

**Research Advisory Committee on  
Gulf War Veterans' Illnesses (RACGWVI)  
— PubMed Research Citations  
for July, August, September 2023**

Prepared by Staff of the RACGWVI.

## **RACGWVI: Gulf War Illness — PubMed Citations for July, Aug, Sept 2023**

The following is a list of published research projects that focus on Gulf War Illness (GWI) for the months of July, August and September 2023.

For further VA research updates please visit, VA RESEARCH CURRENTS — Research News from the U.S. Department of Veterans Affairs. [VA Research Currents - Home](#)

### **Hyperlinks Guide:**

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**Article Title:** The title on each page (excluding table of contents), links to the abstract at PubMed.

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## Associations between risky alcohol use, disability, and problem-solving impairment among Veterans with Gulf War Illness: Secondary data analysis of a randomized clinical trial

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### Abstract

**Objective:** Gulf War Illness (GWI) and alcohol use are both major sources of disability among Gulf War Veterans. The goal of this secondary data analysis was to examine associations between risky alcohol use, problem-solving impairment, and disability among Veterans in a randomized clinical trial of problem-solving treatment (PST) for GWI. We examined cross-sectional associations and conducted longitudinal analyses to test if alcohol use moderated treatment outcome of PST.

**Methods:** Participants were 268 United States military Veterans with GWI randomized to PST or a control intervention. Participants were assessed at four timepoints. Measures included the World Health Organization Disability Assessment Schedule 2.0 (WHO-DAS 2.0), Problem Solving Inventory (PSI), and Alcohol Use Disorders Identification Test-Concise (AUDIT-C). We conducted multivariate regression (cross-sectional) and mixed model analyses (longitudinal) with separate models for WHO-DAS 2.0 and PSI. All models included AUDIT-C and household income. This analysis was pre-registered on the Open Science Framework.

**Results:** Cross-sectional analyses revealed a significant negative association with small effect size between AUDIT-C and WHO-DAS 2.0 ( $p = 0.006$ ;  $f^2 = 0.05$ ); worse disability was associated with less risky alcohol use. There was no evidence that risky alcohol use moderated effects of PST on disability or PSI.

**Conclusion:** If replicated, the cross-sectional findings suggest high levels of disability may deter heavy drinking among Veterans with GWI. We did not find evidence that risky alcohol use moderated treatment outcome of PST for GWI. More research is needed to identify moderators of GWI interventions and to understand risky drinking among Veterans with complex health problems.

## Genetic association between the APOE $\epsilon$ 4 allele, toxicant exposures and Gulf war illness diagnosis

Environ Health. 2023 Jul 6;22(1):51. doi: [10.1186/s12940-023-01002-w](https://doi.org/10.1186/s12940-023-01002-w).

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### Abstract

**Introduction:** Exposure to nerve agents, pyridostigmine bromide (PB), pesticides, and oil-well fires during the 1991 Gulf War (GW) are major contributors to the etiology of Gulf War Illness (GWI). Since the apolipoprotein E (APOE)  $\epsilon$ 4 allele is associated with the risk of cognitive decline with age, particularly in the presence of environmental exposures, and cognitive impairment is one of the most common symptoms experienced by veterans with GWI, we examined whether the  $\epsilon$ 4 allele was associated with GWI.

**Methods:** Using a case-control design, we obtained data on APOE genotypes, demographics, and self-reported GW exposures and symptoms that were deposited in the Boston Biorepository and Integrative Network (BBRAIN) for veterans diagnosed with GWI ( $n = 220$ ) and healthy GW control veterans ( $n = 131$ ). Diagnosis of GWI was performed using the Kansas and/or Center for Disease Control (CDC) criteria.

**Results:** Age- and sex-adjusted analyses showed a significantly higher odds ratio for meeting the GWI case criteria in the presence of the  $\epsilon$ 4 allele (Odds ratio [OR] = 1.84, 95% confidence interval [CI] = 1.07-3.15,  $p \leq 0.05$ ) and with two copies of the  $\epsilon$ 4 allele (OR = 1.99, 95% CI [1.23-3.21],  $p \leq 0.01$ ). Combined exposure to pesticides and PB pills (OR = 4.10 [2.12-7.91],  $p \leq 0.05$ ) as well as chemical alarms and PB pills (OR = 3.30 [1.56-6.97]  $p \leq 0.05$ ) during the war were also associated with a higher odds ratio for meeting GWI case criteria. There was also an interaction between the  $\epsilon$ 4 allele and exposure to oil well fires (OR = 2.46, 95% CI [1.07-5.62],  $p \leq 0.05$ ) among those who met the GWI case criteria.

