Alzheimer's & Dementia 10 (2014) S236-S241

Prisoner of war status, posttraumatic stress disorder, and dementia in older veterans☆

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Abstract

Background: It is not known whether prisoners of war (POWs) are more likely to develop dementia independently of the effects of posttraumatic stress disorder (PTSD).
Methods: We performed a retrospective cohort study in 182,879 U.S. veterans age 55 years and older, and examined associations between POW status and PTSD at baseline (October 1, 2000–September 30, 2003), and incident dementia during follow-up (October 1, 2003–September 30, 2012).
Results: A total of 484 veterans (0.3%) reported being POWs, of whom 150 (31.0%) also had PTSD. After adjusting for demographics, medical and psychiatric comorbidities, period of service, and the competing risk of death, the risk of dementia was increased in veterans who were POWs only (hazard ratio [HR], 1.61; 95% confidence interval [CI], 1.30–1.98) or had PTSD only (HR, 1.52; 95% CI, 1.41–1.64) and was greatest in veterans who were POWs and also had PTSD (HR, 2.24; 95% CI, 1.72–2.92).
Conclusions: POW status and PTSD increase risk of dementia in an independent, additive manner in older veterans.
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Keywords: Dementia; Risk factors; Veterans; Aged; POW; Posttraumatic stress disorder

1. Introduction

Prisoners of war (POWs) are members of the United States armed forces divisions who were captured and held against their will during times of war. A total of 142,246 U.S. veterans have been POWs during the past century, most of whom served in World War II, Korea, or Vietnam, and nearly 30,000 were still alive at the end of 2005 [1]. During their imprisonment, POWs were often subjected to intense physical harm, psychological stress, isolation, and nutritional deprivation. These extreme conditions may have left the survivors more vulnerable to physical and psychiatric sequelae over time.

A 2002 report commissioned by the Department of Veterans Affairs (VA) to provide a better understanding of the POW experience identified a wide range of conditions that could potentially be attributed to having been held in captivity [2]. These conditions included vitamin and nutritional deficiencies, ischemic cardiomyopathy, gastrointestinal disorders, infectious diseases, and psychiatric conditions such as psychosis, generalized anxiety disorder, posttraumatic stress disorder (PTSD), obsessive compulsive disorder, and depression.

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Publication of this article was supported by the United States Army Medical Research and Materiel Command.

K.Y. has served on DSMBs for Takeda Inc. and the NIH, has served as consultant to Novartis and Pfizer Inc., and has served on the medical advisory board for NeurExpand. The other authors have no conflict of interest to report.

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1552-5260/$ - see front matter © 2014 Published by Elsevier Inc. on behalf of The Alzheimer's Association.
http://dx.doi.org/10.1016/j.jalz.2014.04.004

However, the current body of literature that has examined the association between POW status and cognitive outcomes has been mixed. Although some studies have found that POWs perform significantly worse than non-POWs on tests of cognitive function, or have evidence of neurological impairment, particularly those who lost more than 35% of their body weight during captivity [3–5], others have found no differences between POWs and non-POWs in levels of cognitive function or risk of dementia [6,7], and some studies have even found better cognitive outcomes in POWs [8,9].

One potential explanation for these discrepant findings is that most prior studies have not controlled adequately for potential confounding factors such as PTSD. Other studies have found consistently that POWs are more likely than non-POWs to experience PTSD and depression as a result of their experiences [10–16]. In addition, several recent studies have found that both PTSD [17–19] and depression [20] are important risk factors for dementia in older veterans. Prior studies also have not considered mortality as a competing risk for dementia, which is particularly important when mortality rates are high in comparison with the outcome of interest [21,22]. It is possible that differential mortality rates may explain differences in findings in prior studies.

Therefore, the primary objective of the current study was to examine the association between POW status and the risk of dementia in older veterans, accounting for potential confounders and the competing risk of mortality. In addition, we sought to determine whether there was evidence of an interactive association between POW status and PTSD, which are likely to have co-occurred in some veterans and may be a marker of intensity of exposure. Gaining a better understanding of the risk factors for dementia in older veterans is critical for developing strategies to identify high-risk veterans and to diminish dementia risk in future armed forces personnel.

