

# Predictors of Current DSM-5 PTSD Diagnosis and Symptom Severity Among Deployed Veterans: Significance of Predisposition, Stress Exposure, and Genetics

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**Background:** Previously we reported a genetic risk score significantly improved PTSD prediction among a trauma-exposed civilian population. In the current study, we sought to assess this prediction among a trauma-exposed military population.

**Methods:** We examined current PTSD diagnosis and PTSD symptom severity among a random sample of 1042 community-based US military veterans. Main effects and interaction effects were assessed for PTSD genetic risk by trauma exposure using cross-product terms for PTSD x trauma exposures, including combat, lifetime trauma, and adverse childhood exposures. The PTSD risk variants studied were within genetic loci previously associated with PTSD, including *CRHRI*, *CHRNA5*, *RORA*, and *FKBP5* genetic variants, which were used to calculate a total PTSD genetic risk score (range=0–8, mean=3.6, SD=1.4).

**Results:** Based on DSM-5 PTSD criteria, 7.1% of veterans (95% CI=5.6–8.8) met criteria for current PTSD. The PTSD genetic risk count was significantly higher among PTSD cases vs non-cases (3.92 vs 3.55,  $p=0.027$ ). Since the PTSD genetic risk score was not significant in the PTSD diagnosis model, we assessed this association using PTSD symptom severity. Because these symptom data were skewed (mean=9.54, SD=12.71, range=0–76), we used negative binomial regression to assess this outcome. This symptom model included a PTSD genetic risk score, demographic factors, trauma exposures, current insomnia, current depression, concussion history, and attention-deficit disorder, expressed as incident rate ratios (IRR), which is an estimate of one-unit increase in PTSD severity, given other variables are held constant. Variables in the final model included age and sex (both  $p<0.001$ ), PTSD genetic risk (IRR=1.02,  $p=0.028$ ), warzone tours (IRR=0.94,  $p=0.003$ ), childhood abuse (IRR=1.50,  $p<0.0001$ ), current depression (IRR=1.89,  $p<0.0001$ ), current insomnia (IRR=2.58,  $p<0.0001$ ), low social support (IRR=1.19,  $p<0.0001$ ), attention-deficit disorder (IRR=1.51,  $p<0.0001$ ), agreeable personality (IRR=0.77,  $p<0.0001$ ), and concussion (IRR=1.38,  $p<0.0001$ ). Significant interactions were detected for combat and lifetime trauma exposure by PTSD genetic risk (both  $p<0.0001$ ), suggesting that the impact of trauma exposures on PTSD severity was lower when the PTSD genetic risk was higher.

**Conclusion:** Both warzone and non-warzone factors predicted current PTSD symptoms among veterans, including a PTSD genetic risk score. Interaction effects were detected for combat exposure and lifetime trauma by genetic risk score for PTSD symptoms, suggesting that PTSD symptom manifestation was more dependent on PTSD risk variants than the level of trauma or combat exposure. This suggests that controlling for other factors, the absence of genetic risk variants may confer PTSD resilience. Further research is planned.

**Keywords:** posttraumatic stress disorder, veterans, combat exposure, trauma, warzone deployment, genetic risk, resilience

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## Introduction

While studies suggest that most individuals have experienced lifetime traumatic events, relatively few develop posttraumatic stress disorder (PTSD).<sup>1–3</sup> Studies indicate that PTSD is moderately heritable, with approximately 30% of variance accounted for by genetic factors.<sup>4</sup> Currently, genetic components for PTSD have been identified, which may explain this risk.<sup>5–8</sup> As we describe below, these genetic components include biologic pathways involving the hypothalamic-pituitary-adrenal (HPA), locus coeruleus, noradrenergic, and the limbic system, among others.<sup>6,9–11</sup> Recent large-scale genome-wide association studies (GWAS) of PTSD have provided new insights and have suggested overlap with other disorders, such as schizophrenia and bipolar disorder.<sup>12,13</sup> In particular, the Psychiatric Genomics Consortium-Posttraumatic Stress Disorder group (PGC-PTSD) combined genome-wide data across multiethnic studies to quantify PTSD heritability, to examine potential shared genetic risk with schizophrenia, bipolar disorder, and major depressive disorder and to identify risk loci for PTSD.<sup>12</sup> We review and discuss these GWAS findings in the discussion section of the paper. Recent research suggests that PTSD genetics are complex, multicausal and that the biologic pathways for this disorder are yet to be elucidated.<sup>14,15</sup> As described below, the genetic risk factors for PTSD that we assessed were among outpatients, all of whom were formerly deployed military veterans receiving care in a large multi-hospital system in central Pennsylvania.<sup>16–19</sup> Although the number of veterans in these settings with PTSD has varied, about 7–10% of them have been diagnosed with current PTSD in recent years,<sup>16,18,20</sup> which is consistent with the prevalence rate in the current study.

