The Impact of Post-Traumatic Stress on Symptom Presentation of Women With Gulf War Illness

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Abstract

Background: Gulf War Illness (GWI) is a chronic, multi-symptomatic disorder characterized by fatigue, muscle pain, cognitive problems, insomnia, rashes, and gastrointestinal issues affecting an estimated 30% of the ~750,000 returning military Veterans of the 1990–1991 Persian Gulf War. Female Veterans deployed to combat in this war report medical symptoms, like cognition and respiratory troubles, at twice the rate compared to non-deployed female Veterans of the same era. The heterogeneity of GWI symptom presentation complicates diagnosis as well as the identification of effective treatments. This is exacerbated by the presence of co-morbidities. Defining subgroups of the illness may help alleviate these complications. One clear grouping is along the lines of gender. Our aim is to determine if women with GWI can be further subdivided into distinct subgroups based on post-traumatic stress disorder (PTSD) symptom presentation.

Methods: Veterans diagnosed with GWI (n = 35) and healthy sedentary controls (n = 35) were recruited through the Miami Veterans Affairs Medical Health Center. Symptoms were assessed via the RAND short form health survey, the multidimensional fatigue inventory, and the Davidson trauma scale. Hierarchal regression modeling was performed on measures of health and fatigue with PTSD symptoms as a covariate. This was followed by univariate analyses conducted with two separate GWI groups based on a cut-point of 70 for their total Davidson trauma scale value and performing heteroscedastic t-tests across all measures.

Results: Based on the distinct differences found in PTSD symptomology regarding all health and trauma symptoms, two subgroups were derived within female GWI Veterans. Hierarchical regression models displayed the comorbid effects of GWI and PTSD, as both conditions had measurable impacts on physical and social outcomes of poor health (ΔR^2 = 0.08- 0.672), with notable differences in mental and emotional measures. Overall, in women with GWI individuals with PTSD, a cut point analysis indicated poorer health outcomes within all measures in comparison to those of women without PTSD symptoms and healthy controls.

Conclusions: Our current findings support the understanding that comorbid symptoms of GWI and PTSD subsequently result in poorer experienced health outcomes, along with establishing the possibility of varying clinical presentations.

Background

Gulf War Illness (GWI) continues to negatively impact at least 25 percent of the 700,000 deployed US military personnel to the 1990–1991 Gulf War (1). Of those 700,000 deployed nearly 50,000 were women (2). GWI is a chronic condition expressed as a combination of fatigue, pain, headache, difficulty concentrating, memory loss, sleep disturbance, respiratory issues, gastrointestinal problems, and skin rash (3). Identifying the pathology of GWI is complicated by the disease's interaction with multiple systems of the body including the central nervous system, autonomic nervous system, immune system, and endocrine system (i.e., hypothalamic-pituitary-adrenal [HPA] axis, hypothalamic-pituitary-adrenal [HPG] axis; (4) Research Advisory Committee on Gulf War Veterans' Illnesses (1). The etiology of GWI is further complicated when considering the role of gender or how the pathobiological expression of GWI may differ between male and female Veterans (1).

The Gulf War had the largest proportion of women serving in a military zone, comprising of 7 percent of those deployed to the Gulf War. Furthermore, military roles for women expanded which increased their exposure to combat and neurotoxicants (5). However, research pertaining to woman health issues is relatively sparse for female Veterans of the Gulf War (6) and predominately focused on reproductive health (i.e., stillbirths, pregnancies, birth defects).

Early research investigating female and male Veterans of the Gulf War provided initial support for a differential expression by gender regarding health outcomes. A preliminary analysis found that female Gulf War Veterans had increased mortality rates from digestive system diseases in comparison to non-deployed female Veterans (7, 8). Additionally, female Veterans had more pronounced autonomic nervous system (ANS) distinctions in comparison to male Veterans on an electrocardiogram test (9). However, additional autonomic research found comparable rates between female and male Veterans with GWI (10). Furthermore, like the general population incidence rates of multiple sclerosis were three times higher in female Veterans in comparison to male Veterans who served from 1990 to 2007 (11). Likewise, female Gulf War Veterans were more likely to report osteoporosis, bipolar disorder, depression, irritable bowel syndrome, migraines, asthma, and thyroid issues in comparison to their male counterparts (12). Female Veterans also report poorer health and medical diagnoses (outside of diabetes and cardiovascular diseases) at higher rates than male Veterans (12). Finally, female Veterans have a higher prevalence of symptom-based conditions including chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome, and migraines, suggesting higher burden of symptom-based conditions (13).