2. Methods

2.1. Subject population

Data were extracted from the Veterans Health Administration (VHA) National Patient Care Database, an electronic database that captures information on all inpatient and outpatient encounters that occur at VHA health care facilities nationwide. Subjects were a random sample of 200,000 veterans who (1) were age 55 years or older at the beginning of the baseline period (October 1, 2000–September 30, 2003), (2) had at least one inpatient or outpatient visit during the baseline period, (3) did not die before the start of the follow-up (October 1, 2003), and (4) had at least one inpatient or outpatient visit during the follow-up period (October 1, 2003–September 30, 2012). Of these veterans, 11,236 (5.6%) were excluded because they had a dementia diagnosis during the baseline period, and an additional 5885 (2.9%) were excluded because they served during the post-Vietnam era, when few POWs were taken. Therefore, the final sample size was 182,879.

This study was approved by the Committee on Human Research at the University of California, San Francisco; the Research & Development Committee at the San Francisco VA Medical Center; and the Human Research Protection Office of the U.S. Army Medical Research and Materiel Command. Informed consent was waived because this was a low-risk, retrospective analysis of existing medical record data, and it would not have been practical to obtain consent because many study participants had died. We did not have access to identifying information such as names or contact information, and scrambled social security numbers were used to track participants over time.

2.2. Measures

Information related to all inpatient and outpatient medical encounters that occur within the VHA system are entered by the clinician into a national electronic medical record system. Required data include diagnostic codes related to the reasons for the visit and procedure codes related to any procedures performed. Diagnoses and inpatient procedures are coded using the International Classification of Diseases, ninth revision, Clinical Modification (ICD-9-CM).

2.2.1. POW Status and PTSD

POW status is maintained in the Patient Information Management System and is included as a variable in all inpatient and outpatient data sets. POW status has been collected since 1976. PTSD was determined based on ICD-9-CM codes from inpatient and outpatient visits (309.81).

2.2.2. Dementia

Dementia at baseline was defined using a broad range of diagnostic codes that was developed to maximize sensitivity and to identify as many prevalent cases as possible [23,24]. Dementia at follow-up was defined using previously defined criteria based on a restricted set of codes to maximize specificity [17,20]. Codes for incident dementia included Alzheimer's disease (331.0), vascular dementia (290.4), senile dementia (290.0, 290.2, 290.3, 331.2), frontotemporal dementia (331.1), Lewy body dementia (331.82), and dementia not otherwise specified (294.8).

2.2.3. Mortality

Date of death was determined using the VA Vital Status file, which combines information from the VA, the Center for Medicare and Medicaid Services, and the Social Security Administration to determine date of death [25]. Prior studies have found that the VA Vital Status file is comparable with the National Death Index in terms of accuracy and completeness [26].

2.2.4. Other measures

Demographic variables included age and sex. Socioeconomic status was determined based on neighborhood education and income data from the 2000 U.S. Census. Education was dichotomized based on whether veterans were living in a zip

code tabulation area where 25% or less, or more than 25% of the adult population had completed a college degree (bachelor's degree or higher). Income was defined using tertiles of median income in the zip code tabulation area. ICD-9-CM codes were used to identify veterans with specific medical diagnoses (diabetes, hypertension, myocardial infarction, cerebrovascular disease, peripheral vascular disease, traumatic brain injury, chronic pulmonary disease, renal disease, obesity) and psychiatric diagnoses in addition to PTSD (major depressive disorder, alcohol abuse, drug abuse, tobacco use) at baseline.

2.3. Statistical analyses

Veterans were classified as having a history of being a POW at baseline (2000–2003), and characteristics of those who were and were not POWs were compared using *t* tests for continuous variables and χ^2 for categorical variables.

Fine-Gray proportional hazards models were used to examine time to dementia onset, with age as the timescale while accounting for the competing risk of death [21]. Traditional Cox proportional hazards models treat subjects who die as censored (i.e., missing), and the model assumes they would still be "at risk" if additional follow-up data had been available [22]. In contrast, Fine-Gray models treat mortality as an alternate "competing risk," and those who die are excluded from the at-risk group.

Cumulative incidence of dementia accounting for the competing risk of death was plotted by age at diagnosis for veterans who were and were not POWs. In addition, to examine the effects of PTSD on the association, cumulative incidence of dementia was plotted for those with POW history only, PTSD only, both, or neither.