## Methods

### Sample

The population for the current study included a sample of community-based veterans of Vietnam, Persian Gulf, Iraq/Afghanistan, and/or other recent conflicts, who were receiving care in a large non-VA multihospital system in Pennsylvania.<sup>17,18</sup> We examined post-deployment PTSD status among a cross-sectional survey of 1730 veterans, who were receiving outpatient care in Pennsylvania at a Geisinger Clinic facility. Approximately 95% of the veterans were male (mean age=61.4 [SD=12.1]). For the study, 65 min diagnostic interviews were conducted by telephone, and DNA samples were collected via postage-paid return mail following

the survey. To date, approximately 35,000 patients have provided this military information, and this database was used to select a random sample of veterans for the current study.<sup>18</sup> Geisinger Clinic serves more than 3 million residents throughout 45 counties in central, south-central and northeast Pennsylvania, which encompasses a 25,000 square mile (40,000 square kilometer) primary service area.<sup>21</sup>

With patient consent, trained interviewers administered a structured health interview by telephone from February 2016 through February 2017. All veterans recruited had one or more warzone deployments. Veteran status and deployment history were confirmed based on military records provided by the veteran. Among the veterans selected for the surveys, all were under 76 and served in Vietnam or in another post-Vietnam conflict. After 10 telephone calls per household, we were able to complete 1730 interviews for an estimated survey cooperation rate of 55% among those eligible for the survey.<sup>22,23</sup> Deceased patients, nursing home patients, institutionalized patients, those who did not serve in Vietnam, Iraq, Afghanistan, Global War on Terrorism, Persian Gulf, or other recent post-Vietnam conflicts were excluded, as were those who were cognitively impaired, and those unavailable during the survey period. Of those who were surveyed, 65% (n=1074) returned usable DNA samples by mail. Oragene DNA saliva kits, manufactured by Genotek (Ottawa, Ontario, Canada), were used to collect the DNA. To avoid confounding results due to genetic admixture,<sup>24</sup> non-Caucasian veterans (n=40) were excluded from the analyses, resulting in a final DNA sample of 1042 veterans.

### Genetic Methods

Genotyping was performed on an Applied BioSystems 7500 real-time PCR platform (Foster City, CA), using TaqMan kits following the manufacturer's protocols. Quality control measures included visual inspection of the allelic discrimination plots, monitoring concordance of cross-plated duplicate pairs, monitoring the overall call rate, and monitoring agreement with Hardy-Weinberg expectations.<sup>25</sup> The overall call rate for the current study was approximately 95% and the genotypes for the current study met Hardy-Weinberg expectations.<sup>25</sup>

### PTSD Measures and Study Predictor Variables

To assess PTSD in our study, we used an instrument based on the Diagnostic and Statistical Manual of Mental

Disorder, Fifth Edition (DSM-5), the *PTSD Checklist for Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (PCL-5)*.<sup>26,27</sup> To receive a diagnosis of current PTSD, veterans had to meet the DSM-5 diagnostic criteria A through G within the past 12 months.<sup>28</sup> In addition to a PTSD diagnosis, we also included a count of current DSM-5 PTSD symptom severity (mean=9.54, SD=12.71, range =0–76). This PTSD scale has been used in recent PTSD studies and appears to produce valid and reliable results (Cronbach Alpha=0.92).<sup>18,29–31</sup>

Predictor variables in the current study also included demographic variables (age, sex, marital status), number of warzone deployments (one vs more than one), childhood abuse history, combat exposure, lifetime traumatic event exposure, current level of social support, history of attention-deficit symptoms, history of in-service concussion, current depression, current insomnia, and select personality traits.<sup>32,33</sup> Childhood abuse was measured by the Adverse Childhood Experiences (ACE) scale, a measure used and validated in numerous studies (Cronbach Alpha=0.84).<sup>34–36</sup> Combat exposure was measured by the Combat Experience Scale (CES), which is a widely used measure of combat used in Vietnam veteran studies.<sup>37,38</sup> Versions of this scale have been used in studies since the 1970s.<sup>39–43</sup> Based on previous research, scale measurement for combat exposure was divided into low vs high cut-points described elsewhere (Cronbach Alpha=0.84).<sup>20,44,45</sup> To assess trauma exposure, the Lifetime Traumatic Event Scale was used, which measured the occurrence of 12 lifetime traumatic events (e.g., forced sexual contact, domestic abuse, a serious accident, experiencing a major disaster).<sup>46</sup> Based on previous research,<sup>20</sup> we collapsed these exposures into high vs low count categories. This traumatic event scale was developed from other trauma studies, used in the previous research, and had good reported reliability and validity.<sup>20,46–49</sup>

Current social support was also measured by a version of a social support scale used in the Medical Outcomes Study.<sup>50</sup> This scale has been used in previous trauma studies and is considered a reliable and valid measure of current social support (Cronbach Alpha=0.84).<sup>46,48,51</sup> This scale was used as a categorical measure in the current study, with low social support defined as the lowest quintile.<sup>49</sup> Attention-Deficit/Hyperactivity Disorder was measured by a scale included in the World Health Organization Attention Attention-Deficit Disorder instrument (Cronbach Alpha=0.65).<sup>52</sup> History of in-service concussion was measured based on reported concussions experienced during military deployments (e.g., ever

dazed, confused, saw stars, or knocked out), and for this, we used the Brief TBI Screen,<sup>53</sup> a scale used in the previous research.<sup>20,54</sup> Personality measures assessed included the “agreeable” personality trait, which was measured by the 10-item Personality Inventory, a widely used and validated personality measure.<sup>32,33</sup> This trait was selected because it tended to be protective for the onset of mental health disorders.<sup>55,56</sup>

