, tobacco use).

high levels of cortisol or other stress markers, and increased vascular disease.[41–43] These results highlight the possibility that early and more targeted treatment of PTSD and depression might reduce the risk of developing dementia.

Depression, PTSD, and TBI often co-occur[44–46]; however, few studies consider the effects of these risk factors together. In our cohort, almost 80% of women with PTSD also had depression or TBI, and almost half of women with TBI also had a psychiatric diagnosis. For those female veterans with a combination of military-related risk factors, dementia risk was found to increase >2-fold. Although the mechanisms remain unclear, having co-occurring conditions may increase an individual's vulnerability to dementia through increased neural damage[1,4,41] or decreased cognitive reserve,[47] consequences that are common across brain injuries, PTSD, and depression. While the proportion of women in our cohort reporting combat exposure was small, ≈2%, these numbers are expected to increase with the changing roles of women in the military, which could result in greater numbers of female veterans with TBI, PTSD, and depression. Additional longitudinal research is needed to understand the interplay between these risk factors and to determine the potential benefits of targeted prevention for high-risk veterans with multiple military-related risk factors.

Notably, although TBI, PTSD, and depression were associated with incident dementia in our study, these effects were attenuated after accounting for the number of medical follow-up visits. Women with TBI, depression, or PTSD had 2 to 3 times as many visits as women without any diagnosis. This closer follow-up may allow the opportunity to receive a dementia

Figure Cumulative incidence of dementia among older female veterans



PTSD = posttraumatic stress disorder; TBI = traumatic brain injury.

diagnosis earlier because providers have more opportunities to note changes in a veteran's cognition or functioning. Alternatively, individuals with dementia and cognitive decline have an increased risk for hospitalization[48,49] and are more likely to present with challenges concerning treatment and diagnosis,[50] which can also increase the number of follow-up visits required.

This study has a number of important strengths, including its longitudinal design to determine the effects of military-related risk factors on dementia risk in a large sample of older female veterans. We adjusted for critical medical and demographic variables (although we only had ZIP code–level estimates of education and income) to test the robustness of our findings, and we accounted for possible detection bias by adjusting our models for the number of follow-up visits per year. In the interpretation of these results, it is also necessary to consider the limitations of this study, particularly the use of ICD-9-CM codes to establish diagnoses. Administrative diagnostic codes are less sensitive than structured diagnostic interviews, and it is likely that female veterans with less severe symptoms of depression, PTSD, mild TBI, and dementia did not receive diagnoses. Misdiagnosis and miscoding of military-related risk factors and dementia are also probable. While we conducted a sensitivity analysis requiring 2 diagnoses for our exposures of interest, we were not able to conduct validation studies for these diagnostic codes. However, we expect that such misclassification would most likely lead to a bias toward the null. In addition, despite the results of our sensitivity analysis imposing a 2-year lag, we cannot completely eliminate the possibility that these associations reflect prodromal relationships or reverse causality. Finally, we had limited ability to examine dementia subtypes, so we cannot determine whether the military-related risk factors increase dementia risk differentially.

In a very large cohort of older female veterans, military-related risk factors increased dementia risk by 50% to 80% when occurring independently and 2-fold when occurring together. These results emphasize the need for more comprehensive studies of dementia risk among women, particularly female veterans, and highlight the potential role of military-related risk factor screening and treatment to reduce dementia risk.

Author contributions

K.Y. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. K.Y. obtained funding and designed and supervised the study. K.Y., C.B.P., S.J.L., F.X., and T.D.H. were responsible for acquisition, analysis, and interpretation of data. All authors contributed to the writing and review of the manuscript.

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Disclosure

K. Yaffe serves on the Data Safety Monitoring Board for Takeda Inc and a National Institute on Aging–sponsored study and is member of the Beeson Scientific Advisory Board. S. Lwi, T. Hoang, F. Xia, D. Barnes, S. Maguen, and C. Peltz report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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