Archival Report

Biological Psychiatry

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

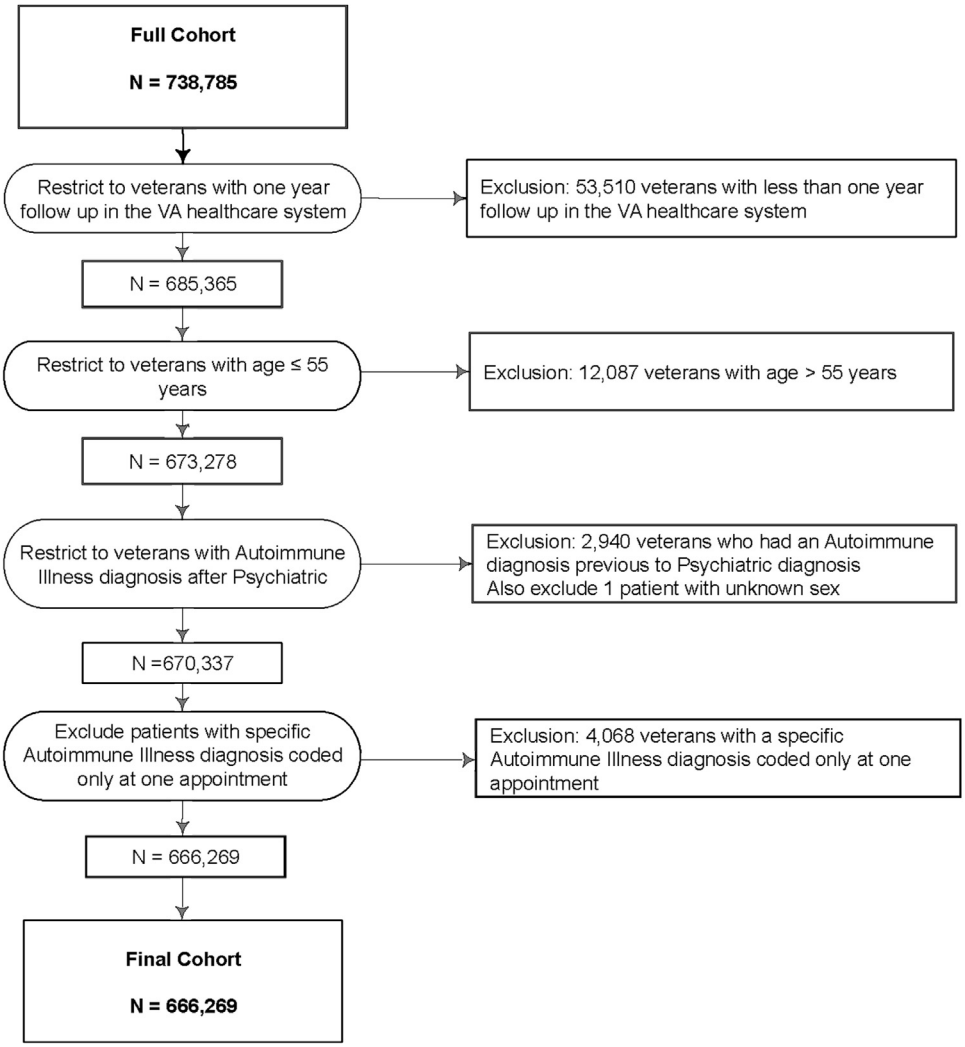

Figure 1. Flow chart detailing exclusion criteria applied to identify study population.

any psychiatric diagnoses; and 2) veterans with psychiatric diagnoses other than PTSD. In follow-up analyses, we stratified by gender and assessed the interaction between gender and psychiatric disorder group. We also used generalized linear models to examine the contribution of common comorbid psychiatric disorders and MST. In follow-up analyses, we assessed risk for autoimmune disorders associated with depressive, anxiety, adjustment, psychotic, and alcohol and substance use disorders with and without PTSD. We did not conduct separate analyses for veterans with PTSD alone without any comorbid psychiatric disorders because the symptoms of PTSD overlap with other common psychiatric disorders (e.g., depression and anxiety). In fact, individuals with severe PTSD who have most or all of the symptoms must by definition also meet criteria for major depression. Nonetheless, there is a lot of variability in the number of comorbid diagnoses received by individuals with PTSD and other psychiatric disorders, and this psychiatric burden may also predict outcomes (34). Thus, we computed a psychiatric burden variable based on the sum of depression, anxiety, adjustment, psychotic, alcohol use, and substance use disorders (range 0–6 disorders) to examine the effects of number of comorbidities on risk for autoimmune disorders. Finally, in follow-up analyses testing the reverse of our primary hypothesis, we examined the RR and ARR for diagnosis with PTSD and other psychiatric disorders in veterans with versus without autoimmune disorders, excluding veterans who had a diagnosis of a psychiatric disorder before their autoimmune disorder. Models were adjusted for age, gender, race, and number of primary care visits. Analyses were conducted using SAS software 9.3 (SAS Institute Inc, Cary, North Carolina) and STATA 13.1 (Statacorp, College Station, Texas). All tests of significance were two-sided with an α of $p < .05$.