**Conclusion:** These findings suggest that the presence of the  $\epsilon$ 4 allele was associated with meeting the GWI case criteria. Gulf War veterans who reported exposure to oil well fires and have an  $\epsilon$ 4 allele were more likely to meet GWI case criteria. Long-term surveillance of veterans with GWI, particularly those with oil well fire exposure, is required to better assess the future risk of cognitive decline among this vulnerable population.

**Delayed cognitive impairments in a rat model of Gulf War Illness are stimulus-dependent**

Brain Behav Immun. 2023 Jul 10;113:248-258. doi: [10.1016/j.bbi.2023.07.003](https://doi.org/10.1016/j.bbi.2023.07.003). Online ahead of print.

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**Abstract**

Gulf War Illness (GWI) collectively describes the multitude of central and peripheral disturbances affecting soldiers who served in the 1990-1991 Gulf War. While the mechanisms responsible for GWI remain elusive, the prophylactic use of the reversible acetylcholinesterase inhibitor, pyridostigmine bromide (PB), and war-related stress have been identified as chief factors in GWI pathology. Post-deployment stress is a common challenge faced by veterans, and aberrant cholinergic and/or immune responses to these psychological stressors may play an important role in GWI pathology, especially the cognitive impairments experienced by many GWI patients. Therefore, the current study investigated if an immobilization stress challenge would produce abnormal responses in PB-treated rats three months later. Results indicate that hippocampal cholinergic responses to an immobilization stress challenge are impaired three months after PB administration. We also assessed if an immune or stress challenge reveals deficits in PB-treated animals during hippocampal-dependent learning and memory tasks at this delayed timepoint. Novel object recognition (NOR) testing paired with either acute saline or lipopolysaccharide (LPS, 30 µg/kg, i.p.), as well as Morris water maze (MWM) testing was conducted approximately three months after PB administration and/or repeated restraint stress. Rats with a history of PB treatment exhibited 24-hour hippocampal-dependent memory deficits when challenged with LPS, but not saline, in the NOR task. Similarly, in the same cohort, PB-treated rats showed 24-hour memory deficits in the MWM task. Ultimately, these studies highlight the long-term effects of PB treatment on hippocampal function and provide insight into the progressive cognitive deficits observed in veterans with GWI.

## **Mitochondrial impairment but not peripheral inflammation predicts greater Gulf War illness severity**

Sci Rep. 2023 Jul 12;13(1):10739. doi: [10.1038/s41598-023-35896-w](https://doi.org/10.1038/s41598-023-35896-w).

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### **Abstract**

Gulf War illness (GWI) is an important exemplar of environmentally-triggered chronic multisymptom illness, and a potential model for accelerated aging. Inflammation is the main hypothesized mechanism for GWI, with mitochondrial impairment also proposed. No study has directly assessed mitochondrial respiratory chain function (MRCF) on muscle biopsy in veterans with GWI (VGWI). We recruited 42 participants, half VGWI, with biopsy material successfully secured in 36. Impaired MRCF indexed by complex I and II oxidative phosphorylation with glucose as a fuel source (CI&CIIOXPHOS) related significantly or borderline significantly in the predicted direction to 17 of 20 symptoms in the combined sample. Lower CI&CIIOXPHOS significantly predicted GWI severity in the combined sample and in VGWI separately, with or without adjustment for hsCRP. Higher-hsCRP (peripheral inflammation) related strongly to lower-MRCF (particularly fatty acid oxidation (FAO) indices) in VGWI, but not in controls. Despite this, whereas greater MRCF-impairment predicted greater GWI symptoms and severity, greater inflammation did not. Surprisingly, adjusted for MRCF, higher hsCRP significantly predicted lesser symptom severity in VGWI selectively. Findings comport with a hypothesis in which the increased inflammation observed in GWI is driven by FAO-defect-induced mitochondrial apoptosis. In conclusion, impaired mitochondrial function-but not peripheral inflammation-predicts greater GWI symptoms and severity.

**Adverse effect propensity: A new feature of Gulf War illness predicted by environmental exposures**

iScience. 2023 Jul 13;26(8):107363. doi: [10.1016/j.isci.2023.107363](https://doi.org/10.1016/j.isci.2023.107363). eCollection 2023 Aug 18.

