# Research Advisory Committee on Gulf War Veterans' Illnesses (RACGWVI) — PubMed Research Citations for January, February, March 2024

Prepared by Staff of the RACGWVI.

**RACGWVI: Gulf War Illness — PubMed Citations for Jan, Feb, March 2024**

The following is a list of published research projects that focus on Gulf War Illness (GWI) for the months of January, February and March 2024.

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## Dry eye symptoms and signs in United States Gulf War era veterans with myalgic encephalomyelitis/chronic fatigue syndrome

Clin Exp Ophthalmol. 2024 Jan-Feb;52(1):10-21. doi: 10.1111/ceo.14313. Epub 2023 Nov 12.

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### Abstract

**Background:** To examine ocular symptoms and signs of veterans with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) diagnosis, ME/CFS symptoms, and controls.

**Methods:** This was a prospective, cross-sectional study of 124 South Florida veterans in active duty during the Gulf War era. Participants were recruited at an ophthalmology clinic at the Miami Veterans Affairs Hospital and evaluated for a diagnosis of ME/CFS, or symptoms of ME/CFS (intermediate fatigue, IF) using the Canadian Consensus criteria. Ocular symptoms were assessed via standardised questionnaires and signs via comprehensive slit lamp examination. Inflammatory blood markers were analysed and compared across groups.

**Results:** Mean age was 55.1 ± 4.7 years, 88.7% identified as male, 58.1% as White, and 39.5% as Hispanic. Ocular symptoms were more severe in the ME/CFS (n = 32) and IF (n = 48) groups compared to controls (n = 44) across dry eye (DE; Ocular Surface Disease Index [OSDI]: 48.9 ± 22.3 vs. 38.8 ± 23.3 vs. 19.1 ± 17.8, $p < 0.001$; 5 item Dry Eye Questionnaire [DEQ-5]: 10.8 ± 3.9 vs. 10.0 ± 4.6 vs. 6.6 ± 4.2, $p < 0.001$) and pain-specific questionnaires (Numerical Rating Scale 1-10 [NRS] right now: 2.4 ± 2.8 vs. 2.4 ± 2.9 vs 0.9 ± 1.5; $p = 0.007$; Neuropathic Pain Symptom Inventory modified for the Eye [NPSI-E]: 23.0 ± 18.6 vs. 19.8 ± 19.1 vs. 6.5 ± 9.0, $p < 0.001$). Ocular surface parameters and blood markers of inflammation were generally similar across groups.

**Conclusion:** Individuals with ME/CFS report increased ocular pain but similar DE signs, suggesting that mechanisms beyond the ocular surface contribute to symptoms.

## Experiential Avoidance, Pain, and Suicide Risk in a National Sample of Gulf War Veterans

Arch Suicide Res. 2024 Jan-Mar;28(1):295-309. doi: 10.1080/13811118.2022.2160681. Epub 2022 Dec 26.

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**Abstract**

**Objective:** Pain confers risk for suicidal thoughts and behaviors. Experiential avoidance (EA), which is relevant to both pain and suicide risk, has not been studied as a potential mechanism for this relationship. The present study tested the hypothesis that pain indirectly impacts suicide risk through EA in a national sample of Gulf War veterans.

**Methods:** Participants included a stratified random sample of United States veterans (N = 1,012, 78% male) who had served in the Gulf War region between August 1990 and July 1991. Validated scales were used to quantify levels of pain, EA, and suicide risk.

**Results:** Regression analyses indicated independent associations between pain, EA, and suicide risk; moreover, the association between pain and suicide risk was no longer significant once EA was included in model. Bootstrapping analyses confirmed that EA partially accounted for the cross-sectional association between pain and suicide risk, independent of common co-occurring problems, such as depression, PTSD, and alcohol use disorder symptoms.

**Conclusions:** EA could be a key modifiable risk factor to target in people experiencing pain.

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

Cytoskeleton (Hoboken). 2024 Jan;81(1):41-46. doi: 10.1002/cm.21786. Epub 2023 Sep 13.

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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.

## Effects of a diet low in excitotoxins on PTSD symptoms and related biomarkers

Nutr Neurosci. 2024 Jan;27(1):1-11. doi: 10.1080/1028415X.2022.2152932. Epub 2022 Dec 9.