RESULTS

Sample Characteristics

Table 1 describes the sample characteristics. PTSD with and without other psychiatric diagnoses was diagnosed in 203,766 veterans (30.6%), and psychiatric disorders other than PTSD were diagnosed in an additional 129,704 veterans (19.5%).

Table 1. Sample Characteristics

Characteristic	Number 666,269	No Psychiatric Disorder *n* (%) 332,799 (49.9)	Other Psychiatric Disorders *n* (%) 129,704 (19.5)	PTSD *n* (%) 203,766 (30.6)	*p* Value
Sex					
Female	79,356	40,141 (12.1)	19,310 (14.9)	19,905 (9.8)	<.001
Male	586,913	292,658 (87.9)	110,394 (85.1)	183,861 (90.2)	<.001
Age: Mean (SD)[a]	31.2 (8.7)	32.2 (9.0)	30.8 (8.5)	30.0 (8.0)	<.001
Age Group[a]					
18–24	186,736	84,076 (25.3)	37,847 (29.2)	64,813 (31.8)	<.001
25–34	263,743	124,286 (37.3)	53,353 (41.1)	86,104 (42.3)	<.001
35–44	149,104	84,056 (25.3)	26,502 (20.4)	38,546 (18.9)	<.001
45–54	66,686	40,381 (12.1)	12,002 (9.3)	14,303 (7.0)	<.001
Race/Ethnicity					
White	326,101	158,349 (47.6)	64,941 (50.1)	102,811 (50.5)	<.001
Non-White	340,168	174,450 (52.4)	64,763 (49.9)	100,955 (49.5)	<.001
Marital Status					
Married	293,775	153,482 (46.1)	52,881 (40.8)	87,412 (42.9)	<.001
Never married	341,868	164,598 (49.5)	70,483 (54.4)	106,787 (52.4)	<.001
Divorced/widowed/other	30,211	14,494 (4.4)	6249 (4.8)	9468 (4.6)	<.001
Military Rank					
Enlisted	610,646	292,609 (87.9)	122,056 (94.1)	195,981 (96.2)	<.001
Other	55,623	40,190 (12.1)	7648 (5.9)	7785 (3.8)	<.001
Active Duty or Reserve					
Active duty	371,342	184,043 (55.3)	70,365 (54.3)	116,934 (57.4)	<.001
Reserve/National Guard	294,927	148,756 (44.7)	59,339 (45.7)	86,832 (42.6)	<.001
Military Branch					
Army	407,870	182,187 (54.7)	78,166 (60.3)	147,517 (72.4)	<.001
Air Force	79,184	55,187 (16.6)	14,489 (11.2)	9508 (4.7)	<.001
Marines	91,928	41,746 (12.5)	15,981 (12.3)	34,201 (16.8)	<.001
Navy	87,287	53,679 (16.1)	21,068 (16.2)	12,540 (6.2)	<.001
Multiple Deployments	265,833	132,555 (39.9)	48,242 (37.2)	85,036 (41.8)	<.001
Urban	370,146	180,437 (62.0)	75,026 (62.8)	114,683 (60.0)	<.001
Primary Care Visits: Mean (SD)[b]	1.6 (2.0)	1.1 (1.4)	2.0 (2.2)	2.3 (2.4)	<.001
Mental Health Visits: Mean (SD)[b]	2.5 (9.4)	0.1 (.6)	2.4 (7.7)	6.7 (15.0)	<.001
Military Sexual Trauma[c]	13,650	1548 (.5)	3187 (2.5)	8915 (4.4)	<.001
Psychiatric Diagnoses					
PTSD	203,766	–	–	203,766 (100.0)	<.001
Depression	184,109	–	57,313 (44.2)	126,796 (62.2)	<.001
Anxiety disorder	123,819	–	44,632 (34.4)	79,187 (38.9)	<.001
Adjustment disorder	110,626	–	47,516 (36.6)	63,110 (31.0)	<.001
Psychosis	9570	–	2377 (1.8)	7193 (3.5)	<.001
Alcohol use disorder	86,082	–	25,913 (20.0)	60,169 (29.5)	<.001
Substance use disorder	41,370	–	10,382 (8.0)	30,988 (15.2)	<.001
Comorbid Psychiatric Disorders: Mean (SD)[d]	1.7 (1.2)	–	1.5 (1.0)	1.8 (1.3)	<.001

PTSD, posttraumatic stress disorder; VA, U.S. Department of Veterans Affairs.