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**Abstract**

A third of 1990-1 Gulf-deployed personnel developed drug/chemical-induced multisymptom illness, "Gulf War illness" (GWI). Veterans with GWI (VGWI) report increased drug/exposure adverse effects (AEs). Using previously collected data from a case-control study, we evaluated whether the fraction of exposures that engendered AEs ("AE Propensity") is increased in VGWI (it was); whether AE Propensity is related to self-rated "chemical sensitivity" (it did); and whether specific exposures "predicted" AE Propensity (they did). Pesticides and radiation exposure were significant predictors, with copper significantly "protective"-in the total sample (adjusted for GWI-status) and separately in VGWI and controls, on multivariable regression. Mitochondrial impairment and oxidative stress (OS) underlie AEs from many exposures irrespective of nominal specific mechanism. We hypothesize that mitochondrial toxicity and interrelated OS from pesticides and radiation position people on the steep part of the curve of mitochondrial impairment and OS versus symptom/biological disruption, amplifying impact of new exposures. Copper, meanwhile, is involved in critical OS detoxification processes.

**Co-Administration of Nanowired Monoclonal Antibodies to Inducible Nitric Oxide Synthase and Tumor Necrosis Factor Alpha Together with Antioxidant H-290/51 Reduces SiO<sub>2</sub> Nanoparticles-Induced Exacerbation of Pathophysiology of Spinal Cord Trauma**

Adv Neurobiol. 2023;32:195-229. doi: [10.1007/978-3-031-32997-5\\_5](https://doi.org/10.1007/978-3-031-32997-5_5).

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**Abstract**

Military personnel are often exposed to silica dust during combat operations across the globe. Exposure to silica dust in US military or service personnel could cause Desert Storm Pneumonitis also referred to as Al Eskan disease causing several organs damage and precipitate autoimmune dysfunction. However, the effects of microfine particles of sand inhalation-induced brain damage on the pathophysiology of traumatic brain or spinal cord injury are not explored. Previously intoxication of silica nanoparticles (50-60 nm size) is shown to exacerbates spinal cord injury induces blood-spinal cord barrier breakdown, edema formation and cellular changes. However, the mechanism of silica nanoparticles-induced cord pathology is still not well known. Spinal cord injury is well known to alter serotonin (5-hydroxytryptamine) metabolism and induce oxidative stress including upregulation of nitric oxide synthase and tumor necrosis factor alpha. This suggests that these agents are involved in the pathophysiology of spinal cord injury. In this review, we examined the effects of combined nanowired delivery of monoclonal antibodies to neuronal nitric oxide synthase (nNOS) together with tumor necrosis factor alpha (TNF- $\alpha$ ) antibodies and a potent antioxidant H-290/51 to induce neuroprotection in spinal cord injury associated with silica nanoparticles intoxication. Our results for the first time show that co-administration of nanowired delivery of antibodies to nNOS and TNF- $\alpha$  with H-290/51 significantly attenuated silica nanoparticles-induced exacerbation of spinal cord pathology, not reported earlier.

## Comparison of Health Outcomes Over Time Among Women 1990-1991 Gulf War Veterans, Women 1990-1991 Gulf Era Veterans, and Women in the U.S. General Population

Womens Health Issues. 2023 Jul 24;S1049-3867(23)00123-8. doi: [10.1016/j.whi.2023.06.006](https://doi.org/10.1016/j.whi.2023.06.006).  
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### Abstract

**Introduction:** The aim of this study is to examine health over almost 20 years of follow-up among women Gulf War veterans and women Gulf Era veterans and compare their health to women in the U.S. general population.

**Methods:** We used data from a health survey of 1,274 women Gulf War veteran and Gulf Era veteran participants of the Gulf War Longitudinal Study who responded to all three waves. Data on the U.S. population of women came from the 1999-2000, 2005-2006, and 2011-2014 National Health and Nutrition Examination Survey (NHANES). Generalized estimating equations (GEE) were used to compare the report of disease over time in women Gulf War and Gulf Era veterans. Differences in prevalence at the three survey timepoints were calculated between women Gulf War veterans and the NHANES women population, and women Gulf War Era veterans and the NHANES women population.

**Results:** Women veterans who deployed to the 1990-1991 Gulf War report poorer health than women veterans who served during the same time but did not deploy. Women veterans reported a lower prevalence of hypertension, stroke, and diabetes than women in the NHANES sample. Women veterans also reported a higher prevalence of arthritis, chronic obstructive pulmonary disease, and skin cancer than women in the NHANES sample.