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### Abstract

Post-traumatic stress disorder (PTSD) develops after trauma exposure and involves symptoms of avoidance, intrusive re-experiencing, mood and cognitive dysfunction, and hypervigilance. PTSD is often comorbid with Gulf War Illness (GWI), a neurological condition involving widespread pain, cognitive dysfunction, digestive problems, and other symptoms, in Gulf War veterans. PTSD tends to be more severe when comorbid with GWI. Low cortisol and elevated homocysteine levels have been found in PTSD, making them potential PTSD biomarkers. The low-glutamate diet, which aims to reduce excitotoxicity by eliminating the consumption of free glutamate and aspartate, has been shown to significantly reduce GWI and PTSD symptoms. This study examined whether changes in serum cortisol and homocysteine are associated with reduced PTSD severity in veterans with GWI after one month on the low-glutamate diet, and whether reducing the consumption of dietary excitotoxins was associated changes in PTSD and serum biomarkers. Data were analyzed for 33 veterans. No serum biomarkers significantly changed post-diet; however, cortisol increased as dietary excitotoxin consumption decreased, which held in a multivariable linear regression after adjustment for sex. Reduced dietary excitotoxin consumption was also associated with reduced hyperarousal symptoms, which held in a multivariable linear regression after adjustment for sex. Cortisol increase was associated with reduced avoidance symptoms after adjustment for change in BMI, and was marginally associated with overall PTSD reduction. Change in homocysteine was not significantly related to dietary adherence nor change in PTSD. Results suggest that reducing the consumption of dietary excitotoxins may normalize cortisol levels, which has been associated with alleviating PTSD.

## Disentangling the effects of PTSD from Gulf War Illness in male veterans via a systems-wide analysis of immune cell, cytokine, and symptom measures

Mil Med Res. 2024 Jan 2;11(1):2. doi: 10.1186/s40779-023-00505-4.

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### Abstract

**Background:** One-third of veterans returning from the 1990-1991 Gulf War reported a myriad of symptoms including cognitive dysfunction, skin rashes, musculoskeletal discomfort, and fatigue. This symptom cluster is now referred to as Gulf War Illness (GWI). As the underlying mechanisms of GWI have yet to be fully elucidated, diagnosis and treatment are based on symptomatic presentation. One confounding factor tied to the illness is the high presence of post-traumatic stress disorder (PTSD). Previous research efforts have demonstrated that both GWI and PTSD are associated with immunological dysfunction. As such, this research endeavor aimed to provide insight into the complex relationship between GWI symptoms, cytokine presence, and immune cell populations to pinpoint the impact of PTSD on these measures in GWI.

**Methods:** Symptom measures were gathered through the Multidimensional fatigue inventory (MFI) and 36-item short form health survey (SF-36) scales and biological measures were obtained through cytokine & cytometry analysis. Subgrouping was conducted using Davidson Trauma Scale scores and the Structured Clinical Interview for Diagnostic and statistical manual of mental disorders (DSM)-5, into GWI with high probability of PTSD symptoms (GWIH) and GWI with low probability of PTSD symptoms (GWIL). Data was analyzed using Analysis of variance (ANOVA) statistical analysis along with correlation graph analysis. We mapped correlations between immune cells and cytokine signaling measures, hormones and GWI symptom measures to identify patterns in regulation between the GWIH, GWIL, and healthy control groups.

**Results:** GWI with comorbid PTSD symptoms resulted in poorer health outcomes compared with both Healthy control (HC) and the GWIL subgroup. Significant differences were found in basophil levels of GWI compared with HC at peak exercise regardless of PTSD symptom comorbidity (ANOVA $F = 4.7$, $P = 0.01$,) indicating its potential usage as a biomarker for general GWI from control. While the unique identification of GWI with PTSD symptoms was less clear, the GWIL subgroup was found to be delineated from both GWIH and HC on measures of IL-15 across an exercise challenge (ANOVA $F > 3.75$, $P < 0.03$). Additional differences in natural killer (NK) cell

numbers and function highlight IL-15 as a potential biomarker of GWI in the absence of PTSD symptoms.

**Conclusion:** We conclude that disentangling GWI and PTSD by defining trauma-based subgroups may aid in the identification of unique GWI biosignatures that can help to improve diagnosis and target treatment of GWI more effectively.

## The Million Veteran Program 1990-1991 Gulf War Era Survey: An Evaluation of Veteran Response, Characteristics, and Representativeness of the Gulf War Era Veteran Population

Int J Environ Res Public Health. 2024 Jan 8;21(1):72. doi: 10.3390/ijerph21010072.