Some investigations have found that female Gulf War Veterans have utilized more health services over men. One study found that female Veterans reported more doctor/clinic visits (13). Another study found that women who served in the Gulf War utilized more outpatient services, inpatient services, and Veterans Affairs (VA) compensation in comparison to men (14). Notably, certain groups (i.e., older individuals, those hospitalized before war) of Gulf War female Veterans had higher risk of hospitalizations despite cause (15, 16).

Researchers compared groups based on gender and illness group (i.e., GWI, Chronic Fatigue Syndrome [CFS], and healthy control) and found support for gender specific profiles based on differential immune expression (17). When investigating GWI and CFS in females, Smylie et al. (17) found that interleukin 10 (IL-10) delineated GWI or CFS subjects in females in the context of the interleukin 23 (IL-23)/interleukin 17 (IL-17) axes. Furthermore, the IL-23/IL-17 axis was implicated in GWI expression with sex-specific markers, suggesting that sex hormones modulate the immune response. Researchers have also argued for additional research investigating differential immune expression given that many female Veterans of the Gulf War are developing menopausal symptoms. Therefore, menopause could contribute to cytokine expression, particularly in pro-inflammatory cytokines such as interleukin 1 (IL-1), interleukin 6 (IL-6), and tumor necrosis factor alpha (TNF-alpha; (18)).

Previous investigations have established that deployment to the Gulf War is associated with decreased functioning and poorer health overall in conjunction with a higher prevalence of physical and mental conditions (19–21). However, research on the impact of the Gulf War for female Veterans remains limited, particularly when investigating mental health outcomes. One of the few studies found that female Gulf War Veterans were more likely than their male counterparts to test positive on a screen for psychological disorders (i.e., major depressive disorder, anxiety, PTSD; (13)). Wolfe et al. (22) found female Veterans of the Gulf War were at higher risk of developing PTSD than their male men counterparts. Smith et al. (23) found that post-trauma symptoms mediated the relationship between sexual harassment and assault during deployment and military sexual trauma and physical symptoms (gastrointestinal, genitourinary, musculoskeletal, and neurological).

Previous research has also established that PTSD or stress-related symptoms have an impact on Gulf War Veterans despite the lower prevalence rate (1). PTSD, a more severe presentation after trauma exposure, was associated with poor quality of life from health consequences (24) as well as higher endorsement of physical symptoms (25, 26). Even exposure to traumatic events was linked to more mental health services utilized (27). However, once again, research in trauma specific to female Gulf War Veterans remains sparse.

Research into PTSD symptoms and stressors of female Gulf War Veterans has investigated combat trauma as well as non-military sources of trauma (i.e., interpersonal distress, sexual trauma). A study by Wolfe et al. (28) found that sexual assault was more influential to PTSD symptoms over combat exposure. Furthermore, sexual harassment was predictive of PTSD symptoms outcome. Vogt, Pless, King and King (29) found that female Veterans endorsed more interpersonal stressors over their male counterparts, and these had a stronger impact on their mental health. Another study by Rosen and colleagues (30) found that anticipation of combat was a significant stressor for female Veterans of the Gulf War and was identified as a significant predictor of increased psychological symptoms. However, Sutker and colleagues (31) reported that women were not necessarily more vulnerable to psychological distress in comparison to Veterans belonging to an ethnic minority group.

As both PTSD and GWI have been linked to poor health and mental outcomes in women who served in the Gulf War, this study aimed to investigate both the unique and combined influence of PTSD and GWI on self-reported measures of health functioning. The analyses investigated potential trends in grouping female Veterans on measures of health outcomes, PTSD, and GWI status. The overall hypothesis is that female Veterans with combined GWI and high PTSD symptoms will endure worse health outcomes. Although this study is novel in its investigation of functional consequences, it is expected that female Veterans will have similar trends to male Veterans in that a combined presentation of GWI with PTSD symptoms will have worse consequences (32).

Methods

Ethics Statement

All participants signed an informed consent approved by the Institutional Review Board (IRB) of the Miami VA Medical Health Center (MVAMHC), the University of Miami and/or the IRB of Nova Southeastern University. Ethics review and approval for data analysis was also obtained by the IRB of Nova Southeastern University. All methods were carried out in accordance with relevant guidelines and regulations.