Depression was assessed using the Major Depressive Disorder (MDD) measure developed from the DSM-IV,<sup>57–59</sup> which was used extensively in previous trauma studies.<sup>20,47,49,60,61</sup> Data related to the validity of this depression scale were previously reported and suggest this scale can be used to diagnose depression in population studies (Cronbach Alpha=0.87).<sup>47,60</sup> To meet the criteria for MDD in the study, subjects had to meet the full DSM-IV criteria for major depression within the past 12 months. Insomnia was assessed using scale items related to difficulty staying or falling asleep in the past year, which was included in the previous research.<sup>62,63</sup>

## Genetic Risk Factor Approach

Much like our previous study, we used a genetic risk score approach, which included 4 SNP genetic variants.<sup>8</sup> The SNPs included in the PTSD genetic risk model are presented in Table 1. These SNP markers were combined into a cumulative risk allele count, as is common in these genetic analyses.<sup>62</sup> For the current study, we assessed 4 genetic markers using a cumulative risk-allele model to test for an association with PTSD among outpatients, comparable to what has been undertaken to predict genetic associations in other clinical areas.<sup>64,65</sup> Extending previous research,<sup>8,10</sup> we specifically genotyped SNPs located within the FK506 binding protein-5 (*FKBP5*), retinoid-related orphan receptor alpha (*RORA*), cholinergic receptor nicotinic alpha-5 (*CHRNA5*), and the corticotropin-releasing hormone receptor-1 (*CRHR1*) gene clusters and assessed these markers for cumulative risk for current PTSD.

The *RORA* genetic marker examined (rs8042149) is associated with PTSD in recent research.<sup>66,67</sup> The *FKBP5* genetic marker studied (rs9470080) regulates glucocorticoid receptor sensitivity, is functionally involved in HPA axis activity, and is also associated with PTSD.<sup>5,6,10,68</sup> The *CHRNA* genetic marker investigated (rs16969968), which encodes components of the nicotinic acetylcholine receptor (nAChR), is associated with nicotine dependence and cigarette smoking,<sup>69,70</sup> substance misuse,<sup>71</sup> and PTSD.<sup>10</sup> The

**Table 1** Profile of Single Nucleotide Polymorphisms (SNPs) Included in PTSD Genetic Risk Model

SNP	Gene	Position (GRCh38.p12)	MAF (Minor/Common)	Functional Annotation	PTSD Risk Allele
rs110402	<i>CRHR1</i>	chr17:45802681	44.4% (A/G)	Intron	G
rs16969968	<i>CHRNA5</i>	chr15:78590583	26.6% (A/G)	Missense (D ↔ N)	A
rs8042149	<i>RORA</i>	chr15:60832754	44.9% (G/T)	Intron	G
rs9470080	<i>FKBP5</i>	chr6:35678658	37.4% (T/C)	Intron	T

**Notes:** PTSD risk alleles counted for each of the 4 genetic variants included (0, 1, 2), resulting in genetic risk score ranging from 0 to 8 (mean = 3.56, SD = 1.41) using the risk alleles variants (A, G, T, respectively) shown in Table 1. This genetic risk method has been described in detail elsewhere.<sup>8</sup> Allele frequencies: *CRHR1*: A/A = 208 (18.9%); A/G = 535 (48.7%); G/G = 355 (32.3%). *CHRNA5*: G/G = 446 (40.8%); A/G = 488 (44.6%); A/A = 160 (14.6%). *RORA*: T/T = 283 (25.6%) G/T = 513 (46.5%) G/G = 308 (27.9%). *FKBP5*: C/C = 496 (45.2%) C/T = 482 (43.9%) T/T = 119 (10.9%).

**Abbreviation:** MAF, minor allele frequency.

*CRHR1* genetic marker studied (rs110402) is a polypeptide hormone and neurotransmitter involved in corticotropin-releasing hormone activity associated with the stress response. Studies suggest that this gene also regulates HPA axis function and is associated with the impact of traumatic stress exposure and PTSD.<sup>68,72</sup>

PTSD risk alleles were counted for each of the 4 genetic variants included, which resulted in a genetic risk score ranging from 0 to 8 (mean=3.56, SD=1.41), using the PTSD risk alleles variants (A, G, T, respectively) shown in Table 1. This genetic risk method has been described in detail elsewhere<sup>8</sup> Assessment of these 4 PTSD genetic markers indicated that all were positively associated with PTSD, with two markers (*RORA* and *FKBP5*), significantly associated (both p-values < 0.05). In addition, the cumulated unadjusted PTSD genetic risk score was also significantly associated with PTSD diagnosis (p-value = 0.0275). This genetic risk score was then used as a covariate in our statistical analyses using standard bivariate and multivariate tests.<sup>8</sup> PTSD risk alleles counted for each of the 4 genetic variants included 0, 1, 2 risk alleles, resulting in genetic risk score ranging from 0–8 (mean=3.56, SD=1.41), using the risk alleles variants (A, G, T, respectively). The frequencies for these alleles in the current study were *CRHR1*: A/A = 208 (18.9%); A/G = 535 (48.7%); G/G = 355 (32.3%). *CHRNA5*: G/G = 446 (40.8%); A/G = 488 (44.6%); A/A = 160 (14.6%). *RORA*: T/T = 283 (25.6%) G/T = 513 (46.5%) G/G = 308 (27.9%). *FKBP5*: C/C = 496 (45.2%) C/T = 482 (43.9%) T/T = 119 (10.9%) (see Table 1).