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### Abstract

To address gaps in understanding the pathophysiology of Gulf War Illness (GWI), the VA Million Veteran Program (MVP) developed and implemented a survey to MVP enrollees who served in the U.S. military during the 1990-1991 Persian Gulf War (GW). Eligible Veterans were invited via mail to complete a survey assessing health conditions as well as GW-specific deployment characteristics and exposures. We evaluated the representativeness of this GW-era cohort relative to the broader population by comparing demographic, military, and health characteristics between respondents and non-respondents, as well as with all GW-era Veterans who have used Veterans Health Administration (VHA) services and the full population of U.S. GW-deployed Veterans. A total of 109,976 MVP GW-era Veterans were invited to participate and 45,270 (41%) returned a completed survey. Respondents were 84% male, 72% White, 8% Hispanic, with a mean age of 61.6 years (SD = 8.5). Respondents were more likely to be older, White, married, better educated, slightly healthier, and have higher socioeconomic status than non-respondents, but reported similar medical conditions and comparable health status. Although generally similar to all GW-era Veterans using VHA services and the full population of U.S. GW Veterans, respondents included higher proportions of women and military officers, and were slightly older. In conclusion, sample

characteristics of the MVP GW-era cohort can be considered generally representative of the broader GW-era Veteran population. The sample represents the largest research cohort of GW-era Veterans established to date and provides a uniquely valuable resource for conducting in-depth studies to evaluate health conditions affecting 1990-1991 GW-era Veterans.

## The role of the brainstem in sleep disturbances and chronic pain of Gulf War and Iraq/Afghanistan veterans

Front Mol Neurosci. 2024 Jan 8:16:1266408. doi: 10.3389/fnmol.2023.1266408. eCollection 2023.

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**Abstract**

**Introduction:** Gulf War Illness is a type of chronic multisymptom illness, that affects about 30% of veterans deployed to the 1990-91 Persian Gulf War. Veterans deployed to Iraq/Afghanistan after 2000 are reported to have a similar prevalence of chronic multisymptom illness. More than 30 years after the Persian Gulf War, Gulf War Illness still has an unexplained symptom complex, unknown etiology and lacks definitive diagnostic criteria and effective treatments. Our recent studies have found that substantially smaller brainstem volumes and lower fiber integrity are associated with increased sleep difficulty and pain intensity in 1990-91 Persian Gulf War veterans. This study was conducted to investigate whether veterans deployed to Iraq/Afghanistan present similar brainstem damage, and whether such brainstem structural differences are associated with major symptoms as in Gulf War Illness.

**Methods:** Here, we used structural magnetic resonance imaging and diffusion tensor imaging to measure the volumes of subcortices, brainstem subregions and white matter integrity of brainstem fiber tracts in 188 veterans including 98 Persian Gulf War veterans and 90 Iraq/Afghanistan veterans.

**Results:** We found that compared to healthy controls, veterans of both campaigns presented with substantially smaller volumes in brainstem subregions, accompanied by greater periaqueductal gray matter volumes. We also found that all veterans had reduced integrity in the brainstem-spinal cord tracts and the brainstem-subcortical tracts. In veterans deployed during the 1990-91 Persian Gulf War, we found that brainstem structural deficits significantly correlated with increased sleep difficulties and pain intensities, but in veterans deployed to Iraq/Afghanistan, no such effect was observed.

**Discussion:** These structural differences in the brainstem neurons and tracts may reflect autonomic dysregulation corresponding to the symptom constellation, which is characteristic of Gulf War Illness. Understanding these neuroimaging and neuropathological relationships in Gulf War and Iraq/Afghanistan veterans may improve clinical management and treatment strategies for modern war related chronic multisymptom illness.

## Susceptibility to radiation adverse effects in veterans with Gulf War illness and healthy civilians

Sci Rep. 2024 Jan 9;14(1):874. doi: 10.1038/s41598-023-50083-7.