Time to event was calculated from the date of first visit or first record of POW history during baseline (October 1, 2000–September 30, 2003) until the date of dementia diagnosis or death (whichever occurred first) during follow-up (October 1, 2003–September 30, 2012). Veterans who did not die or develop dementia were censored at the end of follow-up. Models were unadjusted and adjusted for potential confounders that were associated significantly with POW status at baseline in bivariate analyses by including them as covariates in the final multivariable model. We also tested formally for interaction between POW status and PTSD by including an interaction term in the model. Standard statistical and graphical techniques were used to assess proportional hazards assumptions, with no evidence of violations. All analyses were performed using Stata 12.1 (StataCorp, College Station, TX) or SAS 9.2 (SAS Institute, Cary, NC).

3. Results

A total of 484 veterans (0.3%) had been POWs at baseline, whereas 6114 (3.3%) had been diagnosed with PTSD. Nearly one-third of POWs also had PTSD (31.1%, n = 150). A comparison of the baseline characteristics of veterans with and without POW status is shown in Table 1. Veterans who had been POWs were significantly older (mean age, 77 years) than veterans who had not (68 years, $P < .001$). In addition, POWs were significantly more likely than non-POWs to have served in World War II (80% vs. 34%) and were less likely to have served in Korea (13% vs. 40%) or Vietnam (7% vs. 26%, $P < .001$). POWs also had significantly higher levels of most comorbid medical conditions, including myocardial infarction (21% vs. 7%, $P < .001$), cerebrovascular disease (29% vs. 12%, $P < .001$), and peripheral vascular disease (30% vs. 12.%, $P < .001$). Prevalence of comorbid mental health conditions was also substantially greater in POWs than non-POWs, including PTSD (31% vs. 3%, $P < .001$) and major depression (10% vs. 5%, $P < .001$).

Table 1
Baseline characteristics of 182,879 veterans by prisoner of war (POW) status

Characteristic	POW (n = 484), mean (SD) or number (%)	Non-POW (n = 182,395), mean (SD) or number (%)	*P* value
Demographics			
Age, y	76.51 (4.66)	68.40 (7.85)	<.0001
>25% college degree in zip code*	173 (36.65)	53,830 (30.46)	<.01
Median income tertile in zip code*			<.0001
≤$23,438	220 (46.61)	58,916 (33.33)	
$23,438.01–$30,976.00	157 (33.26)	58,874(33.31)	
>$30,976.00	95 (20.13)	58,966 (33.36)	
Period of service			
World War II	386 (79.75)	61,933 (33.96)	<.001
Korea	62 (12.81)	73,761 (40.44)	
Vietnam	36 (7.44)	46,701 (25.60)	
Medical			
Diabetes	160 (33.06)	53,722 (29.45)	.08
Hypertension	434 (89.67)	132,368 (72.57)	<.0001
Myocardial infarction	100 (20.66)	12,469 (6.84)	<.0001
Cerebrovascular disease	141 (29.13)	21,684 (11.89)	<.0001
Peripheral vascular disease	146 (30.17)	21,861 (11.99)	<.0001
Chronic pulmonary disease	227 (46.90)	47,109 (25.83)	<.0001
Renal disease	71 (14.67)	10,799 (5.92)	<.0001
Obesity	77 (15.91)	31,143 (17.07)	.50
Psychiatric			
Major depression	50 (10.33)	9866 (5.41)	<.0001
Posttraumatic stress disorder	150 (30.99)	5964 (3.27)	<.0001
Alcohol abuse	18 (3.72)	10,270 (5.63)	.07
Drug abuse	5 (1.03)	2984 (1.64)	.29
Tobacco use	87 (17.98)	32,170 (17.64)	.85
TBI, any	4 (0.83)	1199 (0.66)	0.65

Abbreviations: SD, standard deviation; TBI, traumatic brain injury.
*Data missing as follows: Education (n=5,683); income (n=5,651).

Overall, 10.0% of veterans developed dementia during the 9-year follow-up period whereas 40.9% died. The cumulative incidence of dementia accounting for the competing risk of mortality and age (timescale) was 31.6% in POWs vs. 19.5% in non-POWs (unadjusted hazard ratio [HR], 1.76; 95% confidence interval [CI], 1.49–2.07) (Fig. 1).