## Statistical Analysis

Analyses for the current research included describing the profile of genetic variants studied (Table 1), as well as descriptive statistics depicting the study population and evaluating the impact of both stress exposures and genetic factors on PTSD status, including current diagnosis and symptom status. For descriptive purposes, we present the unadjusted,

bivariate baseline characteristics and genetic risk scores of the overall study population in Table 2, with mean (standard deviation) summarized for continuous variables, and frequency (percentage) for categorical variables, by PTSD diagnosis. For multivariate analyses on the PTSD diagnosis outcome, we performed logistic regression, whereby key risk/protective factors (stress exposures, genetic risk score), as well as the interaction term between stress exposures and genetic risk score were included to estimate the odds ratios (ORs), after controlling for age, sex and other factors that might affect the associations by including them in the logistic regression analyses<sup>8,62,73</sup> (Table 3). For multivariate analyses on PTSD symptom severity, we fitted a negative binomial count regression model due to the overdispersion of these symptom data (Figure 1), whereby key risk/protective factors (stress exposures, genetic risk score), as well as the interaction term between stress exposures and the genetic risk score were included to estimate the incidence rate ratios (IRRs), controlling for age, sex and other factors that might affect the associations by including them in the regression analyses<sup>74</sup> (Table 4). The incident rate ratio is an estimate of one-unit increase in PTSD symptom severity, given the other variables are held constant in the model. For the interaction assessment in the multivariate analyses, significant interaction terms between stress exposures and the genetic risk score are presented in Table 5. Analyses were performed in SAS 9.4 (SAS Institute, Cary NC) using the LOGISTIC procedure for logistic model and GENMOD procedure for negative binomial model.

This study was approved by the Institutional Review Boards of the Geisinger Clinic (IRB #2015-0441) and the US Department of Defense. All patients provided their verbal and written informed consent to participate in this study and were offered small monetary incentives for participation. This study was conducted in accordance with the Declaration of Helsinki.

**Table 2** Descriptive Statistics of the Study Sample, Overall and by PTSD Diagnosis (N=1042)

Study Variable	Total		PTSD		No PTSD		p-value*
	N (%)		N (%)		N (%)		
Age							<0.0001
18–50	229	(21.3)	31	(40.8)	198	(19.8)	
51–66	242	(22.5)	14	(18.4)	228	(22.8)	
67–76	603	(56.1)	31	(40.8)	572	(57.3)	
Sex of respondent							0.04
Male	1025	(95.44)	69	(90.79)	956	(95.79)	
Female	49	(4.56)	7	(9.21)	42	(4.21)	
Currently married							0.21
No	235	(21.88)	21	(27.63)	214	(21.44)	
Yes	839	(78.12)	55	(72.37)	784	(78.56)	
High combat exposure							<0.0001
No	842	(78.40)	41	(53.95)	801	(80.26)	
Yes	232	(21.60)	35	(46.05)	197	(19.74)	
Multiple warzone tours							0.82
No	663	(61.73)	46	(60.53)	617	(61.82)	
Yes	411	(38.27)	30	(39.47)	381	(38.18)	
High child abuse/neglect							0.0002
No	890	(82.87)	51	(67.11)	839	(84.07)	
Yes	184	(17.13)	25	(32.89)	159	(15.93)	
Current depression							<0.0001
No	987	(91.99)	38	(50.00)	949	(95.19)	
Yes	86	(8.01)	38	(50.00)	48	(4.81)	
Current Insomnia							<0.0001
No	470	(43.80)	4	(5.26)	466	(46.74)	
Yes	603	(56.20)	72	(94.74)	531	(53.26)	
Lifetime trauma							<0.0001
Low	874	(81.38)	44	(57.89)	830	(83.17)	
High	200	(18.62)	32	(42.11)	168	(16.83)	
Current social support							<0.0001
High	880	(81.94)	48	(63.16)	832	(83.37)	
Low	194	(18.06)	28	(36.84)	166	(16.63)	
Probable ADHD							<0.0001
No	859	(79.98)	34	(44.74)	825	(82.67)	
Yes	215	(20.02)	42	(55.26)	173	(17.33)	
Agreeable personality							0.0001
Low	754	(70.20)	68	(89.47)	686	(68.74)	
High	320	(29.80)	8	(10.53)	312	(31.26)	
In service concussion							<0.0001
No	769	(71.60)	25	(32.89)	744	(74.55)	
Yes	305	(28.40)	51	(67.11)	254	(25.45)	
Age							<0.0001
N (mean)	1042	(61.41)	75	(55.97)	967	(61.83)	
PTSD genetic score							0.027
N (mean)	1042	(3.57)	75	(3.92)	967	(3.55)	