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### Abstract

We evaluated whether veterans with Gulf War illness (VGWI) report greater ionizing radiation adverse effects (RadAEs) than controls; whether radiation-sensitivity is tied to reported chemical-sensitivity; and whether environmental exposures are apparent risk factors for reported RadAEs (rRadAEs). 81 participants (41 VGWI, 40 controls) rated exposure to, and rRadAEs from, four radiation types. The relations of RadAE-propensity (defined as the ratio of rRadAEs to summed radiation exposures) to Gulf War illness (GWI) presence and severity, and to reported chemical-sensitivity were assessed. Ordinal logistic regression evaluated exposure prediction of RadAE-propensity in the full sample, in VGWI, and stratified by age and chemical-sensitivity. RadAE-propensity was increased in VGWI (vs. controls) and related to GWI severity ($p < 0.01$) and chemical-sensitivity ($p < 0.01$). Past carbon monoxide (CO) exposure emerged as a strong, robust predictor of RadAE-propensity on univariable and multivariable analyses ($p < 0.001$ on multivariable assessment, without and with adjustment for VGWI case status), retaining significance in age-stratified and chemical-sensitivity-stratified replication analyses. Thus, RadAE-propensity, a newly-described GWI-feature, relates to chemical-sensitivity, and is predicted by CO exposure-both features reported for nonionizing radiation sensitivity, consistent with shared mitochondrial/oxidative toxicity across radiation frequencies. Greater RadAE vulnerability fits an emerging picture of heightened drug/chemical susceptibility in VGWI.

## Frontotemporal disorders: the expansive panoply of syndromes and spectrum of etiologies

Front Neurol. 2024 Jan 9:14:1305071. doi: 10.3389/fneur.2023.1305071. eCollection 2023.

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**Abstract**

**Background:** Frontotemporal lobe disorders (FTD) are amongst the most common brain neurodegenerative disorders. Their relatively covert, frequently subtle presentations and diverse etiologies, pose major challenges in diagnosis and treatments. Recent studies have yielded insights that the etiology in the majority are due to environmental and sporadic causes, rather than genetic in origin.

**Aims:** To retrospectively examine the cognitive and behavioral impairments in the veteran population to garner the range of differing syndrome presentations and etiological subcategories with a specific focus on frontotemporal lobe disorders.

**Methodology:** The design is a retrospective, observational registry, case series with the collection of epidemiological, clinical, cognitive, laboratory and radiological data on people with cognitive and behavioral disorders. Inclusion criteria for entry were veterans evaluated exclusively at Orlando VA Healthcare System, neurology section, receiving a diagnosis of FTD by standard criteria, during the observation period dated from July 2016 to March 2021. Frontotemporal disorders (FTD) were delineated into five clinical 5 subtypes. Demographic, cardiovascular risk factors, cognitive, behavioral neurological, neuroimaging data and presumed etiological categories, were collected for those with a diagnosis of frontotemporal disorder.

**Results:** Of the 200 patients with FTD, further cognitive, behavioral neurological evaluation with standardized, metric testing was possible in 105 patients. Analysis of the etiological groups revealed significantly different younger age of the traumatic brain injury (TBI) and Gulf War Illness (GWI) veterans who also had higher Montreal Cognitive Assessment (MOCA) scores. The TBI group also had significantly more abnormalities of hypometabolism, noted on the PET brain scans. Behavioral neurological testing was notable for the findings that once a frontotemporal disorder had been diagnosed, the four different etiological groups consistently had abnormal FRSBE scores for the 3 principal frontal presentations of (i) abulia/apathy, (ii) disinhibition, and (iii) executive dysfunction as well as abnormal Frontal Behavioral Inventory (FBI) scores with no significant difference amongst the etiological groups. The most common sub-syndromes associated with frontotemporal syndromes were the Geschwind-Gastaut syndrome (GGS), Klüver-Bucy syndrome (KBS), involuntary emotional expression disorder (IEED), cerebellar cognitive affective syndrome (CCA), traumatic encephalopathy syndrome (TES) and prosopagnosia. Comparisons with the three principal frontal lobe syndrome clusters (abulia, disinhibition, executive dysfunction) revealed a significant association with abnormal disinhibition FRSBE T-scores with the GGS. The regression analysis supported the potential contribution of disinhibition behavior that related to this complex, relatively common behavioral syndrome in this series. The less common subsyndromes in particular, were notable, as they constituted the initial overriding, presenting symptoms and syndromes characterized into 16 separate conditions.

**Conclusion:** By deconstructing FTD into the multiple sub-syndromes and differing etiologies, this study may provide foundational insights, enabling a more targeted precision medicine approach for future studies, both in treating the sub-syndromes as well as the underlying etiological process.

## Gulf War illness with or without post-traumatic stress disorder: differential symptoms and immune responses

Mil Med Res. 2024 Jan 12;11(1):5. doi: 10.1186/s40779-023-00508-1.

