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Short Communication

Post-Traumatic Stress Disorder and Risk of Parkinson's Disease in a Veteran Cohort

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Abstract. Post-traumatic stress disorder (PTSD) may be a risk factor for Parkinson's disease (PD). We examined the relation between PTSD and PD in a cohort of 158,122 Veterans who had any Veterans Health Administration (VHA) or Medicare health care utilization between 10/1/1999–2/17/2021. Using a nested case-control design we matched 10 controls to each Veteran with PD by sex, race, and rank. In conditional logistic regression models adjusted for camp and smoking, a PTSD diagnosis was significantly associated with PD (OR = 1.35; $p = 0.0002$); odds were higher if PTSD was coded before PD (OR = 1.53, $p < 0.0001$). PTSD may be a risk factor for PD.

Keywords: PTSD, Parkinson's disease, Veterans, epidemiology, stress

Stress has been proposed as a risk factor for development of Parkinson's disease (PD) but the data are limited. Post traumatic stress disorder (PTSD) is an increasingly well-recognized condition in military Veterans, with an estimated prevalence up to 15% in those previously deployed, compared to 7.8% in the general population.[1,2] PTSD is a disorder that results when a person experiences a traumatic event and develops a set of symptoms that persist for more than one month. Many individuals experience symptoms for more than a year and/or can have symptoms that are intermittent or relapsing.[3]

Several papers have examined the association between PTSD and PD. Chan examined the relationship between PTSD and PD using the national Taiwanese Health Insurance Research database.[4] They identified 1,456 persons with PTSD and matched them on age and sex to 5,824 persons without PTSD. There was an increased risk of having a subsequent PD diagnosis for those individuals who had PTSD with a hazard ratio of 3.46 (95%CI:1.72–6.96).

White and colleagues examined whether PTSD is associated with increased risk of PD in Veterans who also had traumatic brain injury (TBI).[5] Using a national cohort of Veterans from VA administrative data files between fiscal year (FY) 2000 and

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FY2013 they found 176,871 cases with a diagnosis of PD and matched them to 707,484 Veterans without a PD diagnosis. Single-factor, race-adjusted analyses found an odds ratio of 2.71 (95%CI:2.66–2.77) for PD in individuals with a PTSD diagnosis. A study in Israel compared a matched group of adults with a single diagnosis of PTSD prior to a diagnosis of PD to group without PTSD and found an increased risk of PD (HR = 1.48, $p = 0.04$).[6]

These studies reporting associations between PTSD and subsequent diagnosis of PD were limited to using ICD codes to identify PD. The objective of this paper was to examine the relationship between PTSD and PD in a cohort of US military Veterans with a medical record validated diagnosis of PD. We hypothesized that Veterans who experience PTSD are more likely to develop PD.

METHODS

This was a retrospective cohort study of two groups of Veterans living at one of two Marine Corps base camps between 1975 and 1985. We obtained data from the Agency for Toxic Substances and Disorders Registry (ATSDR) for 340,489 US Veterans who were based at Camp Lejeune, North Carolina or Camp Pendleton, California, and identified those who utilized any VHA health care services (through 2/17/2021) and/or had Medicare claims (through 12/31/2018). 158,122 Veterans (46% of initial cohort) had any healthcare utilization. We reviewed the VHA electronic medical records (EMR) of all Veterans with $\geq$1 diagnostic codes for PD (ICD9 332.0 or ICD10 G20) to validate this diagnosis based on documentation in the EMR including symptomatology and PD medication use and to determine incident date of diagnosis. After validation, we identified 430 Veterans with PD; as previously reported in Goldman et al. a significantly higher proportion of these Veterans had resided at Camp Lejeune.[7]

We defined a Veteran as having had PTSD if s/he had $\geq$ two encounters, at least 3 months apart, with a documented diagnosis of PTSD based on ICD9 (309.81) or ICD10 (F43.10, F43.11, F43.12) codes in the VHA EMR or in Medicare claims files. Using a nested case-control design, we tested associations of PTSD and PD by matching 10 controls to each Veteran with PD based on age at PD diagnosis ("index date"), sex, race, and rank (i.e., enlisted, officer). We adjusted for Camp (Lejeune, Pendleton) in conditional logistic regression models, and conducted sensitivity analyses restricted to cases and controls with any VHA usage prior to index date, in sex and race-specific strata (White, non-White), and in each Camp separately. We also tested models including cigarette smoking (ever/never), though this variable was missing for a substantial proportion of cases. Camp and smoking status were included to remove them as potential confounders in our analyses.