Cohort

The research cohort was recruited via the Klimas clinic at the MVAMHC under two VA merit awards, I01CX000205-01 (Klimas PI; GWI: $n = 7$, Healthy Controls (HC): $n = 6$), and I01CX001050-01A1 (Klimas PI; GWI: $n = 27$), a National Institutes of Health R01 award 5R01NS090200-02 (Fletcher PI; HC: $n = 29$), and a Department of Defense Congressionally Directed Medical Research Program award W81XWH-09-2-0071 (Klimas PI; GWI: $n = 1$). Therefore, the full sample for the univariate analyses included 35 female Veterans with GWI and 35 healthy controls. The demographic factors are presented in Table 1. The sample consisted of 42.9% Black, 1.4% Asian, 1.4% Pacific Islander/ Native American, 40% White, and 14.3% White Hispanic. All participants were female with an average age of 51.51 years with an average BMI of 27.98. Inclusion criteria for GWI participants was derived from Fukuda et al. (33) to identify Veterans deployed to the theater of operations between August 8, 1990, and July 31, 1991. Veterans in the GWI group endorsed the presence of one or more symptoms for 6 months from at least 2 of the following categories: fatigue; mood and cognitive complaints; and musculoskeletal complaints. Participants were in good health prior to 1990 and had no current exclusionary diagnoses defined by Reeves et al. (34). This includes exclusion of major dementias of any type and alcoholism or drug abuse, medical conditions including organ failure, rheumatologic disorders, and use of medications that impact immune function, such as steroids or immunosuppressives. Collins et al. (35) supports the use of the Fukuda definition in GWI. Control participants consisted of age and BMI matched civilians self-defined as healthy with no exclusionary diagnoses, and sedentary (no regular exercise program, sedentary employment).

Table 1
Cohort Demographics

Group	Total	GWI	GWI+	GWI-	HC	p_2	p_3
N	70	35	19	16	35		
Mean Age (y)	48.23 ± 1.08	51.29 ± 1.28	49.79 ± 1.46	53.06 ± 2.17	51.74 ± 1.47	*0.818*	*0.486*
Mean BMI	27.43 ± 0.56	28.75 ± 0.87	27.99 ± 1.16	29.61 ± 1.32	26.99 ± 0.91	*0.167*	*0.263*
Race/Ethnicity						*0.213*	*0.182*
Asian	1.4%	0.0%	0.0%	0.0%	2.9%		
Black	42.9%	54.3%	63.2%	43.8%	31.4%		
White Hispanic	14.3%	11.4%	15.8%	6.3%	17.1%		
White	40.0%	31.4%	15.8%	50.0%	48.6%		
Other	1.4%	2.9%	5.3%	0.0%	0.0%		
Marital Status						*0.325*	*0.532*
Married	28.6%	28.6%	21.1%	37.5%	34.3%		
Widowed	4.3%	8.6%	10.5%	6.3%	0.0%		
Divorced	31.4%	34.3%	31.6%	37.5%	28.6%		
Never Married	10.0%	5.7%	10.5%	0.0%	14.3%		
Not Answered	24.3%	22.9%	26.3%	18.8%	22.9%		
Employed	41.4%	31.4%	42.1%	18.8%	51.4%	*0.089*	*0.089*
Education						*0.516*	*0.527*
High School	32.9%	28.6%	21.1%	37.5%	37.1%		
College	47.1%	48.6%	52.6%	43.8%	45.7%		
Not Answered	20.0%	22.9%	26.3%	18.8%	17.1%		

Measures

All participants received a physical examination and medical history including the GWI symptom checklist as per the case definition. Symptom questionnaires included the Multidimensional Fatigue Inventory (MFI; (36)), a 20-item self-report instrument designed to measure fatigue with five resulting composite scores, the RAND Medical Outcomes Study 36-item short-form survey (RAND SF-36; (37, 38)) assessing health-related quality of life with eight resulting composite scores, and the Davidson Trauma Scale (DTS; (39)), a self-rating measurement of the frequency and severity of Posttraumatic Stress Disorder (PTSD) symptoms in three clusters: intrusion, avoidance, and hyperarousal.