[a]Age refers to age at initial VA appointment.

[b]Visits refer to mean annual number of primary care or mental health visits.

[c]Military sexual trauma exposure is based on VA clinical encounters coded for military sexual trauma.

[d]Refers to number of psychiatric diagnoses excluding PTSD. Total column reflects 333,470 patients with one or more psychiatric diagnoses.

Veterans with psychiatric disorders were younger ($p < .001$), more likely to be male ($p < .001$) and non-White ($p < .001$), and had a higher number of visits to primary care in the prior year ($p < .001$) than veterans with no psychiatric disorders. The median follow-up time from first appointment to the study end date was 1502 days (interquartile range, 913–2186 days) with a minimum of 366 and a maximum of 3819 days.

Autoimmune Disorders

Within the sample of 666,269 veterans, 9743 (1.5%) received a diagnosis of an autoimmune diagnosis at two or more separate VA clinical encounters: 6963 (1.0%) with thyroiditis, 1460 (.2%) with inflammatory bowel diseases, 562 (.1%) with rheumatoid arthritis, 535 (.1%) with multiple sclerosis, and 339 (.1%) with lupus erythematosus. Based on previous epidemiologic studies that used a wider age range of participants and balanced samples of male and female subjects, our relatively young and mostly male veteran sample had slightly lower rates of thyroiditis (1% vs. 1.95%) (35), inflammatory bowel diseases (.2% vs. .4%) (36), and rheumatoid arthritis (.1% vs. .5% to 1%) (37) but similar rates of systemic lupus erythematosus (.1% vs. .1%) (38) and higher rates of multiple sclerosis (.1% vs. .01%) (39). The median time between first psychiatric diagnosis and first autoimmune disorder diagnosis was 220 days (interquartile range, 6–807 days).

PTSD and Risk for Autoimmune Disorders

Veterans diagnosed with PTSD had significantly higher risk for diagnosis with any of the autoimmune disorders alone or in combination and for all of the autoimmune disorders considered individually compared with veterans with no psychiatric disorders (Figure 2, Table 2). Veterans with psychiatric disorders other than PTSD also had significantly higher risk for any of the autoimmune disorders alone or in combination with other autoimmune disorders, as well as for thyroiditis, multiple sclerosis, and lupus erythematosus, compared with veterans with no psychiatric disorders (Figure 2, Table 2).

In all cases, the effect size for the ARR associated with psychiatric disorders other than PTSD was smaller than that associated with PTSD. Moreover, compared with veterans with other psychiatric disorders, veterans with PTSD had significantly higher risk for diagnosis with any autoimmune disorder alone or in combination (ARR = 1.51, 95% CI, 1.43–1.59; $p < .001$), as well as for thyroiditis (ARR = 1.56; 95% CI, 1.47–1.66; $p < .001$), inflammatory bowel disorders (ARR = 1.45; 95% CI, 1.23–1.67; $p < .001$), and rheumatoid arthritis, (ARR = 2.01; 95% CI, 1.52–2.51; $p < .001$) but not multiple sclerosis (ARR = 1.03; 95% CI, .82–1.25; $p = .63$) or lupus erythematosus (ARR = 1.18; 95% CI, .85–1.51; $p = .12$) individually.

In follow-up analyses, we examined if the addition of comorbid PTSD was associated with elevated risk for autoimmune disorders in veterans with other specific psychiatric diagnoses including depressive, anxiety, adjustment, psychotic, substance use, and alcohol use disorders. These analyses indicated that in each case, the addition of PTSD conferred significantly higher risk for developing an autoimmune disorder (Table 3). Veterans with PTSD in our sample had a higher number of comorbid psychiatric diagnoses than veterans with other psychiatric disorders (*p*s $< .001$) (Table 1 and Table S1 in Supplement 1). Thus, we reran our analyses adjusting for number of comorbid psychiatric disorders (excluding PTSD) and found that PTSD-related increased risk for autoimmune disorders remained significant in analyses adjusted for age, gender, race/ethnicity, and number of primary care visits (ARR = 1.36; 95% CI, 1.29–1.42; $p < .001$). In the same model, number of comorbidities itself was an independent risk factor for autoimmune disorders (ARR = 1.22; 95% CI, 1.20–1.25; $p < .001$).