This study was reviewed and approved by the institutional review boards of the University of California San Francisco, the San Francisco VA and Hines VA Hospital.

RESULTS

PTSD was identified in 15.1% ($n = 65$) of Veterans with PD and 12.6% ($n = 544$) of matched controls (Table 1). Veterans with PD were less likely than controls to have ever smoked (38.1% versus 47%, $p < 0.0005$).

In regression models adjusted for camp, the risk of PD was significantly higher in Veterans with PTSD (OR 1.23, 95%CI 1.09–1.40) (Table 2). Inclusion of smoking had minimal impact on the association with PTSD. Risk was similar in models restricted to males or females-only, though statistical power was limited for the latter given the small number of females. Risk was also similar in White and non-white Veterans (data not shown).

In camp-specific models, the association of PD and PTSD was stronger in Veterans from Camp Pendleton than in those from Camp Lejeune (OR 1.66 versus 1.17), but a multiplicative interaction term was not statistically significant ($p = 0.34$).

When we only included cases ($n = 259$) and matched controls ($n = 2{,}515$) with any VHA health care use prior to being diagnosed with PD, the association with PTSD was strengthened (OR = 1.49; CI: 1.29–1.72; $p < 0.0001$). Limiting analyses to cases in which a PTSD diagnosis occurred before the first PD diagnosis, resulted in a 1.53 times greater odds of developing PD than not having a prior PTSD diagnosis ($p < 0.0001$; Table 2). Finally, restricting our sample to only cases where PTSD was documented at least one year prior to the PD diagnosis resulted in a non-significant association for PTSD and PD.

DISCUSSION

We found a statistically significant association of PTSD and PD using rigorous case-finding methods,

Table 1
Demographic comparisons of PD cases and 1 : 10 matched controls

	Parkinson's disease cases ($n = 430$)	Matched controls ($n = 4,300$)	p
Age (mean/sd)	61.63 (4.4)	62.61 (4.3)	0.93
Gender (male)	96.05%	96.05%	1.0
Rank (enlisted)	8.84%	8.84%	1.0
Duration at camp in months (mean/sd)	25.71 (18.6)	25.31 (17.4)	0.65
Duration receiving VHA care* in years (mean/sd)	12.26 (6.9)	11.88 (7.5)	0.29
Ever smoked?	38.14%	46.98%	0.0005
Missing smoking	23.49%	28.00%	0.046
Camp Lejeune	64.88%	51.12%	<0.0001
PTSD diagnosis	15.12%	12.65%	0.15

*Duration was calculated based on the earliest encounter after 9/30/1999 to death or study end of 2/17/2021.

Table 2
Risk of PD diagnosis associated with a diagnosis of PTSD – multiple models

Models examined	Odds ratio for PTSD	95% CI	p
1. Adj for camp	1.34	1.15–1.57	0.0002
2. Adj for camp & smoking status	1.35	1.15–1.58	0.0002
3. Males Only: adj for camp & smoking status	1.36	1.16–1.60	0.0002
4. Females only: adj for camp & smoking status	0.65	0.22–1.94	0.437
5. Camp Pendleton only: adj for smoking	1.79	1.23–2.60	0.0022
6. Camp Lejeune only: adj for smoking	1.31	1.01–1.70	0.045
7. Restricted to cases with any VA health care use prior to PD index diagnosis	1.49	1.29–1.72	<0.0001
8. Including only cases in which PTSD diagnosis was coded before PD diagnosis; adj. for camp and smoking status	1.53	1.30–1.81	<0.0001
9. Including only cases in which PTSD diagnosis was > 1 year prior to PD diagnosis	0.95	0.84–1.11	0.55

