Archival Report

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Elevated Risk for Autoimmune Disorders in Iraq and Afghanistan Veterans with Posttraumatic Stress Disorder

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ABSTRACT

BACKGROUND: Posttraumatic stress disorder (PTSD) is associated with endocrine and immune abnormalities that could increase risk for autoimmune disorders. However, little is known about the risk for autoimmune disorders among individuals with PTSD.

METHODS: We conducted a retrospective cohort study of 666,269 Iraq and Afghanistan veterans under age 55 who were enrolled in the Department of Veterans Affairs health care system between October 7, 2001, and March 31, 2011. Generalized linear models were used to examine if PTSD, other psychiatric disorders, and military sexual trauma exposure increased risk for autoimmune disorders, including thyroiditis, inflammatory bowel disease, rheumatoid arthritis, multiple sclerosis, and lupus erythematosus, adjusting for age, gender, race, and primary care visits.

RESULTS: PTSD was diagnosed in 203,766 veterans (30.6%), and psychiatric disorders other than PTSD were diagnosed in an additional 129,704 veterans (19.5%). Veterans diagnosed with PTSD had significantly higher adjusted relative risk (ARR) for diagnosis with any of the autoimmune disorders alone or in combination compared with veterans with no psychiatric diagnoses (ARR = 2.00; 95% confidence interval, 1.91–2.09) and compared with veterans diagnosed with psychiatric disorders other than PTSD (ARR = 1.51; 95% confidence interval, 1.43–1.59; $p < .001$). The magnitude of the PTSD-related increase in risk for autoimmune disorders was similar in women and men, and military sexual trauma exposure was independently associated with increased risk in both women and men.

CONCLUSIONS: Trauma exposure and PTSD may increase risk for autoimmune disorders. Altered immune function, lifestyle factors, or shared etiology may underlie this association.

Keywords: Autoimmune disorders, Glucocorticoids, Immune system, Inflammation, Military sexual trauma, Posttraumatic stress disorder, Traumatic stress, Veterans

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Posttraumatic stress disorder (PTSD) is associated with a number of biological abnormalities that could increase risk for autoimmune disorders. First, PTSD appears characterized by lower levels of the immunomodulatory glucocorticoid hormone cortisol and reduced signaling through anti-inflammatory glucocorticoid receptor transcriptional control pathways (1–5). Second, accumulating evidence links PTSD with increased inflammatory activity, as indexed by elevated levels of proinflammatory cytokines and higher signaling through proinflammatory nuclear factor-κB transcriptional control pathways (4–7). Third, investigators have observed altered patterns of gene expression in immune cells (8,9) and reduced methylation of immune-related genes (10) in patients with PTSD. Finally, emerging evidence suggests that PTSD is associated with accelerated immune cell aging, as indexed by shorter age-adjusted telomere length (11,12), which has been linked with elevated inflammation in vivo and in vitro (13,14). This pattern of abnormalities in the hypothalamic-pituitary-adrenal axis, immune system, and telomere maintenance system may increase risk for autoimmune disorders by increasing inflammation and impairing the function of immune cells (15–18). Nonetheless, relatively little is known about the risk for autoimmune disorders associated with PTSD.

In one previous study, PTSD was associated with higher prevalence of self-reported autoimmune disorders in a sample of 2490 male Vietnam veterans (19). In another study, PTSD was associated with increased risk for physician-diagnosed rheumatoid arthritis in a sample of 3143 pairs of male twins (20). However, no prior study has examined if PTSD increases risk for a range of physician-diagnosed autoimmune disorders with definitive diagnostic criteria, and it is not known if the risk for autoimmune disorders is greater in individuals with PTSD compared with those with other psychiatric disorders. Moreover, although the risk for, or severity of, many autoimmune

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disorders is substantially higher in women compared with men (21–26), no studies have examined the risk for autoimmune disorders in women with PTSD.

To assess the risk for autoimmune disorders associated with PTSD and other psychiatric disorders, we conducted the present study in a national sample of Iraq and Afghanistan veterans enrolled in the U.S. Department of Veterans Affairs (VA) health care system. Emerging data indicate high rates of PTSD and other psychiatric disorders (27,28), as well as high rates of military sexual trauma (MST) exposure (29) in this population of veterans. In the present study, we assessed risk for autoimmune disorders associated with PTSD, other psychiatric disorders, and MST, focusing our analyses on the most prevalent autoimmune disorders in the United States that have definitive diagnostic criteria or diagnostic tests (i.e., thyroiditis, rheumatoid arthritis, inflammatory bowel disorders, multiple sclerosis, and lupus erythematosus) (30).