We also reran our analyses for lupus erythematosus, excluding patients with lupus erythematosus (ICD-9 code 695.4) and focusing only on those specifically diagnosed with systemic lupus erythematosus (ICD-9 code 710.0). Results indicated that the pattern of results for the combined lupus erythematosus category was the same as that for systemic lupus erythematosus alone. In fact, the effect size for PTSD-related increased risk was larger for systemic lupus erythematosus alone than for the combination of lupus erythematosus and systemic lupus erythematosus (ARR = 1.65; 95% CI, 1.14–2.40; $p = .008$).

Gender Differences

Table S1 in Supplement 1 describes sample characteristics stratified by gender. Women had significantly higher risk for autoimmune disorders overall with 4.6% of women versus 1.7% of men being diagnosed with an autoimmune disorder. In models adjusted for age, race, and primary care visits, women relative to men had more than three times higher risk for any of the autoimmune disorders alone or in combination (ARR = 3.03; 95% CI, 2.89–3.16; $p < .001$) and significantly elevated risk for thyroiditis (ARR = 3.48; 95% CI, 3.31–3.67;

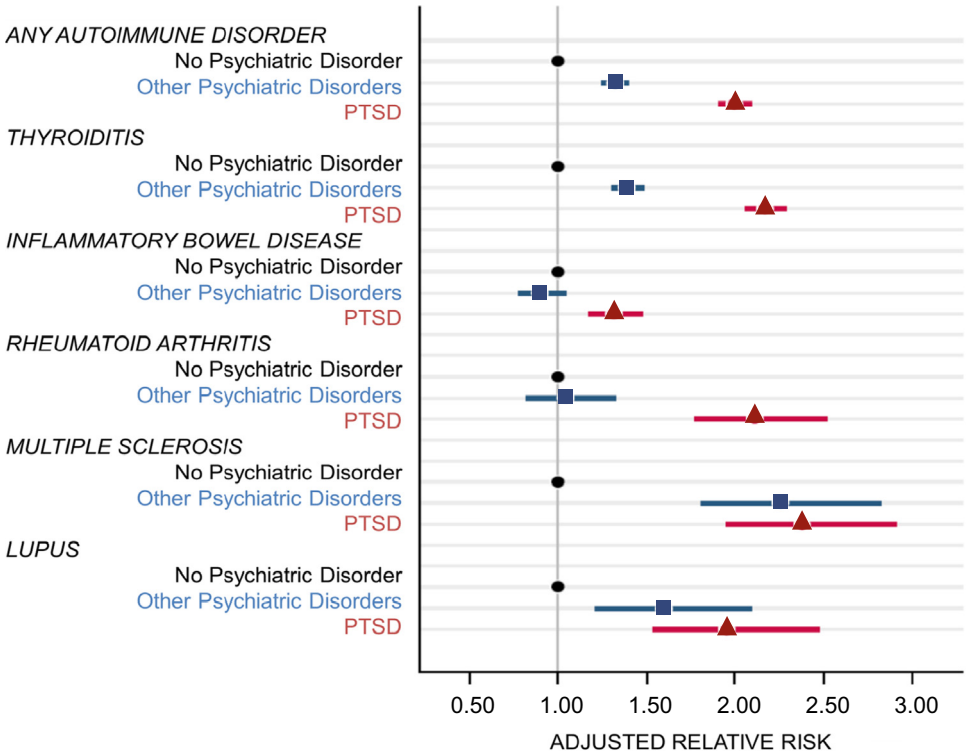

Figure 2. Adjusted relative risk for autoimmune disorder diagnoses in veterans without any psychiatric disorder (black circles), with psychiatric disorders other than posttraumatic stress disorder (PTSD) (blue squares), and with PTSD with and without other psychiatric disorders (red triangles) adjusted for age, gender, race, and primary care visits. Dots represent adjusted relative risk and lines represent 95% confidence intervals.