**Conclusions:** This study is the first to characterize the health of a population-based cohort of women Gulf War and women Gulf Era veterans over time and compare it with women's health in a civilian NHANES population. This demonstrates the value of epidemiological research on women veterans and the importance of developing longitudinal cohorts across genders.

**Is exposure to chemical pollutants associated with sleep outcomes? A systematic review**

Sleep Med Rev. 2023 Aug;70:101805. doi: [10.1016/j.smrv.2023.101805](https://doi.org/10.1016/j.smrv.2023.101805). Epub 2023 Jun 16.

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**Abstract**

Environmental exposures may influence sleep; however, the contributions of environmental chemical pollutants to sleep health have not been systematically investigated. We conducted a systematic review to identify, evaluate, summarize, and synthesize the existing evidence between chemical pollutants (air pollution, exposures related to the Gulf War and other conflicts, endocrine disruptors, metals, pesticides, solvents) and dimensions of sleep health (architecture, duration, quality, timing) and disorders (sleeping pill use, insomnia, sleep-disordered breathing)). Of the 204 included studies, results were mixed; however, the synthesized evidence suggested associations between particulate matter, exposures related to the Gulf War, dioxin and dioxin-like compounds, and pesticide exposure with worse sleep quality; exposures related to the Gulf War, aluminum, and mercury with insomnia and impaired sleep maintenance; and associations between tobacco smoke exposure with insomnia and sleep-disordered breathing, particularly in pediatric populations. Possible mechanisms relate to cholinergic signaling, neurotransmission, and inflammation. Chemical pollutants are likely key determinants of sleep health and disorders. Future studies should aim to evaluate environmental exposures on sleep across the lifespan, with a particular focus on developmental windows and biological mechanisms, as well as in historically marginalized or excluded populations.

## The Department of Veterans' Affairs Depleted Uranium Cohort in the Time of COVID-19: Translating a Traditional Surveillance Protocol to a Telehealth Platform

J Occup Environ Med. 2023 Aug 1;65(8):670-676. doi: [10.1097/JOM.0000000000002875](https://doi.org/10.1097/JOM.0000000000002875). Epub 2023 May 12.

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### Abstract

**Objective:** In 2021, 37 members of a cohort of depleted uranium-exposed Gulf War I veterans were evaluated using a protocol tailored to accommodate COVID-19 safety practices on a telehealth platform.

**Methods:** Individual elements of the legacy protocol were reviewed for urgency and feasibility of inclusion in a modified, telehealth platform.

**Results:** The redesigned protocol included a participant readiness for telehealth assessment, nurse and physician telehealth visits, collection of usual health questionnaires, and urine collections for exposure monitoring for uranium and other fragment-related metal measures.

**Conclusions:** Despite some limitations in scope, the telehealth platform permitted a visual "visit" with surveillance participants who expressed a high comfort level with the format. The telehealth platform has apparent utility for occupational surveillance and should be explored as a standard approach for surveillance outside of public health emergencies.

## A population-based investigation into the prevalence of chronic fatigue syndrome in United States military Veterans with chronic pain

Fatigue: Biomedicine, Health & Behavior, 11:2-4, 129-141, DOI: [10.1080/21641846.2023.2239977](https://doi.org/10.1080/21641846.2023.2239977)

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### ABSTRACT

#### Objective

Chronic fatigue syndrome (CFS) is a debilitating illness characterized by persistent fatigue among other symptoms. Pain symptoms are common and included in the diagnostic criteria for CFS but are not required for diagnosis. Despite the association between CFS and pain, few studies have examined CFS in the context of chronic pain (CP) conditions. The current study estimates the period prevalence of comorbid CFS among military Veterans with CP and compares sociodemographic characteristics and CP conditions of Veterans with CP + CFS to those with CP without CFS.

#### Methods

This study included Veterans Health Administration (VHA) data on 2,261,030 patients with chronic pain in 2018. Sociodemographic characteristics included age, sex, race, ethnicity, and rurality. Descriptive statistics were used to describe the sample and between-group comparisons included independent samples t-tests and chi-square tests of independence. Effect sizes were also examined.

#### Results

A total of 15,248 (0.67%) of Veterans with CP also had a diagnosis of CFS. Veterans diagnosed with CP + CFS were younger and were more likely to be female, White, non-Hispanic, and rural-dwelling. However, small and weak effect sizes were observed for these differences. The majority of Veterans with CP + CFS had limb/extremity (69.20%) back pain (53.44%), or abdominal/bowel pain (24.11%).