The cumulative incidence of dementia accounting for the competing risk of death in veterans with POW status alone, PTSD alone, both, or neither is shown in Fig. 2. There was more than a 50% increase in the risk of dementia in veterans with POW status alone (HR, 1.56; 95% CI, 1.26–1.92), more than a 75% increased risk in veterans with PTSD alone (HR, 1.78; 95% CI, 1.66–1.90), and more than a twofold increased risk in veterans with both POW status and PTSD (HR, 2.39; 95% CI, 1.84–3.11). The interaction term between POW status and PTSD was not statistically significant ($P = .41$), which is consistent with an additive (i.e. independent) association. Results were similar after additional adjusting for other demographic factors, medical conditions, psychiatric comorbidities, and period of service, with the risk of dementia increased by approximately 50% in veterans with either POW status or PTSD alone, and more than twofold in those with both risk factors (Table 2).

4. Discussion

In a nationally representative sample of more than 180,000 older veterans, we found that POW history was associated with an increased risk of developing incident dementia, even after accounting for the competing risk of death. Furthermore, we observed evidence of an additive association between POW status and PTSD, such that the risks of dementia were more than two times greater in veterans with both POW status and PTSD compared with veterans with neither, even after adjusting for potential confounders and accounting for the competing risk of mortality.

Few prior studies have examined the association between POW status and dementia in veterans. One study compared

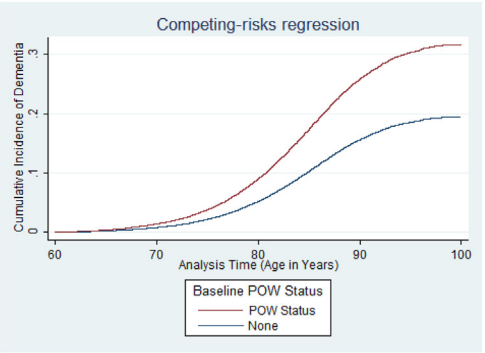

Fig. 1. Cumulative incidence of dementia in veterans who were and were not prisoners of war (POWs), accounting for the competing risk of death. The cumulative incidence of dementia was more than 75% greater in POWs (red line) than non-POWs (blue line) in competing-risks proportional hazards regression analyses that modeled mortality as the competing risk and used age as the timescale. HR, hazard ratio.

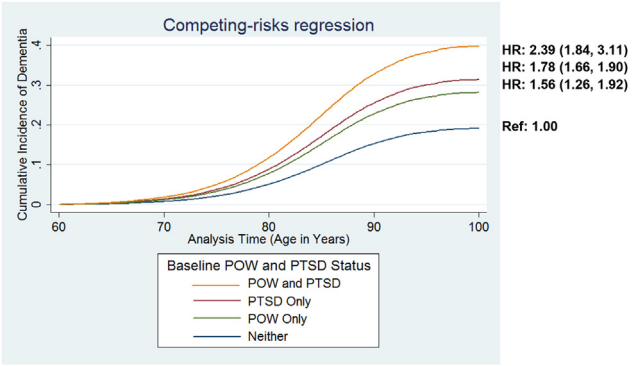

Fig. 2. Cumulative incidence of dementia in veterans with and without prisoner of war (POW) exposure and posttraumatic stress disorder (PTSD). There was evidence of an additive association between POW status and PTSD on risk of dementia, such that cumulative incidence was increased more than 50% with POW status only (green line), more than 75% with PTSD only (red line), and nearly 240% with both POW status and PTSD (yellow line) compared with those with neither risk factor (blue line). All models accounted for the competing risk of mortality and adjusted for age as the timescale. HR, hazard ratio.

the prevalence of a wide range of medical conditions in 101 Australian POWs and a comparison group of non-POW combatants from the same theater of war [6]. POWs reported significantly more somatic symptoms and had more medical diagnoses, including cognitive disorders such as delirium; however, the prevalence of dementia did not differ between the two groups, similar to the findings of another study in Australian POWs [7]. Another study found that, in veterans with dementia, those who were former POWs exhibited different behavioral disturbances than those who had not been POWs, including more paranoia and less verbal agitation [27].

Studies that have compared cognitive function in POWs and non-POWs also have had mixed results. Three studies found that POWs subjected to extreme loss of body weight performed significantly worse in tests of memory and learning several decades after their imprisonment [3–5], with a pattern of impairment similar to patients with

Table 2
Prisoner of war status (POW), posttraumatic stress disorder (PTSD), and risk of dementia

	Hazard ratio (95% confidence interval)*		
Risk factors	Unadjusted	Additive	Fully adjusted
POW	1.76 (1.49, 2.07)	1.56 (1.26, 1.92)	1.61 (1.30, 1.98)
PTSD	—	1.78 (1.66, 1.90)	1.52 (1.41, 1.64)
POW + PTSD†	—	2.39 (1.84, 3.11)	2.24 (1.72, 2.92)

*All models adjusted for the competing risk of mortality and age as the timescale. Fully adjusted model also adjusted for education, income, hypertension, diabetes, myocardial infarction, cerebrovascular disease, peripheral vascular disease, chronic pulmonary disease, renal disease, major depressive disorder, and period of service.