Table 2. Unadjusted and Age-Adjusted Relative Risk for Each Autoimmune Disorder According to Psychiatric Status

	Relative Risk (95% CI)			Adjusted[a] Relative Risk (95% CI)		
Psychiatric Status	No Psychiatric Disorder	Other Psychiatric Disorders	PTSD	No Psychiatric Disorder	Other Psychiatric Disorders	PTSD
All Veterans						
Any autoimmune disorder	1.00 [reference]	1.33 (1.26, 1.41)[b]	1.81 (1.73, 1.89)[b]	1.00 [reference]	1.32 (1.25, 1.39)[b]	2.00 (1.91, 2.09)[b]
Thyroiditis	1.00 [reference]	1.40 (1.31, 1.49)[b]	1.92 (1.82, 2.03)[b]	1.00 [reference]	1.39 (1.30, 1.48)[b]	2.17 (2.06, 2.29)[b]
Inflammatory bowel diseases	1.00 [reference]	.92 (.79, 1.06)	1.34 (1.20, 1.50)[b]	1.00 [reference]	.89 (.77, 1.04)	1.30 (1.16, 1.46)[b]
Multiple sclerosis	1.00 [reference]	2.35 (1.88, 2.93)[b]	2.23 (1.83, 2.73)[b]	1.00 [reference]	2.29 (1.83, 2.86)[b]	2.36 (1.93, 2.89)[b]
Rheumatoid arthritis	1.00 [reference]	1.00 (.78, 1.28)	1.70 (1.42, 2.04)[b]	1.00 [reference]	1.01 (.79, 1.30)	2.04 (1.70, 2.45)[b]
Lupus erythematosus	1.00 [reference]	1.66 (1.26, 2.19)[b]	1.63 (1.28, 2.09)[b]	1.00 [reference]	1.57 (1.19, 2.08)[c]	1.85 (1.45, 2.37)[b]
Female Veterans						
Any autoimmune disorder	1.00 [reference]	1.26 (1.14, 1.39)[b]	2.14 (1.97, 2.33)[b]	1.00 [reference]	1.27 (1.14, 1.40)[b]	2.09 (1.92, 2.29)[b]
Thyroiditis	1.00 [reference]	1.20 (1.07, 1.34)[c]	2.10 (1.91, 2.31)[b]	1.00 [reference]	1.22 (1.09, 1.37)[b]	2.09 (1.89, 2.31)[b]
Inflammatory bowel diseases	1.00 [reference]	1.31 (.90, 1.93)	1.99 (1.42, 2.78)[b]	1.00 [reference]	1.28 (.86, 1.92)	1.92 (1.34, 2.76)[b]
Multiple sclerosis	1.00 [reference]	2.63 (1.72, 4.02)[b]	2.92 (1.93, 4.41)[b]	1.00 [reference]	2.68 (1.73, 4.15)[b]	2.90 (1.91, 4.40)[b]
Rheumatoid arthritis	1.00 [reference]	1.22 (.81, 1.81)	2.58 (1.86, 3.56)[b]	1.00 [reference]	1.20 (.80, 1.80)	2.39 (1.72, 3.33)[b]
Lupus erythematosus	1.00 [reference]	1.37 (.92, 2.06)	2.05 (1.43, 2.94)[b]	1.00 [reference]	1.34 (.89, 2.02)	1.89 (1.30, 2.75)[b]
Male Veterans						
Any autoimmune disorder	1.00 [reference]	1.29 (1.21, 1.38)[b]	1.79 (1.70, 1.88)[b]	1.00 [reference]	1.34 (1.26, 1.44)[b]	1.95 (1.85, 2.06)[b]
Thyroiditis	1.00 [reference]	1.41 (1.30, 1.52)[b]	1.97 (1.85, 2.10)[b]	1.00 [reference]	1.48 (1.37, 1.60)[b]	2.22 (2.08, 2.36)[b]
Inflammatory bowel diseases	1.00 [reference]	.87 (.74, 1.02)	1.28 (1.13, 1.44)[b]	1.00 [reference]	.84 (.72, .99)[c]	1.23 (1.09, 1.39)[b]
Multiple sclerosis	1.00 [reference]	2.14 (1.65, 2.78)[b]	2.14 (1.70, 2.70)[b]	1.00 [reference]	2.16 (1.65, 2.81)[b]	2.18 (1.73, 2.76)[b]
Rheumatoid arthritis	1.00 [reference]	.83 (.61, 1.13)	1.52 (1.22, 1.88)[b]	1.00 [reference]	.91 (.66, 1.25)	1.88 (1.50, 2.43)[b]
Lupus erythematosus	1.00 [reference]	1.69 (1.16, 2.47)[c]	1.57 (1.12, 2.19)[c]	1.00 [reference]	1.78 (1.21, 2.62)[c]	1.73 (1.22, 2.45)[c]

CI, confidence interval; PTSD, posttraumatic stress disorder.

[a]Relative risk adjusted for age, gender, race, and primary care visits.

[b]$p \leq .001$ when compared with veterans with no psychiatric disorder.

[c]$.001 < p < .05$.