#### Conclusion

As CDC treatment recommendations for CFS include treating pain first, studying CFS in the context of CP is critically important. Veterans diagnosed with CP + CFS appear demographically similar, compared to Veterans with CP without CFS. Examining the utilization of pain-related healthcare services among this group would be a useful next step.

**Love Is Not All You Need: Understanding the Association Between Relationship Status and Relationship Dysfunction With Self-Directed Violence in Veterans**

Arch Suicide Res. 2023 Aug 7;1-16. doi: [10.1080/13811118.2023.2237097](https://doi.org/10.1080/13811118.2023.2237097). Online ahead of print.

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**Abstract**

**Introduction:** Research indicates that being married is associated with reduced risk of suicide and self-directed violence (SDV) relative to being divorced. Simultaneously, difficulties within relationships predict poorer health outcomes. However, research on relationship status rarely examines relationship functioning, obfuscating the joint contribution of these variables for SDV risk.

**Method:** Veterans (N = 1,049) completed a survey that included assessment of relationship status, relationship functioning, and SDV history. Logistic regression models tested how (a) relationship status, (b) relationship dysfunction, and (c) being divorced compared to being in a low- or high-dysfunction relationship were associated with SDV, controlling for several intrapersonal risk factors.

**Results:** Veterans in a relationship did not differ in SDV history compared to divorced/separated veterans. However, more dysfunction within relationships was associated with greater odds of a history of SDV and suicidal cognitions. Finally, SDV histories were more likely among veterans endorsing high-dysfunction relationships compared with (a) low-dysfunction relationships and (b) divorced veterans.

**Conclusion:** It may be insufficient to only consider relationship status when evaluating interpersonal risk factors for SDV. A single item assessing relationship dysfunction was associated with enacted SDV and suicidal cognitions over and above intrapersonal risk factors. Integrating such single-item measures into clinical practice could improve identification and subsequent tailored intervention for veterans at greater risk for SDV.

## **Cannabis use and suicide risk among Gulf War veterans**

Death Stud. 2023;47(5):618-623. doi: [10.1080/07481187.2022.2108944](https://doi.org/10.1080/07481187.2022.2108944). Epub 2022 Aug 8.

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### **Abstract**

Cannabis use has been indicated as a risk factor for suicide in veterans. This study of Gulf War veterans tested the relationship between self-report past year cannabis use and (a) past year suicidal ideation and (b) risk for suicidal behavior. Data were from a national sample (N = 1126) of Gulf War veterans. Logistic regression models indicated cannabis use was associated with past year suicidal ideation and elevated risk for suicidal behavior, independent of key covariates. In corroboration with research on other military populations, this study indicates a potentially concerning association between cannabis use and suicide risk in Gulf War veterans.

## Women of the Gulf War: Understanding Their Military and Health Experiences Over 30 Years

Mil Med. 2023 Aug 29;188(9-10):3191-3198. doi: [10.1093/milmed/usac283](https://doi.org/10.1093/milmed/usac283).

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### Abstract

**Introduction:** Women Veterans of the Persian Gulf War (GW) expanded the military roles they had filled in previous military eras, with some women engaging in direct combat for the first time. Many GW service members, including women, had unique combat exposures to hazardous agents during deployment, which might have contributed to the development of chronic health problems. This study aims to understand the experiences of women GW Veterans (GWVs) as it is related to their military service and subsequent health in order to better inform and improve their clinical care.

**Materials and methods:** We conducted in-depth interviews with 10 women GWVs to understand their experiences and perspectives about how their military service in the Gulf has impacted their lives and health. We used an integrated approach of content analysis and inductive thematic analysis to interpret interview data.

**Results:** Besides having many of the same war-related exposures as men, women faced additional challenges in a military that was inadequately prepared to accommodate them, and they felt disadvantaged as women within the military and local culture. After service, participants had emergent physical and mental health concerns, which they described as developing into chronic and complex conditions, affecting their relationships and careers. While seeking care and service connection at Veterans Health Administration (VA), women voiced frustration over claim denials and feeling dismissed. They provided suggestions of how VA services could be improved for women and GWVs. Participants found some nonpharmacological approaches for symptom management and coping strategies to be helpful.