Data Analysis

Hierarchical Multiple Regression Analysis: Investigators utilized univariate hierarchical regression analysis to investigate if GWI co-morbid with higher PTSD symptom load predicted worse outcomes as measured by mental and physical health self-report measures. The hierarchical regression analyses were conducted in MATLAB v2021a using the *stepwiselm* function to investigate the impact of GWI and PTSD symptoms on self-reported levels of health parameters (RAND SF-36) and fatigue (MFI). The first block (Model 1) contained the categorical variable of health condition as defined by either a healthy control or a participant with GWI. The second block (Model 2) was comprised of the continuous variable of the total DTS score giving a measure of overall PTSD symptoms. These two blocks were assessed to find the contribution to the Coefficient of Determinization (R^2) for the eight scales of the RAND-36 and the five subscales of the MFI. All analyses were interpreted with the alpha level of 0.05. Effect sizes for GWI and PTSD symptom levels were interpreted using multiple R^2 change cutoffs as determined by (40) with a negligible effect being smaller than 0.02, a small effect being above 0.02, a medium effect being above 0.13, and a large effect being 0.26 or higher. Finally, missing data was minimal (maximum percentile missing = 3.9%) and coded as missing.

Cut-point Analysis:

The Davidson Trauma Scale (DTS) is a self-reporting and rating questionnaire that measures the frequency and severity of DSM-IV symptoms of PTSD within three specific clusters: Intrusion, Avoidance/Numbing, and Hyperarousal (39). These clusters were scored separately, and PTSD probability was determined through the total scores as well as individual ratings. The total scores were reflective of the frequency and severity ratings of all 17 items within the DTS. According to McDonald et al. (41) a simple cut off score of 70 as the total DTS score has shown effectiveness in predicting PTSD diagnosis in individuals with a 90% classification accuracy rate in all cases based on Kraemer's *kappa*. The application of this cut point analysis within the study enabled us to stratify GWI subjects, establishing individuals with DTS scores 70 and above as probable PTSD positive (GWI+; n = 19), while individuals below 70 were considered as probable PTSD negative (GWI−; n = 16). Values between the assigned groups were then compared using two sample t-tests with unequal variances. The linear step-up procedure introduced by Benjamini and Hochberg was applied to correct multiple comparisons and ultimately control the false discovery rate (42). Effect size for the difference between each group was also considered and interpreted in the following ranges (43): negligible, lower than 0.01, very small, 0.01–0.20, small 0.20–0.50, medium 0.50–0.80, large 0.80–1.20, very large 1.20–2.00, and huge 2.00 or higher. Values were estimated through the corrected Hedges g* equation,

$$g^* = \left(1 - \frac{3}{4\left(n_1 + n_2\right) - 9}\right) \frac{\bar{x}_1 - \bar{x}_2}{s^*}$$

where $\bar{x}$ was defined as the mean value of the variable for a group, *n* the size of the group, and s^* the pooled standard deviation for the variable further defined as,

$$s^* = \sqrt{\frac{(n_1 - 1)\, s_1^2 + (n_2 - 1)\, s_2^2}{n_1 + n_2 - 2}}$$

where s^2 is the group variance for the variable. The purpose of utilizing the corrected Hedges g^* was to ensure any bias within the population effect size was accounted for, and to overall provide better estimates for smaller sample sizes.

Results

Demographics

Demographics for the cohort are given in Table 1. Statistical comparisons were made between both GWI and HC groups (p_2), as well as between the GWI+, GWI−, and HC groups (p_3) using ANOVA for continuous variables and the χ^2 test for categorical variables. No statistical differences were found in age, BMI, racial representation, marital status, or education level. While the employment status of the groups did not reach a statistical difference ($p < 0.05$) there was a trend ($p < 0.089$) that GWI participants were less employed compared to HC, with GWI- participants showing the lowest overall employment rate.

Hierarchical Multiple Regression

In the first set of hierarchical regression models, the eights scales of the RAND SF-36 were analyzed in separate models. Predictor blocks were held constant across models: Model 1 (GWI or Healthy Control) and Model 2 (PTSD Symptoms). Hierarchical regression models were constructed with the two blocks of predictor variables to assess how these variables changed the outcome on each of the five scales of the MFI, and the eight scales of the RAND SF-36. A summary of the increase in the Coefficients of Determination (R^2) of the symptom measures for each model is presented in Table 2.