METHODS AND MATERIALS

Study Population

The Department of Veterans Affairs national Operation Enduring Freedom (OEF), Operation Iraqi Freedom (OIF), and Operation New Dawn (OND) Roster includes veterans deployed in OEF/OIF/OND who have separated from service and enrolled in the VA health care system. We identified 738,785 male and female Iraq and Afghanistan veterans in the OEF/OIF/OND Roster who first received VA health care from October 7, 2001, to March 31, 2011. We excluded veterans without at least 1 year of follow-up within the VA and the study end date was therefore March 31, 2012. Veterans aged over 55 years (1.6%) were excluded from our analyses because our goal was to assess the risk for autoimmune disorders in a more homogenous group of veterans without confounds associated with older age. Veterans who remain in the military later in life—making them older than 55 during their first VA appointment following service in OEF/OIF/OND—may also differ from the general population of veterans because military service personnel are usually eligible for retirement after 20 years of service. Veterans who already had a diagnosis of one of the target autoimmune disorders before receiving a psychiatric diagnosis were excluded to avoid any confounding of psychiatric diagnoses with autoimmune disorder-related symptoms or distress. Finally, to exclude potential inaccurate or rule-out diagnoses, we excluded veterans who had received an autoimmune disorder diagnosis at only one appointment. See Figure 1 for a more complete description of exclusions. After exclusions, our study population included 666,269 veterans. The study was approved by the Committees on Human Research at the University of California, San Francisco, and the San Francisco VA Medical Center.

Data Sources

We used the VA OEF/OIF/OND Roster to obtain basic demographic and military service information for Iraq and Afghanistan veterans (31) and the VA electronic medical record database, the National Patient Care Database (NPCD), to obtain information on VA clinical visits and clinical diagnoses based on ICD-9-CM codes.

Sociodemographic and Clinical Information

The OEF/OIF/OND Roster was used to identify sociodemographic information including age, gender, and race, as well as military service information including military rank, component type, service branch, and multiple deployments. The VA NPCD was used to obtain clinical information including clinical diagnoses based on ICD-9-CM and number of primary care visits. We also used the VA NPCD to assess the presence of MST-related clinical encounters, and we used the presence of these encounters as an index of MST. Basic sociodemographic, military service, and clinical information for our full sample is provided in Table 1 and stratified by gender in Table S1 in Supplement 1.

Psychiatric Disorders

Based on psychiatric diagnoses received within the VA system, we classified patients into three groups: 1) veterans with PTSD alone or combined with other psychiatric disorders; 2) veterans with psychiatric disorders other than PTSD; and 3) veterans with no psychiatric disorders. Psychiatric diagnoses were identified by ICD-9-CM codes from the VA NPCD database and the codes used were as described previously (31).

Autoimmune Disorders

We identified the most prevalent autoimmune disorders that have definitive diagnostic criteria and/or diagnostic tests based on epidemiologic data and clinical diagnostic criteria (30). These disorders included thyroiditis, rheumatoid arthritis, inflammatory bowel disorders, multiple sclerosis, and lupus erythematosus. The VA NPCD was then used to obtain information on diagnoses of these autoimmune disorders in our population, based on ICD-9-CM codes (Table S2 in Supplement 1).

Covariates

The VA OEF/OIF/OND Roster was used to ascertain age, gender, and race, and the NPCD was used to ascertain number of primary care visits. Due to the frequent misclassification of race/ethnicity in administrative data (32,33), we adjusted only for White versus non-White in our models. Because greater health care utilization in patients with psychiatric disorders produces a potential ascertainment bias, we adjusted for the number of primary care visits in the year before the autoimmune disorder diagnosis for each patient diagnosed with an autoimmune disorder. For veterans without an autoimmune disorder diagnosis, we adjusted for the number of primary care visits in the year before their most recent VA encounter.

Statistical Analyses

Generalized linear models with Poisson distribution and robust error variance were used to estimate relative risks (RR), adjusted relative risks (ARR), and 95% confidence intervals (CIs). In our primary models, we estimated RR and ARR for any of the autoimmune disorders alone or in combination, as well as risk for each autoimmune disorder separately in veterans with a diagnosis of PTSD compared with 1) veterans without

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