†No evidence of interaction between POW and PTSD, suggesting an independent, additive association: additive model, P value for interaction = .41; fully adjusted model, P value for interaction = .67.

alcoholic Korsakoff's syndrome [4]. However, other studies have found either no difference in cognitive test performance between POWs and non-POWS, even when considering the amount of weight loss [7], or better intellectual function in POWs [8]. These latter counterintuitive findings may reflect a selection bias, in which those POWs who chose to participate in the study were "healthy survivors" whereas those who experienced more adverse effects of being POWs (including cognitive impairment) may have been less likely to participate in the study, either because of choice or mortality. The current study minimizes this potential bias because it uses medical record data, which are available for all veterans who seek medical care within the VHA system, and because it accounts for the competing risk of mortality, which was substantial in this study population of older veterans.

Although prior studies have focused on severe malnutrition as a potential explanation for the long-term adverse health effects of being held as a POW, another possibility is the altered activity of cortisol as part of the stress response. The extreme amounts of physical and psychological stress to which POWs were subjected may have led to chronic changes in the activity of cortisol. Studies examining veterans and mock POW simulations have shown that these experiences have both altered hypothalamic–pituitary–adrenal axis functioning [28] and increased acute cortisol release [29]. Cortisol release during extreme stress has been found to impair recall and cognitive function significantly [30]. In addition, both observational and interventional studies have demonstrated the influence of increased cortisol levels on decreased cognitive ability later in life [31–35]. The results of these studies raise the possibility that the altered influence of cortisol during captivity may contribute to late-life dementia in POWs.

In our study, we found an additive detrimental effect on risk of dementia when a diagnosis of PTSD was combined with POW status. This additive effect of PTSD and POW status may suggest that the mechanism behind the influence of PTSD on dementia is different biologically from the mechanisms hypothesized for POW status. In prior studies, PTSD has been linked with significant decreases in hippocampal size and abnormalities in frontal–limbic structures such as the amygdala and anterior cingulate cortex [36,37], possibly stemming from disinhibition of general inflammatory mediators [38] and decreases in hippocampal brain-derived neurotrophic factor expression [39]. In addition, those with chronic PTSD have been found to have increased cerebrospinal fluid levels of norepinephrine [40], suggesting another alternate biological route for cognitive deterioration that may function in an overstimulatory manner analogous to cortisol. Thus, it is possible that the independent, additive effects of POW status and PTSD reflect the cumulative effect of these different underlying mechanisms. Alternatively, it is possible that PTSD is simply a marker of the severity of conditions experienced while in captivity.

This study has several important strengths and limitations that should be considered when interpreting the findings. Key strengths include the large, nationally representative sample of more than 180,000 veterans age 55 years or older who were monitored in the VHA medical system through 2012, which minimizes the potential for selection bias, and the analytic approach that accounted directly for the competing risk of death. However, a limitation of electronic medical records is that codes are entered by clinicians for medical and billing purposes and are likely to result in some misclassification. However, to the extent that misclassification is nondifferential (i.e. misclassification of dementia is similar in POWs and non-POWs), results would be biased toward the null.

Our findings suggest that veterans who were held as POWs have approximately a 50% greater risk of developing dementia, after adjusting for potential confounders and accounting for the competing risk of death. In addition, we observed an additive association between POW status and PTSD, such that veterans with both of these risk factors had more than a twofold increase in the risk of dementia. These findings support efforts to ensure that vulnerable veterans who were held as POWs or who have a history PTSD receive appropriate care for the long-term adverse sequelae of their war-related exposures as they age.

Acknowledgments

This study was supported by the Department of Defense/NCIRE (The Veterans Health Research Institute) (Barnes: W81XWH-11-2-0189, project 1610; Byers: W81XWH-11-2-0189, project 1614; Yaffe: W81XWH-12-1-0581) and the National Institutes of Health (Yaffe: K24 AG031155). The views expressed do not necessarily reflect those of the U.S. government.

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