Within Model 1, GWI Health Status had a positive effect in variation on all measures within the RAND SF-36 as well as MFI scales. More specifically, some of the most significant effects were observed for measures of Physical Functioning and General Health Perceptions from the RAND SF-36 scales with a R^2 change of 0.672 and 0.670 respectively. All other measures had similar significant effects when corresponding to the GWI Health Status. Model 2 addressed the incorporation of DTS score (PTSD symptoms) in relation to all measures. PTSD symptoms appeared to have the most significant effect on Emotional Well-Being, Role Limitations due to Emotional Problems, and Pain within the RAND SF-36 measures with DR^2 of 0.140, 0.091, 0.080, respectively. Within the MFI scale measures of Reduced Activity and General Fatigue were also significantly increased by the presence of past trauma at increases of 0.097 and 0.094, respectively. With the exception of mental fatigue and reduced motivation, where the effects are really small, PTSD symptoms are a meaningful predictor in all other models.

However, while all other measures were increased due to PTSD symptoms, they did not satisfy the criterion for significance. Overall, GWI status had the greatest effect for all symptom reporting, with PTSD symptoms exacerbating all measures.

Table 2
Hierarchical Multiple Regression Model Changes in the Coefficient of Determination for GWI Health Status (Model 1), and with DTS Total Score (Model 2).

	Model 1	**Model 2**
Measure	ΔR^2	ΔR^2
RAND SF-36		
Physical Functioning	0.672****	0.024
Physical Role [a]	0.630****	0.017
General Health Perceptions	0.670****	0.038
Energy/Fatigue (Vitality)	0.652****	0.047
Social Functioning	0.601****	0.053
Emotional Role [b]	0.632****	0.091**
Emotional Well-Being	0.458****	0.140***
Pain	0.433****	0.080*
MFI		
Physical Fatigue	0.536****	0.059
Mental Fatigue	0.569****	0.011
Reduced Activity	0.408****	0.097**
Reduced Motivation	0.416****	0.005
General Fatigue	0.415****	0.094**

Note. *$p < 0.1$, **$p < 0.05$, ***$p < 0.01$, ****$p < 0.001$ [a] Physical Role (Role Limitations due to Physical Health), [b] Emotional Role (Role Limitations due to Emotional Problems)

Cut-point Analysis

As shown in Fig. 1 and Table 3, GWI − and GWI + had higher values in all measures of the SF-36, MFI, and the DTS scales compared to healthy controls. A further analysis within the GWI subgroups indicated an overall trend in which GWI + had higher values for all measures. More specifically, we observed significantly higher values for GWI + within SF-36 Physical Functioning, SF-36 Energy/Fatigue, SF-36 Social Functioning, SF-36 Role Limitations due to Emotional Problems, SF-36 Emotional Wellbeing, MFI Mental Fatigue, and MFI Reduced Motivation. Furthermore, an understanding of the effect differences showed that GWI – and GWI + had large or greater effect differences compared to HC for all measures (Table 3). The data also indicated that GWI + had higher effect differences present in all measures compared to HC than did GWI-. The presence of PTSD symptoms in GWI over GWI alone showed a small effect on MFI Reduced Activity, a medium effect on SF-36 Role Limitations due to Physical Problems, SF-36 Pain, MFI Physical Fatigue, and MFI Reduced Motivation, a medium effect on SF-36 Physical Functioning, SF-36 General Health Perceptions, SF-36 Energy/Fatigue, MFI General Fatigue, and MFI Mental Fatigue, and large effect on SF-36 Social Functioning, SF-36 Role Limitations due to Emotional Problems and SF-36 Emotional Well-being.

Table 3
Comparison of Davidson Trauma Scale Cut-point Derived GWI Subgroups.