$p < .001$), rheumatoid arthritis (ARR = 3.94; 95% CI, 3.30–4.69; $p < .001$), multiple sclerosis (ARR = 2.63; 95% CI, 2.16–3.19; $p < .001$), and lupus erythematosus (ARR = 6.23; 95% CI, 5.01–7.73; $p < .001$), but not inflammatory bowel disorders (ARR = 1.04; 95% CI, .89–1.22; $p = .59$), considered individually.

Relative risks for autoimmune disorders in PTSD, other psychiatric disorders, and no psychiatric disorder are shown separately for women and men in Table 2. PTSD-related increased risk for autoimmune disorders was similar in both genders, and we did not find evidence of a PTSD by gender interaction. However, due to the increased risk for autoimmune disorders in women overall, the absolute prevalence of autoimmune disorders was highest in women with PTSD (Figure 3).

Military Sexual Trauma and Autoimmune Disorders

One factor that differed markedly between women and men was MST, which was much more common in women (13%) than men (.5%). Table 1 shows rates of MST across the sample and Table S1 in Supplement 1 shows MST rates stratified by gender. To examine if MST was contributing to our finding of elevated risk for autoimmune disorders in veterans with PTSD, we compared the risk for autoimmune disorders among veterans with MST without PTSD, veterans with PTSD without MST, veterans with both PTSD and MST combined compared with all other veterans. In the combined sample of male and female subjects, both MST without PTSD (ARR = 1.64; 95% CI, 1.41–1.92; $p < .001$) and PTSD without MST (ARR = 1.84; 95% CI, 1.75–1.93; $p < .001$) were significant risk factors for autoimmune disorder diagnoses and the combination of PTSD and MST was associated with even higher risk (ARR = 2.40; 95% CI, 2.17–2.65; $p < .001$). When we repeated these analyses in the stratified samples of women and men, the pattern of results was similar. The only difference was that in women, the risk for autoimmune disorders with PTSD without MST was higher than risk associated with MST without PTSD (ARR = 1.95 vs. 1.65), whereas in men, the risk for autoimmune disorders associated with MST without PTSD was higher than risk associated with PTSD without MST (ARR = 2.24 vs. 1.80). The combination of MST and PTSD was associated with the highest risk in both women (ARR = 2.57; 95% CI, 2.28–2.89; $p < .001$) and men (ARR = 2.40; 95% CI, 1.81–3.20; $p < .001$). Thus, MST was an independent risk factor for autoimmune disorders in our sample, but it did not fully account for our findings of PTSD-related increased risk.

Autoimmune Disorders and Risk for Psychiatric Disorders

A total of 2940 veterans received a diagnosis of an autoimmune disorder before being diagnosed with a psychiatric disorder. Surprisingly, veterans with autoimmune disorders had lower risk for subsequent diagnosis with PTSD and other

Table 3. Unadjusted and Age-Adjusted Relative Risk for Diagnosis of Any Autoimmune Disorder with Specific Psychiatric Diagnoses without Versus with Comorbid PTSD

Psychiatric Diagnoses without and with PTSD	Number	Autoimmune Disorder Diagnosis Number (%)	Relative Risk (95% CI)	Adjusted Relative Risk[a] (95% CI)
Depression				
Without PTSD	57,313	1245 (2.2)	1.00 [reference]	1.00 [reference]
With PTSD	126,796	3183 (2.5)	1.16 (1.08, 1.23)[b]	1.34 (1.25, 1.43)[b]
Anxiety				
Without PTSD	44,632	775 (1.7)	1.00 [reference]	1.00 [reference]
With PTSD	79,187	2024 (2.6)	1.47 (1.36, 1.60)[b]	1.60 (1.47, 1.73)[b]
Adjustment Disorder				
Without PTSD	47,516	692 (1.5)	1.00 [reference]	1.00 [reference]
With PTSD	63,110	1520 (2.4)	1.65 (1.51, 1.81)[b]	1.78 (1.63, 1.95)[b]
Psychosis				
Without PTSD	2377	76 (3.2)	1.00 [reference]	1.00 [reference]
With PTSD	7193	255 (3.5)	1.11 (.86, 1.43)	1.16 (.89, 1.51)
Alcohol Use Disorder				
Without PTSD	25,913	282 (1.1)	1.00 [reference]	1.00 [reference]
With PTSD	60,169	1157 (1.9)	1.77 (1.55, 2.01)[b]	1.81 (1.61, 2.11)[b]
Substance Use Disorder				
Without PTSD	10,382	126 (1.2)	1.00 [reference]	1.00 [reference]
With PTSD	30,988	660 (2.1)	1.75 (1.45, 2.12)[b]	1.88 (1.54, 2.30)[b]

CI, confidence interval; PTSD, posttraumatic stress disorder.