replicating several prior reports.[4,5] Importantly, accurate PD diagnosis requires a high degree of clinician expertise, and it is often misdiagnosed in administrative datasets.[8,9] We identified PD cases using a combination of ICD codes, and/or use of PD medications and validated diagnoses by chart review. From the list of 1,095 cases with a PD ICD code, chart reviews validated a diagnosis of PD in only 430 cases (39%). This raises concerns for studies that only use diagnostic codes to identify persons with a diagnosis of PD, as many of these individuals may in fact, have other neurologic-related conditions such as secondary parkinsonism from antipsychotic medications.

The association of PTSD and PD is biologically plausible. Stress enhances neuronal monoamine turnover, increases central and peripheral markers of inflammation, activates microglia, and enhances pathologic severity in a variety of animal models of parkinsonism.[10,11]

The validation effort was a strength of this project as we continue to see that PD is both difficult to reliably diagnose and is often not managed by movement disorders neurologists who have specialized training to diagnose PD.[8,9,12] We were also able to draw from both VA and Medicare data to improve the sensitivity of case ascertainment. Of note, however, our study cohort was young (mean age < 63 years), which limited the number likely to utilize Medicare; this may result in reduced power to assess the association between PTSD and PD. While we did not validate the PTSD diagnosis, we required at least two diagnoses in the EMR at least 3 months apart to increase accuracy.

Although PTSD was significantly associated with PD in both Camps, the association was stronger at Camp Pendleton. There are many possible reasons for this including differential rates of combat deployment and/or seeking care within the VA. It may explain why requiring at least a year between PTSD and PD diagnoses resulted in a non-significant association, as more Pendleton cases were dropped, affecting our sample size and statistical power.

The primary limitation to these analyses is the difficulty in determining the temporal association between PTSD and PD. Documentation of PTSD in the EMR likely reflects when the provider learned about the PTSD rather than when it actually occurred. PTSD diagnosis in Veterans is often associated with their military service and would likely be docu-

mented closer to the occurrence of symptoms. The event(s) underlying the PTSD may have occurred much earlier than when it was documented in the VA records, as our data only go back to October 1999. Our cohort of Veterans were active military 15–25 years prior to when we had any diagnostic information for them. Even with this limitation, we did find increased odds of being diagnosed with PD following a documented diagnosis of PTSD in our cohort. Additionally, though we adjusted for potential confounders and explored sensitivity models stratified by sex and race, we were unable to consider other potential modifiers of the relationship between PTSD and PD. For example, a recent paper using a very large cohort of military Veterans found that a prior documented diagnosis of PTSD or traumatic brain injury increased the odds of developing PD and the combination of these conditions increased the odds beyond either diagnosis alone.[13]

PTSD is associated with increased risk of PD in this well-validated cohort of US Marine Corps Veterans. Using a rigorous case-finding approach and a nested case-control design, these results strengthen the evidence of the association between PTSD and PD. Stress mitigation and treatment of PTSD may potentially help to delay or prevent PD.

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The views presented in this paper are those of the authors and do not reflect those of the Department of Veterans Affairs.

CONFLICT OF INTEREST

Dr. Brown reported receiving grants from the Michael J. Fox Foundation and the National Institute on Aging and personal fees from Gateway Consulting, LLC, outside the submitted work. Dr. Tanner reported receiving personal fees from Lundbeck Pharma, CNS Ratings, Adamas, Cadent, and Evidera; serving on advisory boards for Kyowa Kirin, Acorda, Australia Parkinson's Mission; serving on a clinical trial steering committee for Jazz Pharmaceuticals/Cavion; and receiving grants from the National Institutes of Health, Biogen Idec, Parkinson Foundation, Michael J. Fox Foundation, Department of Defense Parkinson's Research Program, Roche, Genentech, BioElectron, and Gateway Institute for Brain Research, LLC, outside the submitted work. No other disclosures were reported.

DATA AVAILABILITY

The data supporting the findings of this study are available upon request of the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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