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**No abstract available**

## Gulf War toxicant-induced reductions in dendritic arbors and spine densities of dentate granule cells are improved by treatment with a Nrf2 activator

Brain Res. 2024 Jan 15:1823:148682. doi: 10.1016/j.brainres.2023.148682. Epub 2023 Nov 19.

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### Abstract

Gulf War Illness (GWI) is a chronic multi-symptom disorder affecting approximately 30 % of Veterans deployed to the Persian Gulf from 1990 to 91. GWI encompasses a wide spectrum of symptoms which frequently include neurological problems such as learning and memory impairments, mood disorders, and an increased incidence of neurodegenerative disorders. Combined exposure to both reversible and irreversible acetylcholinesterase (AChE) inhibitors has been identified as a likely risk factor for GWI. It is possible that the exposures affected connectivity in the brain, and it was also unknown whether this could benefit from treatment. We assessed chronic changes in dendritic architecture in granule cells of the dentate gyrus following exposure to pyridostigmine bromide (PB, 0.7 mg/kg), chlorpyrifos (CPF, 12.5 mg/kg), and N,N-diethyl-m-toluamide (DEET, 7.5 mg/kg) in male C57Bl/6J mice. We also evaluated the therapeutic effects of dietary administration for eight weeks of 1 % tert-butylhydroquinone (tBHQ), a Nrf2 activator, on long-term neuronal morphology. We found that Gulf War toxicant exposure resulted in reduced dendritic length and branching as well as overall spine density in dentate granule cells at 14 weeks post-exposure and that these effects were ameliorated by treatment with tBHQ. These findings indicate that Gulf War toxicant exposure results in chronic changes to dentate granule cell morphology and that modulation of neuroprotective transcription factors such as Nrf2 may improve long-term neuronal health in the hippocampus.

## Ketamine Produces Antidepressant Effects by Inhibiting Histone Deacetylases and Upregulating Hippocampal Brain-Derived Neurotrophic Factor Levels in a Diisopropyl Fluorophosphate-Based Rat Model of Gulf War Illness

J Pharmacol Exp Ther. 2024 Jan 17;388(2):647-654. doi: 10.1124/jpet.123.001824.

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### Abstract

Approximately one-third of Gulf War veterans suffer from Gulf War Illness (GWI), which encompasses mood disorders and depressive symptoms. Deployment-related exposure to organophosphate compounds has been associated with GWI development. Epigenetic modifications have been reported in GWI veterans. We previously showed that epigenetic histone dysregulations were associated with decreased brain-derived neurotrophic factor (BDNF) expression in a GWI rat model. GWI has no effective therapies. Ketamine (KET) has recently been approved by the Food and Drug Administration for therapy-resistant depression. Interestingly, BDNF upregulation underlies KET's antidepressant effect in GWI-related depression. Here, we investigated whether KET's effect on histone mechanisms signals BDNF upregulations in GWI. Male Sprague-Dawley rats were injected once daily with diisopropyl fluorophosphate (DFP; 0.5 mg/kg, s.c., 5 days). At 6 months following DFP exposure, KET (10 mg/kg, i.p.) was injected, and brains were dissected 24 hours later. Western blotting was used for protein expression, and epigenetic studies used chromatin immunoprecipitation methods. Dil staining was conducted for assessing dendritic spines. Our results indicated that an antidepressant dose of KET inhibited the upregulation of histone deacetylase (HDAC) enzymes in DFP rats. Furthermore, KET restored acetylated histone occupancy at the Bdnf promoter IV and induced BDNF protein expression in DFP rats. Finally, KET treatment also increased the spine density and altered the spine diversity with increased T-type and decreased S-type spines in DFP rats. Given these findings, we propose that KET's actions involve the inhibition of HDAC expression, upregulation of BDNF, and dendritic modifications that together ameliorates the pathologic synaptic plasticity and exerts an antidepressant effect in DFP rats. SIGNIFICANCE STATEMENT: This study offers evidence supporting the involvement of epigenetic histone pathways in the antidepressant effects of ketamine (KET) in a rat model of Gulf War Illness (GWI)-like depression. This effect is achieved through the modulation of histone acetylation at the Bdnf promoter, resulting in elevated brain-derived neurotrophic factor expression and subsequent dendritic remodeling in the hippocampus. These findings underscore the rationale for considering KET as a potential candidate for clinical trials aimed at managing GWI-related depression.

## The prevalence of mild cognitive impairment in Gulf War veterans: a follow-up study

Front Neurosci. 2024 Jan 22:17:1301066. doi: 10.3389/fnins.2023.1301066. eCollection 2023.