Measure	Mean (SEM)			p^c			g*		
	HC	GWI-	GWI+	HC / GWI-	HC / GWI+	GWI- / GWI+	HC / GWI-	HC / GWI+	GWI- / GWI+
*RAND SF-36**									
Physical Functioning	3.7 (5.0)	43.4 (5.9)	59.2 (4.8)	< 0.001	< 0.001	0.047	3.06	4.76	0.94
Physical Role [a]	3.6 (7.9)	67.2 (10.6)	85.5 (6.7)	< 0.001	< 0.001	0.156	2.27	3.64	0.50
Pain	10.3 (5.3)	54.7 (4.6)	67.2 (5.1)	< 0.001	< 0.001	0.078	2.71	3.10	0.59
General Health Percept.	14.8 (5.1)	55.3 (5.0)	68.2 (4.2)	< 0.001	< 0.001	0.059	3.04	4.26	0.89
Energy/Fatigue	22.7 (5.1)	59.1 (5.5)	76.3 (3.8)	< 0.001	< 0.001	0.016	2.46	4.29	1.18
Social Funct.	6.6 (5.8)	46.1 (6.9)	71.7 (4.5)	< 0.001	< 0.001	0.004	2.46	5.34	1.43
Emotional Role [b]	5.7 (7.6)	39.6 (10.6)	88.9 (5.9)	0.007	< 0.001	< 0.001	1.35	4.78	1.87
Emotional Well-Being	13.9 (4.0)	35.5 (4.7)	52.9 (3.4)	< 0.001	< 0.001	0.006	1.20	2.33	1.02
MFI									
General Fatigue	14.7 (5.6)	53.2 (7.5)	71.9 (4.8)	< 0.001	< 0.001	0.071	1.61	2.78	0.72
Physical Fatigue	18.7 (5.4)	61.2 (6.3)	69.0 (3.6)	< 0.001	< 0.001	0.345	1.82	2.48	0.37
Mental Fatigue	21.0 (5.5)	49.4 (6.8)	70.3 (4.9)	0.002	< 0.001	0.028	1.10	2.04	0.87
Reduced Activity	14.7 (5.3)	51.7 (7.6)	55.5 (5.6)	0.001	< 0.001	0.728	1.46	1.74	0.13
Reduced Motivation	16.7 (4.8)	41.3 (5.3)	58.8 (5.1)	0.001	< 0.001	0.038	1.20	2.01	0.78

Note: SF-36 scores shown as (100 - score) to invert scale to align with MFI and DTS such that higher values indicate greater disability. [a] Physical Role (Role Limitations due to Physical Health), [b] Emotional Role (Role Limitations due to Emotional Problems), [c] False discovery rate calculated by the method of Benjamini and Hochberg (1995) for all significant p-values is < 0.06.

Measure	Mean (SEM)			p^c			g*		
	HC	GWI-	GWI+	HC / GWI-	HC / GWI+	GWI- / GWI+	HC / GWI-	HC / GWI+	GWI- / GWI+
DTS									
Intrusion	1.4 (2.0)	8.8 (1.8)	26.6 (1.7)	< 0.001	< 0.001	< 0.001	1.46	4.70	2.37
Avoidance/Numbness	1.5 (2.8)	13.8 (2.6)	37.4 (1.8)	< 0.001	< 0.001	< 0.001	1.70	5.86	2.49
Hyperarousal	2.0 (2.5)	14.8 (2.5)	32.5 (1.2)	< 0.001	< 0.001	< 0.001	1.79	5.50	2.21
Total	4.8 (7.1)	37.3 (6.1)	96.5 (3.0)	< 0.001	< 0.001	< 0.001	1.96	7.33	3.02

Note: SF-36 scores shown as (100 - score) to invert scale to align with MFI and DTS such that higher values indicate greater disability. [a] Physical Role (Role Limitations due to Physical Health), [b] Emotional Role (Role Limitations due to Emotional Problems), [c] False discovery rate calculated by the method of Benjamini and Hochberg (1995) for all significant p-values is < 0.06.

Discussion

The purpose of this study was to investigate the unique and combined contributions of GWI status and PTSD symptom severity on grouping trends as well as on measures of health outcomes in female Veterans. This study was specifically designed, given the sparse literature on the functional consequences of conditions linked to military service of GW female Veterans. As such, this study aimed to evaluate whether female Veterans could be grouped by these outcomes, and if these conditions lead to worse health outcomes overall, particularly with co-morbid GWI and high burden of PTSD symptom severity.