**Note:** \*p-values were from chi-square tests, except for age and genetic risk score, which were based on t-tests.

**Table 3** Logistic Regression Results for Predicting PTSD Diagnosis (N=1042)

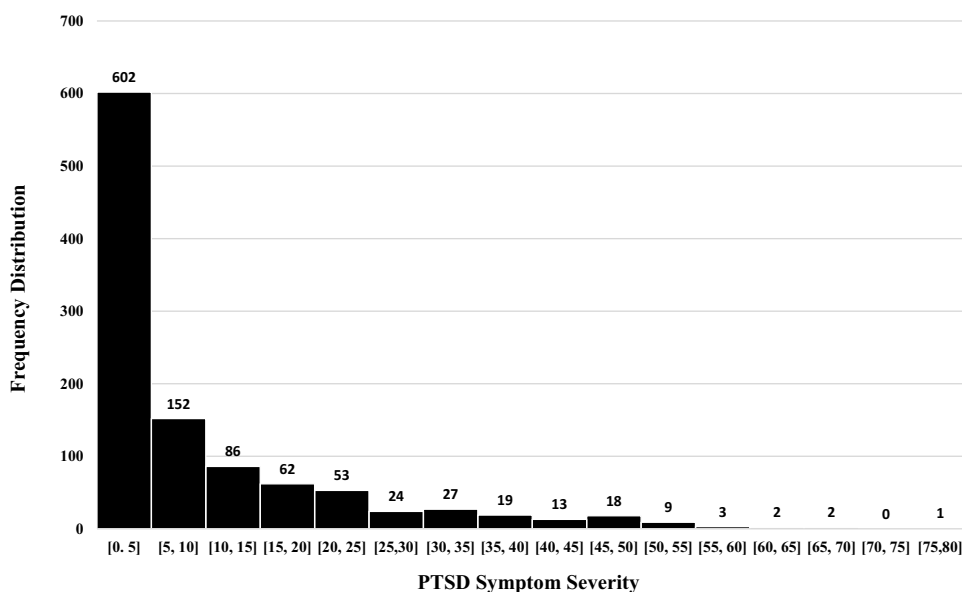
Study Variables	OR	95% CI	p-value
Age (in years)	0.98	(0.96–1.00)	0.0673
Sex: Male vs Female	0.84	(0.46–1.52)	0.5625
Currently married: Yes vs No	0.99	(0.70–1.41)	0.9546
PTSD genetic risk score	1.15	(0.94–1.41)	0.1762
Multiple tours: Yes vs No	0.78	(0.57–1.06)	0.1161
Childhood abuse & neglect: High vs Low	1.28	(0.93–1.75)	0.1323
Current depression: Yes vs No	6.27	(3.31–11.85)	<0.0001
Insomnia: Yes vs No	6.20	(2.12–18.13)	0.0008
Current social support: Low vs High	1.19	(0.86–1.64)	0.2875
Probable ADHD case: Yes vs No	1.45	(1.08–1.95)	0.014
Agreeable personality: High vs Low	0.69	(0.45–1.07)	0.0964
History of concussion: Yes vs No	1.61	(1.19–2.18)	0.0022
High combat exposure: Yes vs No	1.89	(1.02–3.51)	0.0428
Lifetime traumatic events: High vs Low	2.39	(1.30–4.38)	0.0049

Abbreviation: OR, Odds Ratio.

## Results

### Current PTSD Diagnosis and PTSD Symptom Severity

Based on the full DSM-5 criteria, 75 cases were diagnosed with PTSD for an estimated prevalence of 7.1% in the past 12 months (95% CI = 5.6–8.8%). Figure 1 presents the distribution of PTSD symptom severity among the veterans, which was highly skewed. As seen, the unconditional mean of this outcome measure is much lower than its variance (mean score = 9.5 [SD=12.8]), prompting use a negative binomial regression model for our analysis of this outcome.<sup>74</sup>



**Figure 1** Distribution of PTSD symptom severity in study sample (range=0–80; mean=9.54; SD=12.71).

## Descriptive Statistics

Using the psychometric and demographic data collected in the study interview, we present the descriptive statistics using mean with standard deviation for continuous variables and frequency with percentage for categorical variables. Baseline characteristics and PTSD genetic risk scores of the study population are examined by PTSD diagnosis outcome in Table 2. Veterans diagnosed with PTSD tended to be younger (54 vs 60 years old,  $t$ -test = 48.3,  $p < 0.001$ ) and have a higher PTSD genetic risk score (3.92 vs 3.55,  $p = 0.027$ ). Veterans diagnosed with PTSD also are more likely to have high combat exposure (46% vs 20%,  $p < 0.0001$ ), high childhood abuse and neglect (33% vs 16%,  $p = 0.0002$ ), high lifetime trauma event exposure (42% vs 17%,  $p < 0.0001$ ), probable attention deficit (55% vs 17%,  $p < 0.0001$ ), history of concussion (67% vs 25%,  $p < 0.0001$ ), current depression disorder (50% vs 5%,  $p < 0.0001$ ), current insomnia (95% vs 53%,  $p < 0.0001$ ), and more likely to have low social support (37% vs 17%,  $p < 0.0001$ ). Finally, the PTSD-positive veterans are less likely to have an agreeable personality trait (11% vs 31%,  $p = 0.0001$ ), suggesting this trait is protective for PTSD.