**Conclusions:** Women in the GW encountered challenges in military and healthcare systems that were inadequately prepared to address their needs. Women faced chronic health conditions common to GWV and voiced the desire to be understood as a cohort with unique needs. There is an ongoing need to expand services within the VA for women GWVs, particularly involving psychosocial support and management of chronic illness. While the small sample size can limit generalizability, the nature of these in-depth, minimally guided interviews provides a rich narrative of the women GWVs in this geographically diverse sample.

**The Gulf War Illness and the Iraqi Population's Forgotten Pain and Suffering**

Mil Med. 2023 Aug 29;188(9-10):241-243. doi: [10.1093/milmed/usad195](https://doi.org/10.1093/milmed/usad195).

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**Abstract**

Exposure to chemical warfare agents results in long-term biopsychosocial complaints. A recent study has revealed an association between exposure to a low dose of Sarin and Gulf War illness in American veterans from the Gulf War. The prevalence of Gulf War illness has not been studied in the Iraqi population. In light of recent research results, Iraqi chemical warfare agent survivors' multiple physical and mental illnesses should be highlighted. For this reason, establishing both legislation and medical commissions is most needed.

**Vitamin D Deficiency (VDD) and Benefits of Supplementation in Veterans with IBS-D**

Diagnostics (Basel). 2023 Aug 30;13(17):2807. doi: [10.3390/diagnostics13172807](https://doi.org/10.3390/diagnostics13172807).

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**Abstract**

Many veterans deployed to Gulf War areas suffer from persistent chronic diarrhea that is disabling and affects their quality of life. The causes for this condition have eluded investigators until recently and recent literature has shed light on the effect of vitamin D on the brain-gut axis. This study focused on determining clinical causes contributing to diarrhea and assessed whether reversing the identified causes, specifically vitamin D deficiency (VDD), could reduce the incidence of diarrhea in Gulf War veterans (GWVs). All patients completed a workup that included serologies (IBD, celiac), routine laboratory tests (CBC, chemistry panels, TSH, T4, CRP), cultures for enteric pathogens (C diff, bacteria, viruses, small intestinal bacterial overgrowth (SIBO)), and upper and lower endoscopies with histology and a trial of cholestyramine to exclude choloretic diarrhea and rifaximin for dysbiosis. A total of 4221 veterans were screened for chronic diarrhea, yielding 105 GWVs, of which 69 GWVs had irritable bowel syndrome with diarrhea (IBS-D). Paired t-tests demonstrated that all GWVs had VDD (t=11.62, df68 and sig(2-tailed) 0.0001) (defined as a vitamin D level less than 30 ng/mL with normal ranges of 30-100 ng/mL) but no positive serologies, inflammatory markers, abnormal endoscopies, cultures, or histology to explain their persistent diarrhea. There was no correlation with age, BMI, or inflammation. Some zip codes had a higher frequency of GWVs with VDD, but the number of deployments had no impact. Treatment with vitamin D supplementation (3000-5000 units), given in the morning, based on weight, reduced the number of bowel movements per day ( $p < 0.0001$ ) without causing hypercalcemia. We suggest that VDD is important in the etiology of IBS-D in GWVs and that vitamin D supplementation significantly reduces diarrhea.

## **Hormonal changes in veterans with Gulf War Illness**

Life Sci. 2023 Sep 1;328:121908. doi: [10.1016/j.lfs.2023.121908](https://doi.org/10.1016/j.lfs.2023.121908). Epub 2023 Jul 3.

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### **Abstract**

**Aims:** Gulf War Illness (GWI) is a multi-system condition of complex etiology and pathophysiology without specific treatment. There is an overlap between the symptoms of GWI and endocrinopathies. This study aimed to identify hormonal alterations in 1990-91 Gulf War (GW) veterans and the relationship between GWI and hormonal dysregulation.

**Main methods:** Data from 81 GW veterans (54 with GWI and 27 controls without GWI) was analyzed in a cross-sectional, case-control observational study. Participants completed multiple questionnaires, neuropsychiatric assessments, and a comprehensive set of hormone assays including a glucagon stimulation test (GST) for adult growth hormone deficiency (AGHD) and a high-dose adrenocorticotrophic hormone (ACTH) stimulation test for adrenal insufficiency.

**Key findings:** The GWI group had lower quality of life and greater severity of all symptoms compared to controls. Pain intensity and pain-related interference with general activity were also higher in the GWI group. AGHD was observed in 18 of 51 veterans with GWI (35.3 %) and 2 of 26 veterans without GWI (7.7 %) ( $p = 0.012$  for interaction). Veterans with GWI also exhibited reduced insulin-like growth factor 1 (IGF-1) levels and IGF-1 Z-scores compared to controls. One participant with GWI met the criteria for adrenal insufficiency. No significant changes were observed in other hormonal axes.