Given that there is a relationship between post-trauma symptoms, poorer quality of life, and higher physical symptoms (23–26), and we have previously shown that the presence of past trauma increases GWI symptom presentation in men (32), we hypothesized that co-morbid GWI and high PTSD symptom levels lead to higher endorsement of problematic mental and physical health symptoms compared to GWI as a separate stand-alone condition. The hierarchical model examining GWI in the presence of PTSD symptoms was significant for all domains of reported health outcomes measures. Of note is the influence of GWI diagnosis on all health outcomes, negatively affecting physical, mental, emotional, and social aspects of patients. GWI health status had a large effect on all the outcomes. The level of PTSD symptoms also influenced reported health outcome above and beyond the influence of GWI in all domains. This was especially the case for emotional well-being in which PTSD had a significant effect of medium scale. Role limitations to due to emotional problems, pain, reduced activity and general fatigue were also significantly increased at a smaller size. All other measures added a small increase to symptoms although not significantly, expect for role limitations due to physical health, mental fatigue, and reduced motivation which all had non-significant negligible effects. Overall, these results show that the presence of PTSD symptoms increase the symptom burden associated with GWI on a positively correlated scale.

While trauma increases symptom burden in a continuous manner, subtyping requires a distinct grouping of subjects. Here we used a cut off score of 70 on the total DTS score according to (41) to define high and low trauma GWI groups. The cut-point analysis shows that compared to healthy sedentary civilian controls, women with GWI and a probable negative PTSD diagnosis still present with a huge symptom burden. A probable PTSD diagnosis with GWI has again an effect increasing scores above GWI alone in all measures. The largest effects are seen in the social and emotional measures, however medium sized effects are also noted in pain, physical functioning and problems, fatigue (both physical and mental), energy levels and overall health perceptions. As such, the cut-point analysis demarcates the two GWI groups as distinct from each other, while also being distinct from controls. The difference is that all symptom measures reported in GWI alone are exacerbated further in the presence of past traumatic stress as evidenced by the effect size differences between measures. Nevertheless, GWVs who do not endorse prior exposure to trauma still report GWI symptomatology marking GWI was a condition onto itself and making it very unlikely that psychological distress alone is the sole underlying cause of GWI symptoms.

In comparison to male subjects with GWI the finding in female GWI that PTSD symptoms increase overall symptom burden is analogous (32). However, the findings of the hierarchical regression differ, in that PTSD symptoms in male GWI significantly increased all symptom measures, whereas significant changes for females GWI were only noted in emotional measures, pain and fatigue. In the cut point subgrouping both male and female GWI with probable PTSD showed significantly higher values measures of social functioning, role limitations due to emotional problems, emotional wellbeing, and mental fatigue. However, while there appears to be differences in gender with male GWI + additionally showing significant increases in general fatigue, and female GWI + showing significant increases in physical functioning, energy/fatigue levels, and reduced motivation compared to their GWI- counterparts, closer inspection reveals that these measures are trending towards significance ($p < 0.10$) in the other gender. This suggests that the GWI+/GWI- subgroup profiles based on the DTS cut-score of 70 are conserved across gender. Further studies such as this with larger sample size can confirm this.

Overall, our current findings support the understanding that comorbid symptoms of GWI and PTSD subsequently result in poorer health outcomes in female Veterans. This study is not without limitations, namely the small sample size utilized within the study and secondary nature of this analysis. Despite these limitations, the data showed significance measures allowing us to conclude with confidence that both GWI and PTSD have a definitive effect on female Veterans. In the future, additional research would benefit from having groups with differential trauma exposure given the multifaceted nature of PTSD present in female Veterans. It would also benefit from using a wider array of measures in the trauma more specific to females. Additionally, as GWI becomes more identifiable through biological profiles, future research investigating biological data particularly those sensitive to toxin exposure and immunological functioning would greatly aid in clarifying the clinical picture of GWI with and without PTSD symptom presentation. Therefore, it is our hope that this research prompts further investigation and helps inform clinicians about additional patterns they may encounter in female Veteran patients with GWI.

Declarations

Ethics approval and consent to participate:

All participants signed an informed consent approved by the Institutional Review Board (IRB) of the Miami VA Medical Health Center (MVAMHC), the University of Miami and/or the IRB of Nova Southeastern University. Ethics review and approval for data analysis was also obtained by the IRB of Nova Southeastern University. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication:

Not applicable.

Availability of data and materials:

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions:

MJ, CD, TC have made substantial contributions to the conception and design of the work; NS, ES, MJ, FC, JK, CD, MF, NK and TC made substantial contributions to the acquisition, analysis, and interpretation of data; NS, ES, MJ, FC, JK, CD, MF, NK and TC have drafted the work and contributed to its revisions. NS, ES, MJ, FC, JK, CD, MF, NK and TC have approved the submitted version of the work. All authors read and approved the final manuscript.