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**Abstract**

**Introduction:** Gulf War Illness (GWI), also called Chronic Multisymptom Illness (CMI), is a multi-faceted condition that plagues an estimated 250,000 Gulf War (GW) veterans. Symptoms of GWI/CMI include fatigue, pain, and cognitive dysfunction. We previously reported that 12% of a convenience sample of middle aged (median age 52 years) GW veterans met criteria for mild cognitive impairment (MCI), a clinical syndrome most prevalent in older adults (e.g., ≥70 years). The current study sought to replicate and extend this finding.

**Methods:** We used the actuarial neuropsychological criteria and the Montreal Cognitive Assessment (MoCA) to assess the cognitive status of 952 GW veterans. We also examined regional brain volumes in a subset of GW veterans (n = 368) who had three Tesla magnetic resonance images (MRIs).

**Results:** We replicated our previous finding of a greater than 10% rate of MCI in four additional cohorts of GW veterans. In the combined sample of 952 GW veterans (median age 51 years at time of cognitive testing), 17% met criteria for MCI. Veterans classified as MCI were more likely to have CMI, history of depression, and prolonged (≥31 days) deployment-related exposures to smoke from oil well fires and chemical nerve agents compared to veterans with unimpaired and intermediate cognitive status. We also replicated our previous finding of hippocampal atrophy in veterans with MCI, and found significant group differences in lateral ventricle volumes.

**Discussion:** Because MCI increases the risk for late-life dementia and impacts quality of life, it may be prudent to counsel GW veterans with cognitive dysfunction, CMI, history of depression, and high levels of exposures to deployment-related toxicants to adopt lifestyle habits that have been associated with lowering dementia risk. With the Food and Drug Administration's recent approval of and the VA's decision to cover the cost for anti-amyloid β (Aβ) therapies, a logical next step for this research is to determine if GW veterans with MCI have elevated Aβ in their brains.

## Mental health treatment utilization among Gulf War era veterans with probable alcohol use disorder

J Subst Use Addict Treat. 2024 Jan 24:160:209295. doi: 10.1016/j.josat.2024.209295. Online ahead of print.

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**Abstract**

**Introduction:** Alcohol use disorder (AUD) is prevalent among veterans, and excessive alcohol use is associated with significant mental and physical health consequences. Currently, the largest cohort of veterans seeking services at the VA are those from the 1990s Gulf War Era. This cohort of veterans is unique due to the nature of their deployment resulting in a myriad of unexplained symptoms collectively known as "Gulf War Illness" and higher rates of mental health problems. The present study sought to examine the association between probable AUD and mental health treatment utilization in a sample of 1126 (882 male) Gulf War-era veterans.

**Methods:** Veterans completed a self-report survey including the AUDIT-C, questions about mental health treatment engagement, and demographic questions.

**Results:** Results demonstrated that approximately 20 % of the sample screened positive for probable AUD, determined by standard AUDIT-C cutoff scores. Among those screening positive for AUD, 25 % reported engaging in mental health treatment in the past year. Veterans with probable AUD who use VA care had 3.8 times the odds of receiving mental health services than veterans not using VA care. Use of mental health services was associated with mental health comorbidity and identifying as Black/African American.

**Conclusions:** The results of the present study highlight a significant unmet need for mental health treatment among Gulf War-era veterans with AUD.

## Olfactory and cognitive decrements in 1991 Gulf War veterans with gulf war illness/chronic multisymptom illness

Environ Health. 2024 Jan 30;23(1):14. doi: 10.1186/s12940-024-01058-2.

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### Abstract

**Background:** Gulf War illness (GWI)/Chronic Multisymptom Illness (CMI) is a disorder related to military service in the 1991 Gulf War (GW). Prominent symptoms of GWI/CMI include fatigue, pain, and cognitive dysfunction. Although anosmia is not a typical GWI/CMI symptom, anecdotally some GW veterans have reported losing their sense smell shortly after the war. Because olfactory deficit is a prodromal symptom of neurodegenerative diseases like Parkinson's and Alzheimer's disease, and because we previously reported suggestive evidence that deployed GW veterans may be at increased risk for Mild Cognitive Impairment (MCI) and dementia, the current study examined the relationship between olfactory and cognitive function in deployed GW veterans.