[a]Relative risk adjusted for age, gender, race, and primary care visits.

[b]$p \leq .001$ when compared with veterans with no psychiatric disorder.

psychiatric disorders compared with those without autoimmune disorders (ARR = .59; 95% CI, .57–.62; $p < .001$).

DISCUSSION

This study of 666,269 Iraq and Afghanistan veterans indicates that PTSD is associated with increased risk for diagnosis with autoimmune disorders. Specifically, our results showed that veterans with PTSD had twice the risk of being diagnosed with an autoimmune disorder compared with those without any psychiatric disorders and 51% increased risk compared with veterans with psychiatric disorders other than PTSD. Veterans with a higher number of comorbid psychiatric diagnoses were also at increased risk for autoimmune disorders, but high levels of comorbidity did not entirely account for the effect of PTSD on risk. Although the magnitude of PTSD-related increased risk was similar in women and men, women overall had almost three times higher risk for diagnosis with an autoimmune disorder. Thus, the absolute prevalence of autoimmune disorders was highest in women with PTSD. MST was independently associated with risk for autoimmune disorders in both women and men.

Our findings expand upon prior studies in smaller samples that have indicated increased risk for autoimmune disorders in patients with PTSD (19,20). Taken together with the two smaller previous studies, our data indicate that PTSD, and not cohort-specific environmental exposures, may increase risk for autoimmune disorders. Our findings also contribute to

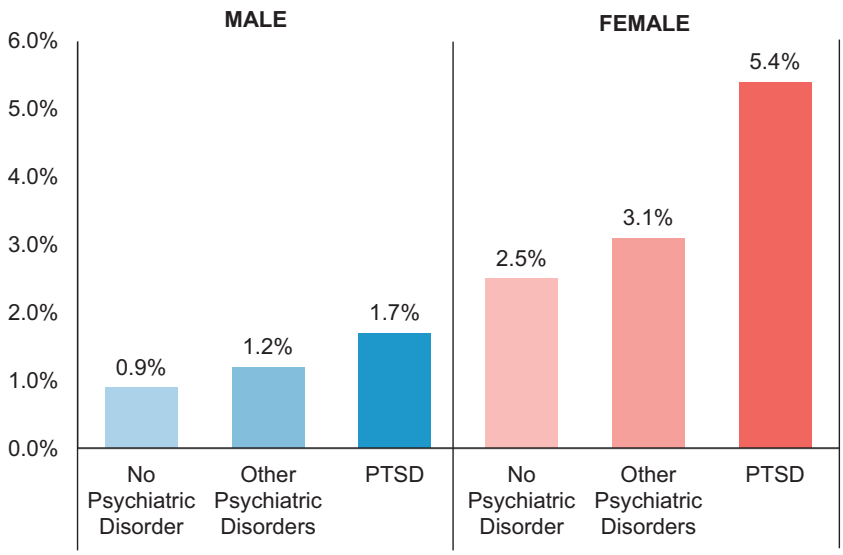

Figure 3. Percentage of female and male veterans with any autoimmune disorder. The absolute prevalence of autoimmune disorders was highest in women with posttraumatic stress disorder (PTSD) at 5.4%, followed by women with psychiatric disorders other than PTSD at 3.1% and women with no psychiatric disorders at 2.5%. Men with PTSD had the next highest prevalence at 1.7%, followed by men with psychiatric disorders other than PTSD at 1.2% and finally men with no psychiatric disorders with the lowest prevalence of the autoimmune disorders at .9%.

a growing literature highlighting the increased risk for other chronic physical diseases in veterans with PTSD and other psychiatric disorders (40–42).

In the present cohort, women had almost threefold higher risk for autoimmune disorders compared with men, which is likely due to sex differences in immunomodulation. Compared with men, women tend to show elevated antibody response to infection, vaccination, and physical trauma, which is thought to confer protection from infectious diseases but greater risk for autoimmune disorders (43,44). Moreover, previous studies have shown sex differences in stress-response systems that may lead to differences in biological and health outcomes in women versus men with PTSD (45–47). However, women and men with PTSD in our population had roughly equivalent levels of increased risk for autoimmune disorders than same-sex veterans without PTSD. Thus, our results suggest no interaction between PTSD and gender in risk for autoimmune disorders. Women had much higher levels of MST exposure compared with men and MST was itself a risk factor for autoimmune disorder diagnoses. However, PTSD without MST remained significantly associated with increased risk for autoimmune disorders in both women and men.