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Figures

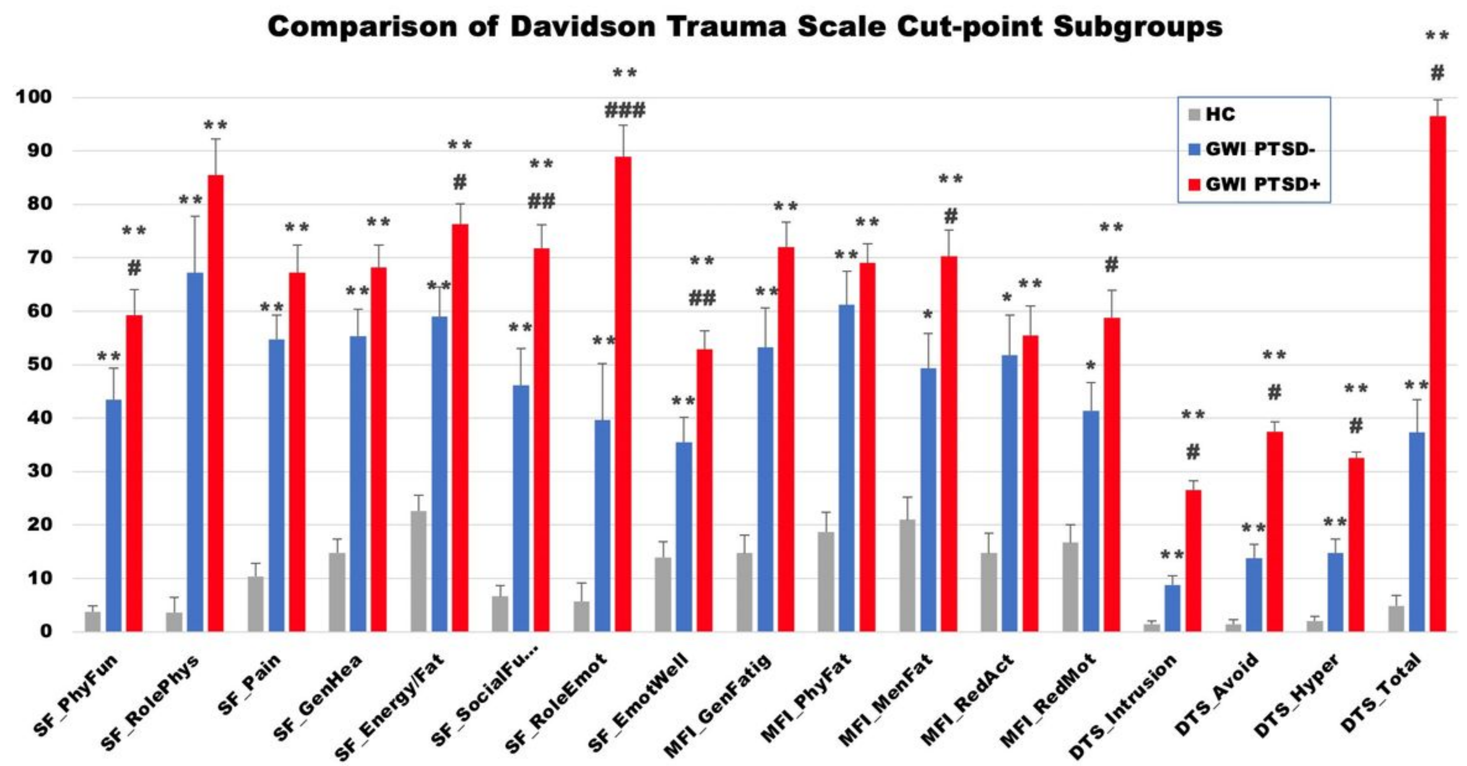

Figure 1

Comparison of symptom scales, and PTSD symptom level scores between Davidson Trauma Scale Cut-point defined groups. Note: SF-36 scores shown as (100 – score) to invert scale to align with MFI and DTS such that higher values indicate greater disability. SEM error bars. *p<0.01; **p<0.001 as compared to HC via heteroscedastic two sampled t-test, #p<0.05; ##p<0.01; ###p<0.001 as compared to GWI via heteroscedastic two sampled t-test