**Methods:** Eighty deployed GW veterans (mean age: 59.9 ±7.0; 4 female) were tested remotely with the University of Pennsylvania Smell Identification Test (UPSIT) and the Montreal Cognitive Assessment (MoCA). Veterans also completed self-report questionnaires about their health and deployment-related exposures and experiences. UPSIT and MoCA data from healthy control (HC) participants from the Parkinson's Progression Markers Initiative (PPMI) study were downloaded for comparison.

**Results:** GW veterans had a mean UPSIT score of 27.8 ± 6.3 (range 9-37) and a mean MoCA score of 25.3 ± 2.8 (range 19-30). According to age- and sex-specific normative data, 31% of GW veterans (vs. 8% PPMI HCs) had UPSIT scores below the 10th percentile. Nearly half (45%) of GW veterans (vs. 8% PPMI HCs) had MoCA scores below the cut-off for identifying MCI. Among GW veterans, but not PPMI HCs, there was a positive correlation between UPSIT and MoCA scores (Spearman's $\rho = 0.39$, $p < 0.001$). There were no significant differences in UPSIT or MoCA scores between GW veterans with and without history of COVID or between those with and without Kansas GWI exclusionary conditions.

**Conclusions:** We found evidence of olfactory and cognitive deficits and a significant correlation between UPSIT and MoCA scores in a cohort of 80 deployed GW veterans, 99% of whom had CMI. Because impaired olfactory function has been associated with increased risk for MCI and dementia, it may be prudent to screen aging, deployed GW veterans with smell identification tests so that hypo- and anosmic veterans can be followed longitudinally and offered targeted neuroprotective therapies as they become available.

## Veteran Beliefs About the Causes of Gulf War Illness and Expectations for Improvement

Int J Behav Med. 2024 Feb;31(1):169-174. doi: 10.1007/s12529-023-10166-1. Epub 2023 Mar 27.

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### Abstract

**Background:** Individuals' beliefs about the etiology of persistent physical symptoms (PPS) are linked to differences in coping style. However, it is unclear which attributions are related to greater expectations for improvement.

**Method and results:** A cross-sectional regression analysis (N = 262) indicated that Veterans with Gulf War Illness (GWI) who attributed their GWI to behavior, (e.g., diet and exercise), had greater expectations for improvement (p = .001) than those who attributed their GWI to deployment, physical, or psychological causes (p values > .05).

**Conclusions:** Findings support the possible clinical utility of exploring perceived contributing factors of PPS, which may increase perceptions that improvement of PPS is possible.

**Trial registration:** ClinicalTrials.gov Identifier: NCT02161133.

## Military exposures and Gulf War illness in veterans with and without posttraumatic stress disorder

J Trauma Stress. 2024 Feb;37(1):80-91. doi: 10.1002/jts.22994. Epub 2023 Nov 23.

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### Abstract

Gulf War illness (GWI) is a chronic multisymptom disorder of unknown etiology that is believed to be caused by neurotoxicant exposure experienced during deployment to the Gulf War. Posttraumatic stress disorder (PTSD) covaries with GWI and is believed to play a role in GWI symptoms. The present study examined the association between self-reported military exposures and GWI, stratified by PTSD status, in veterans from the Gulf War Era Cohort and Biorepository who were deployed to the Persian Gulf during the war. Participants self-reported current GWI and PTSD symptoms as well as military exposures (e.g., pyridostigmine [PB] pills, pesticides/insecticides, combat, chemical attacks, and oil well fires) experienced during the Gulf War. Deployed veterans' (N = 921) GWI status was ascertained using the Centers for Disease Control and Prevention definition. Individuals who met the GWI criteria were stratified by PTSD status, yielding three groups: GWI-, GWI+/PTSD-, and GWI+/PTSD+. Multivariable logistic regression, adjusted for covariates, was used to examine associations between GWI/PTSD groups and military exposures. Apart from insect bait use, the GWI+/PTSD+ group had higher odds of reporting military exposures than the GWI+/PTSD- group, adjusted odds ratio (aOR) = 2.15, 95% CI [1.30, 3.56]-aOR = 6.91, 95% CI [3.39, 14.08]. Except for PB pills, the GWI+/PTSD- group had a higher likelihood of reporting military exposures than the GWI- group, aOR = 2.03, 95% CI [1.26, 3.26]-aOR = 4.01, 95% CI [1.57, 10.25]. These findings are consistent with roles for both PTSD and military exposures in the etiology of GWI.

## Cohort Differences in PTSD Symptoms and Military Experiences: A Life Course Perspective

Gerontologist. 2024 Feb 1;64(2):gnad129. doi: 10.1093/geront/gnad129.