### Logistic Regression Predicting DSM-5 PTSD Diagnosis

Significant variables in the PTSD diagnosis model (Table 3), and expected based on previous research, included current depression (OR=6.27, 95% CI: 3.31–11.85,  $p < 0.0001$ ), current insomnia (OR=6.20, 95% CI: 2.12–18.13,  $p = 0.0008$ ),

history of ADHD (OR=1.45, 95% CI: 1.08–1.95,  $p=0.014$ ), and history of concussion (OR=1.61, 95% CI: 1.19–2.18,  $p=0.0022$ ). Inconsistent with our previous research with non-veterans, however, no interaction effects were detected for the genetic risk score by high trauma or high combat exposure, although both high combat and high trauma exposures were significant (Table 3).

## Negative Binomial Regression Predicting DSM-5 PTSD Symptom Severity

Significant variables in the final PTSD symptom severity model (Table 4), also predicted PTSD symptoms, expressed as incident rate ratios (IRR), which is an estimate of one-unit increase in PTSD severity, given other variables are held constant. As can be seen in Table 4, significant variables included PTSD genetic risk score (IRR =1.02, 95% CI: 1.00–1.05,  $p=0.028$ ), multiple warzone tours (IRR=0.94, 95% CI: 0.90–0.98,  $p=0.003$ ), the latter being protective, childhood abuse/neglect (IRR =1.50, 95% CI: 1.33–1.70,  $p<0.0001$ ), current depression (IRR=1.89, 95% CI: 1.79–1.99,  $p<0.0001$ ), current insomnia (IRR=2.58, 95% CI: 2.44–2.73,  $p<0.0001$ ), low social support (IRR=1.19, 95% CI: 1.14–1.25,  $p<0.0001$ ), history of ADHD (IRR=1.51, 95% CI: 1.44–1.58,  $p<0.0001$ ), and history of in-service concussion (IRR=1.38, 95% CI: 1.32–1.44,  $p<0.0001$ ).

**Table 4** Negative Binomial Regression Results for Predicting PTSD Symptom Severity (N=1042)

Study Variables*	IRR	95% CI	p-value
Age (in years)	0.99	(0.99–1.00)	<0.0001
Sex: Male vs Female	0.85	(0.78–0.92)	0.0002
Married: Yes vs No	1.05	(1.00–1.10)	0.076
PTSD genetic risk score	1.02	(1.00–1.05)	0.028
Multiple warzone tours: Yes vs No	0.94	(0.90–0.98)	0.003
Childhood abuse & neglect: High vs Low <sup>a</sup>	1.50	(1.33–1.70)	<0.0001
Current depression: Yes vs No	1.89	(1.79–1.99)	<0.0001
Current insomnia: Yes vs No	2.58	(2.44–2.73)	<0.0001
Current social support: Yes vs No	1.19	(1.14–1.25)	<0.0001
Probable ADHD: Yes vs No	1.51	(1.44–1.58)	<0.0001
Agreeable personality: High vs Low	0.77	(0.73–0.82)	<0.0001
In-service concussion: Yes vs No	1.38	(1.32–1.44)	<0.0001
High combat exposure: Yes vs No <sup>b</sup>	1.63	(1.46–1.82)	<0.0001
Lifetime traumatic events: High vs Low <sup>b</sup>	1.78	(1.58–2.00)	<0.0001

**Notes:** \*The model was fitted with the additional interaction terms: combat by PTSD genetic risk score, trauma by PTSD genetic risk score, High childhood abuse & neglect score by PTSD genetic risk score. <sup>a</sup>The interaction term of High childhood abuse & neglect by PTSD genetic risk score was insignificant. <sup>b</sup>The interaction terms of combat by PTSD genetic risk score, trauma by PTSD genetic risk score were significant. The detailed interpretation of interaction effects for combat and trauma exposure is presented in Table 5. **Abbreviation:** IRR, incident rate ratio.

## Interaction Terms

Significant interaction effects were detected for traumatic events by genetic risk score. Similar trends were observed for both high combat exposure and high lifetime traumatic event exposure in predicting PTSD symptom severity, whereby the impact on veterans without high combat or high lifetime traumatic events was less than those with combat or lifetime traumatic events, as the genetic risk score increases from 0 to 8.

Table 5 presents the detailed interaction effects from the negative binomial regression model for lifetime trauma exposure (left panel). As can be seen, when the genetic risk score was 1 (relatively low), veterans with high lifetime traumatic events were expected to have 1.72 times in PTSD symptom severity compared to those with low lifetime traumatic events (95% CI: 1.54–1.93,  $p<0.0001$ ). When the genetic risk score was 4 (median), veterans with high lifetime traumatic events were expected to have 1.56 times in PTSD symptom severity compared to those with low lifetime traumatic events (95% CI: 1.39–1.75,  $p<0.0001$ ). When the genetic risk score is 7 (relatively high), veterans with high lifetime traumatic events were expected to have 1.41 times in PTSD symptom severity compared to those with low lifetime traumatic events (95% CI: 1.23–1.62,  $p<0.0001$ ).