**Significance:** The frequency of AGHD was significantly higher in veterans with GWI compared to controls. Recombinant human growth hormone replacement therapy (GHRT) may become a breakthrough therapeutic option for this subgroup. A large clinical trial is needed to evaluate the efficacy of GHRT in patients with GWI and AGHD.

**'She thought the same way I that I thought:' a qualitative study of patient-provider concordance among Gulf War Veterans with Gulf War Illness**

Psychol Health. 2023 Sep 1;1-19. doi: [10.1080/08870446.2023.2248481](https://doi.org/10.1080/08870446.2023.2248481). Online ahead of print.

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**Abstract**

Objective: Medically unexplained symptoms (MUS), such as chronic fatigue syndrome, irritable bowel syndrome, and Gulf War Illness (GWI), are difficult to treat. Concordance-shared understanding between patient and provider about illness causes, course, and treatment-is an essential component of high-quality care for people with MUS. This qualitative paper focuses on the experiences of United States military Veterans living with GWI who have endured unique healthcare challenges. Methods & Measures: Qualitative interviews were conducted with 31 Veterans with GWI to explore factors that contribute to and detract from concordance with their Veteran Affairs (VA) healthcare providers. In addition to being seen by VA primary care, over half of participants also sought care at a War Related Illness and Injury Study Center, which specializes in post-deployment health. Deductive and inductive codes were used to organize the data, and themes were identified through iterative review of coded data. Results: Major themes associated with patient-provider concordance included validation of illness experiences, perceived provider expertise in GWI/MUS, and trust in providers. Invalidation, low provider expertise, and distrust detracted from concordance. Conclusion: These findings suggest providers can foster concordance with MUS patients by legitimizing patients' experiences, communicating knowledge about MUS, and establishing trust.

## Misclassification Bias in the Assessment of Gene-by-Environment Interactions

Epidemiology. 2023 Sep 1;34(5):673-680. doi: [10.1097/EDE.0000000000001635](https://doi.org/10.1097/EDE.0000000000001635). Epub 2023 May 30.

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### Abstract

**Background:** Misclassification bias is a common concern in epidemiologic studies. Despite strong bias on main effects, gene-environment interactions have been shown to be biased towards the null under gene-environment independence. In the context of a recent article examining the interaction between nerve agent exposure and paraoxonase-1 gene on Gulf War Illness, we aimed to assess the impact of recall bias—a common misclassification bias—on the identification of gene-environment interactions when the independence assumption is violated.

**Methods:** We derive equations to quantify the bias of the interaction, and numerically illustrate these results by simulating a case-control study of 1000 cases and 1000 controls. Simulation input parameters included exposure prevalence, strength of gene-environment dependence, strength of the main effect, exposure specificity among cases, and strength of the gene-environment interaction.

**Results:** We show that, even if gene-environment independence is violated, we can bound possible gene-environment interactions by knowing the strength and direction of the gene-environment dependence ( $\rho$ ) and the observed gene-environment interaction ( $\beta$ )—thus often still allowing for the identification of such interactions. Depending on whether  $\beta$  is larger or smaller than the inverse of  $\rho$ , is a lower (if  $\beta < 1/\rho$ ) or upper (if  $\beta > 1/\rho$ ) bound for the true interaction. In addition, the bias magnitude is somewhat predictable by examining other characteristics such as exposure prevalence, the strength of the exposure main effect, and directions of the recall bias and gene-environment dependence.

**Conclusions:** Even if gene-environment dependence exists, we may still be able to identify gene-environment interactions even when misclassification bias is present.

## Examining the current health of Gulf War veterans with the veterans affairs frailty index

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### Abstract

**Introduction:** Gulf War Illness (GWI) is a chronic, multisymptom (e.g., fatigue, muscle/joint pain, memory and concentration difficulties) condition estimated to affect 25–32% of Gulf War (GW) veterans. Longitudinal studies suggest that few veterans with GWI have recovered over time and that deployed GW veterans may be at increased risks for age-related conditions.

**Methods:** We performed a retrospective cohort study to examine the current health status of 703 GW veterans who participated in research studies at the San Francisco VA Health Care System (SFVAHCS) between 2002 and 2018. We used the Veterans Affairs Frailty Index (VA-FI) as a proxy measure of current health and compared the VA-FIs of GW veterans to a group of randomly selected age- and sex-matched, non-GW veterans. We also examined GW veterans' VA-FIs as a function of different GWI case definitions and in relationship to deployment-related experiences and exposures.