The mechanisms of the observed association between PTSD and autoimmune disorders remain unclear. However, a dysregulated hypothalamic-pituitary-adrenal axis, elevated inflammation, accelerated immune cell aging, and altered immune cell gene expression patterns may play a mechanistic role (1–6,8,10,48). In addition, increased tobacco use, impaired sleep, poor diet, and substance and alcohol use may contribute to both biological abnormalities and risk for autoimmune disorders observed in individuals with PTSD (49–52). It is also possible that shared genetic and environmental vulnerability factors, including dysregulated glucocorticoid signaling, accelerated immune cell aging, and childhood trauma, may contribute to the development of PTSD as well as autoimmune disorders (53–55). In fact, prior studies indicate that autoimmune disorders increase risk for subsequent diagnosis with mood disorders and schizophrenia (56,57). Moreover, the autoimmune disorders that we have included in the present study have distinct, as well as overlapping, etiological mechanisms and the pathway from psychiatric disorders to autoimmune disorders may differ among them.

Although studies such as the present one indicate that psychiatric disorders and autoimmune disorders co-occur, causal direction is less clear. In our study, we focused on the risk for autoimmune disorders in individuals with PTSD. The hypothesis that trauma exposure and PTSD may increase risk for the development of autoimmune disorders is supported by some nonhuman experimental stress studies (58,59). However, other investigators have proposed that stress may actually protect against the development of specific autoimmune disorders under some circumstances (60).

Our analyses indicated lower risk for subsequent diagnosis with psychiatric disorders in individuals previously diagnosed with autoimmune disorders, which may be due to diagnostic biases. Autoimmune disorders such as lupus and multiple sclerosis can be accompanied by psychiatric symptoms, including depressive and even psychotic symptoms (61). In the present study, we relied on physician diagnoses made during routine clinical care as indices of psychiatric and autoimmune disorders, which may bias results. For example, once an autoimmune disorder has been diagnosed, psychiatric symptoms (e.g., fatigue, confusion, sadness, and anxiety) may be attributed to the autoimmune disorder rather than to a de novo psychiatric disorder. Further large-scale prospective research studies in different health care settings will be necessary to clarify this issue.

Limitations

The present study benefits from a large sample size comprising most of the population being studied, longitudinal data, physician rather than self-report diagnoses of psychiatric and autoimmune disorders, adjustment for many relevant confounds, and the ability to assess gender differences. However, the study also has several limitations. First, we cannot claim to have shown causal relationships in this retrospective observational study. Moreover, we cannot be confident about temporality because diagnoses were made at the point when VA providers first coded the condition using ICD-9-CM criteria, which may not correspond with emergence of symptoms, and psychiatric and autoimmune disorders may be present for years or even decades before an official diagnosis. Second, the use of codes rather than clinical diagnoses may lead to misclassification errors and our data may be at risk of bias due to underreporting or overreporting of symptoms by veterans seeking VA care (62,63). Third, veterans with PTSD are known to be at increased risk for other chronic physical diseases, and we did not adjust for the presence of these disorders in our analytic models (64,65). Fourth, our focus on Iraq and Afghanistan veterans who have served in conflict relatively recently means that we have a relatively short follow-up time. Later follow-up studies will be necessary to explore if the findings remain consistent over time as veterans age. Fifth, our data on MST may underestimate actual MST in the population because it is based on clinical visits related to MST. However, the rates observed in our sample are similar to those seen in studies that used the VA MST screen (29). Our study also lacks information on other traumatic events that may vary by gender, including other war zone trauma exposures. Finally, our study is based on treatment-seeking veterans using the VA health care system. Although the VA is the largest provider of health care to returning veterans, our results may not generalize to Iraq and Afghanistan veterans not enrolled in VA health care, other veterans, or civilians.

Conclusions

The present results underline high rates of PTSD and other psychiatric diagnoses in Iraq and Afghanistan veterans and highlight the knock-on effects of trauma exposure and PTSD on physical health. Our results indicate that young veterans diagnosed with PTSD have significantly increased risk for diagnosis with autoimmune disorders with definitive diagnostic criteria. Future prospective longitudinal cohort studies are needed to establish causality, measure endocrine and immune system activity in veterans with PTSD, and evaluate whether timely and successful treatment of PTSD reduces risk of autoimmune disorders. However, lower thresholds for

evaluating the presence of autoimmune disorders may be warranted in veterans with PTSD and other psychiatric disorders immediately. Our data underscore the need to identify and treat PTSD and other psychiatric disorders in veterans to enhance not only mental but also physical health.

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