Finally, the right panel in Table 5 shows the interaction effects from the negative binomial regression model for combat exposure and PTSD symptom severity. As can be seen, when the genetic risk score was 1 (relatively low), veterans with high combat exposure were expected to have 1.58 times in PTSD severity score compared to those with low combat exposures (95% CI: 1.42–1.76,  $p<0.0001$ ). When the genetic risk score was 4 (median), veterans with high combat exposures were expected to have 1.43 times in PTSD symptom severity compared to those with low combat exposures (95% CI: 1.27–1.61,  $p<0.0001$ ). When the genetic risk score was 7 (relatively high), veterans with high combat exposures were expected to have 1.29 times in PTSD symptom severity score compared to those with low combat exposures (95% CI: 1.11–1.50,  $p<0.0008$ ).

Table 5 shows the interaction effects from the negative binomial regression model for both trauma and combat exposures and PTSD symptom severity, respectively. Figure 2A and B show the statistical estimates for PTSD symptom severity score with 95% confidence limits for both trauma and combat exposures using these estimates.

**Table 5** Interaction Effects from Negative Binomial Regression\*

Genetic Risk Count	Trauma High vs Low			Combat High vs Low		
	IRR	95% CI	p-value	IRR	95% CI	p-value
Genetic risk score = 0	1.78	(1.58–2.00)	<0.0001	1.63	(1.46–1.82)	<0.0001
Genetic risk score = 1	1.72	(1.54–1.93)	<0.0001	1.58	(1.42–1.76)	<0.0001
Genetic risk score = 2	1.66	(1.49–1.86)	<0.0001	1.53	(1.37–1.71)	<0.0001
Genetic risk score = 3	1.61	(1.44–1.80)	<0.0001	1.48	(1.32–1.66)	<0.0001
Genetic risk score = 4	1.56	(1.39–1.75)	<0.0001	1.43	(1.27–1.61)	<0.0001
Genetic risk score = 5	1.51	(1.33–1.70)	<0.0001	1.38	(1.22–1.57)	<0.0001
Genetic risk score = 6	1.46	(1.28–1.66)	<0.0001	1.34	(1.16–1.54)	<0.0001
Genetic risk score = 7	1.41	(1.23–1.62)	<0.0001	1.29	(1.11–1.50)	0.0008

**Notes:** \*The model was fitted with the variables from Table 4 and the interaction terms: combat by PTSD genetic risk score, trauma by PTSD genetic risk score, High childhood abuse & neglect score by PTSD genetic risk score.

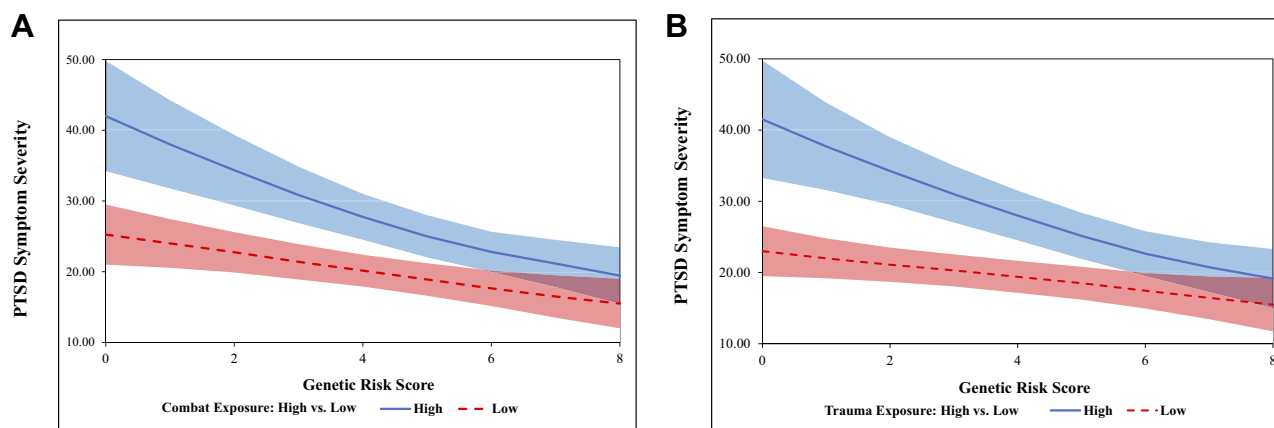
**Abbreviation:** IRR, incident rate ratio.

## Discussion

In the current study, we examined post-deployment PTSD status, including current DSM-5 PTSD diagnosis and PTSD symptom severity, among a sample of 1042 community-based veterans. Interaction effects were also assessed for a genetic PTSD risk score by trauma exposures. As noted, the PTSD risk variants studied were within genetic loci previously associated with PTSD, including *CRHR1*, *CHRNA5*, *RORA*, and *FKBP5* genetic variants, which were used to calculate a PTSD genetic risk score (range=0–8, mean=3.6, SD=1.4). All veterans studied received routine health care in a large multihospital system in Pennsylvania. Based on DSM-5 PTSD criteria, 7.1% of veterans (95% CI=5.6–8.8) met the criteria for current PTSD. The unadjusted PTSD genetic risk count was significantly higher among PTSD cases vs non-cases ( $p=0.027$ ). However, since the PTSD risk score was not significant in the PTSD diagnosis model, we assessed this using DSM-5 PTSD

symptom severity. Because these symptom data were skewed (range 0–76, mean=9.5, SD=12.7), as discussed, we used the negative binomial regression model to assess this association.