**Results:** Compared to matched, non-GW veterans, GW veterans had lower VA-FIs ( $0.10 \pm 0.10$  vs.  $0.12 \pm 0.11$ ,  $p < 0.01$ ). However, the subset of GW veterans who met criteria for severe Chronic Multisymptom Illness (CMI) at the time of the SFVAHCS studies had the highest VA-FI ( $0.13 \pm 0.10$ ,  $p < 0.001$ ). GW veterans who had Kansas GWI exclusionary conditions had higher VA-FI ( $0.12 \pm 0.12$ ,  $p < 0.05$ ) than veterans who were Kansas GWI cases ( $0.08 \pm 0.08$ ) and controls (i.e., veterans with little or no symptoms,  $0.04 \pm 0.06$ ) at the time of the SFVAHCS research studies. The VA-FI was positively correlated with several GW deployment-related exposures, including the frequency of wearing flea collars.

**Discussion:** Although GW veterans, as a group, were less frail than non-GW veterans, the subset of GW veterans who met criteria for severe CDC CMI and/or who had Kansas GWI exclusionary conditions at the time of the SFVAHCS research studies were frailest at index date. This suggests that many ongoing studies of GWI that use the Kansas GWI criteria may not be capturing the group of GW veterans who are most at risk for adverse chronic health outcomes.

## **Is Gulf War Illness a prolonged early phase tauopathy?**

Cytoskeleton (Hoboken). 2023 Sep 13. doi: [10.1002/cm.21786](https://doi.org/10.1002/cm.21786). Online ahead of print.

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### **Abstract**

The work of the Gulf War Illness (GWI) Consortium and that of basic and clinical researchers across the USA have resulted in a better understanding in recent years of the pathological basis of GWI, as well as of the mechanisms underlying the disorder. Among the most concerning symptoms suffered by veterans with GWI are cognitive decrements including those related to memory functioning. These decrements are not severe enough to meet dementia criteria, but there is significant concern that the mild cognitive impairment of these veterans will progress to dementia as they become older. Recent studies on GWI using human brain organoids as well as a rat model suggest that one potential cause of the cognitive problems may be elevated levels of tau in the brain, and this is supported by high levels of tau autoantibodies in the blood of veterans with GWI. There is urgency in finding treatments and preventive strategies for these veterans before they progress to dementia, with added value in doing so because their current status may represent an early phase of tauopathy common to many neurodegenerative diseases.

## Yoga is effective for treating chronic pain in veterans with Gulf War Illness at long-term follow-up

BMC Complement Med Ther. 2023 Sep 13;23(1):319. doi: [10.1186/s12906-023-04145-y](https://doi.org/10.1186/s12906-023-04145-y).

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### Abstract

**Background:** Clinical Practice Guidelines for Gulf War Illness (GWI) recommend integrative health approaches such as yoga for relief from symptoms, yet little is known about the long-term efficacy of yoga in reducing symptoms of GWI. Here, we evaluated the long-term efficacy of yoga and cognitive-behavioral therapy (CBT) chronic pain treatment in a randomized controlled trial (RCT) of 75 Veterans (57 men, 42-71 ± 7.1 years of age) with Gulf War Illness (GWI).

**Methods:** Participants received either 10 weeks of yoga or 10 weeks of CBT for chronic pain. The primary outcome measures were pain severity, and pain interference (Brief Pain Inventory-Short Form). The secondary outcome measures were fatigue, as indicated by a measure of functional exercise capacity (6-Minute Walk Test), depression, autonomic symptom severity, and quality of life. Piecewise linear mixed models were used to examine study hypotheses.

**Results:** Compared to the CBT group, yoga was associated with greater reductions in pain severity during the 6-month follow-up period (group × time interaction:  $b = 0.036$ ,  $se = 0.014$ ,  $p = .011$ ). Although we did not find between-group differences in the other primary or secondary outcome measures during follow-up ( $p$ 's > 0.05), exploratory analyses revealed within-group improvements in pain interference, total pain (an experimental outcome variable which combines pain severity and interference), and fatigue in the yoga group ( $p$ 's < 0.05) but not in the CBT group.

**Conclusions:** This is the first study to report long-term follow-up results of yoga as a treatment for GWI. Our results suggest that yoga may offer long-term efficacy in reducing pain, which is a core symptom of GWI.