The model for PTSD symptom severity included the genetic score, demographic factors (age and sex) trauma exposures, current insomnia, current depression, history of concussion, and history of attention-deficit disorder. Significant variables in the final PTSD symptom severity model included age, sex, PTSD genetic risk score, combat exposure, multiple warzone tours, childhood abuse and neglect, current depression, current insomnia, lifetime traumatic events, social support, history of attention-deficit disorder, and history of in-service concussion, previously identified in the past research.<sup>18,20,44</sup> Significant interaction effects were also detected for both high combat and high lifetime traumatic event exposures by genetic risk score, which suggested the impact of these trauma exposures on



**Figure 2 (A)** PTSD symptom severity for combat exposure by genetic risk score, with 95% confidence limits. **(B)** PTSD symptom severity for lifetime trauma exposure by genetic risk score, with 95% confidence limits.



PTSD symptom severity manifestation was lower when the genetic risk was higher. Thus, our study appears to have replicated previous results with a trauma-exposed civilian population.<sup>8</sup> After deployment, both warzone and non-warzone factors predicted current PTSD among veterans seen in Geisinger Clinic outpatient facilities, including a genetic risk score for PTSD. Interaction effects were detected for combat exposure and lifetime traumatic events by genetic risk score for PTSD symptom severity. One noteworthy finding is the protective effect found for multiple warzone deployments vs only one deployment (Table 4), which may reflect high resilience in these veterans, but further research is required to confirm this.

Study limitations include the fact that our interview data were based on self-report, our sample was limited, and that our study participants were mostly male and drawn from a hospital population in central Pennsylvania. These factors may have biased our results and could limit generalization. The fact that our sample is 95% male is also a potential limitation, since the differences in PTSD biology likely vary significantly by sex.<sup>13,75</sup> Our previous PTSD-genetic study was mostly female.<sup>62</sup> Also, the total number of currently diagnosed PTSD cases in our study was limited (n=75). Thus, our findings will require further replication.

## Conclusion

Previously we reported a lower PTSD prevalence among non-military personnel with no or few PTSD genetic variants, irrespective of trauma exposure,<sup>8</sup> which is consistent with the current findings. In the present study, we show that PTSD symptom severity decreases by level of trauma exposure (for both combat and lifetime trauma exposures) when the PTSD genetic risk score goes up (see: Figure 2A and B), suggesting that PTSD symptom severity may be more dependent on genetic risk variants than level of trauma exposure, per se. We suspect that the absence of these PTSD risk genetic variants may also be associated with resilience to other psychological disorders, such as addiction,<sup>24,71,76,77</sup> but further research is required to confirm this hypothesis. Nevertheless, while the impact of the genetic markers studied was statistically significant, they still were relatively small. Noteworthy, however, is that not only veterans but those employed in law-enforcement, public safety, and emergency medical work, as well as those exposed to disasters and accidents may also be similarly impacted,<sup>78</sup> so these genetic findings may have wider implications.

In summary, our study replicates previous results with a trauma-exposed population. Both warzone and non-warzone factors predicted current PTSD among US veterans, including a PTSD genetic risk score. Interaction effects were detected for combat and lifetime trauma exposures by genetic risk score for PTSD symptom severity, suggesting that PTSD symptom manifestation may be more dependent on having the PTSD genetic risk variants than the level of lifetime trauma or combat exposure, indicating that absence of these risk variants may also confer PTSD genetic resilience.<sup>8</sup> Recently, large-scale genome-wide association studies (GWAS) of PTSD have reported genetic overlap with other major disorders, such as schizophrenia and bipolar disorder,<sup>12,13</sup> suggesting that PTSD genetics are very complex. Other complications include the diagnostic criteria for PTSD, the diversity of study populations, and the contingency of PTSD on the occurrence of trauma exposure.<sup>13</sup> Consequently, given these factors, we may have neither properly controlled for nor have identified all potential risk factors in the current study.

To our knowledge, however, our team was the first to report the association between the cholinergic receptor nicotinic alpha-5 gene and PTSD. This is interesting because PTSD has been associated with increased cigarette smoking post-trauma,<sup>79</sup> which is presumed due to the psychoactive effect of nicotine on PTSD symptom reduction.<sup>10,80</sup> However, this genetic risk may be on both behavioral and biologic causal pathways associated with PTSD.<sup>71</sup> Additionally, it is interesting to note that contemporary discussions of PTSD psychobiology now often include recognition of immunologic and metabolic involvement in PTSD psychopathology,<sup>12,13</sup> something we reported some time ago.<sup>43,81–83</sup> Again, noteworthy, is that nicotine addiction is typically also implicated in both the immunologic and metabolic disease pathways,<sup>81</sup> suggesting additional causal confounding.<sup>14,15</sup> Our plan is to also continue these investigations in the future.

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