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### Abstract

**Background and objectives:** There have been major changes in military service over the past 50 years. Most research on posttraumatic stress disorder (PTSD) among combat Veterans comes from help-seeking Vietnam and WWII cohorts; results from more recent cohort comparisons are mixed. The present study addressed these gaps by exploring cohort differences among Vietnam, Persian Gulf, and Post-9/11 combat Veterans from a life course perspective.

**Research design and methods:** We recruited community-dwelling combat and war zone Veterans (N = 167), primarily from Veterans' associations in Oregon from three cohorts: Vietnam, Persian Gulf, and Post-911. Online surveys assessed current PTSD symptoms, life course (demographics and cohort membership), and experiential variables (combat severity, appraisals of military service, homecoming, and social support).

**Results:** Cohorts were comparable in demographics and war experiences. Step one of a hierarchical regression found that PTSD symptoms were higher among Veterans of color and those with lower incomes, $R2 = 0.37$, $p < .001$. When cohort was added, Vietnam Veterans had higher symptoms than Post-9/11; income and race/ethnicity remained significant, $\Delta R2 = 0.01$, $p = .13$. The final model added experiential variables, $\Delta R2 = 0.38$, $p < .001$; cohort and income were no longer significant, although Veterans of color still reported higher symptoms. Those with more undesirable service appraisals and who sought social support had higher symptoms, while desirable appraisals were protective.

**Discussion and implications:** From a life course perspective, the particular war zone that Veterans served in was less important than demographics and both service and postservice experiences, suggesting generalizability of risk and protective factors, as well as treatment modalities, across cohorts.

## Anthrax Vaccines in the 21st Century

Vaccines (Basel). 2024 Feb 3;12(2):159. doi: 10.3390/vaccines12020159.

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### Abstract

Vaccination against Bacillus anthracis is the best preventive measure against the development of deadly anthrax disease in the event of exposure to anthrax either as a bioweapon or in its naturally occurring form. Anthrax vaccines, however, have historically been plagued with controversy, particularly related to their safety. Fortunately, recent improvements in anthrax vaccines have been shown to confer protection with reduced short-term safety concerns, although questions about long-term safety remain. Here, we (a) review recent and ongoing advances in anthrax vaccine development, (b) emphasize the need for thorough characterization of current (and future) vaccines, (c) bring to focus the importance of host immunogenetics as the ultimate determinant of successful antibody production and protection, and (d) discuss the need for the systematic, active, and targeted monitoring of vaccine recipients for possible Chronic Multisymptom Illness (CMI).

## Gulf war toxicant-induced effects on the hippocampal dendritic arbor are reversed by treatment with a Withania somnifera extract

Front Neurosci. 2024 Feb 21:18:1368667. doi: 10.3389/fnins.2024.1368667. eCollection 2024.

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### ABSTRACT

Gulf War Illness (GWI) is a multi-symptom disorder that manifests with fatigue, sleep disturbances, mood-cognition pathologies, and musculoskeletal symptoms. GWI affects at least 25% of the military personnel that served in Operations Desert Shield and Desert Storm from 1990 to 1991. We modeled Gulf War toxicant exposure in C57BL/6J mice by combined exposure to pyridostigmine bromide (an anti-sarin drug), chlorpyrifos (an organophosphate insecticide), and DEET (an insect repellent) for 10 days followed by oral treatment with Withania somnifera root extract for 21 days beginning at 12 weeks post-exposure. W. somnifera, commonly referred to as ashwagandha, has been used in traditional Ayurvedic medicine for centuries to improve memory and reduce inflammation, and its roots contain bioactive molecules which share functional groups with modern pain, cancer, and anti-inflammatory drugs. Previously, we observed that GWI mice displayed chronic reductions in dendritic arbor and loss of spines in granule cells of the dentate gyrus of the hippocampus at 14 weeks post-exposure. Here, we examined the effects of treatment with W. somnifera root extract on chronic dendrite and spine morphology in dentate granule cells of the mouse hippocampus following Gulf War toxicant exposure. GWI mice showed approximately 25% decreases in dendritic length ($p < 0.0001$) and overall dendritic spine density with significant reductions in thin and mushroom spines. GWI mice treated with the Ayurvedic W. somnifera extract exhibited dendritic lengths and spine densities near normal levels. These findings demonstrate the efficacy of the Ayurvedic treatment for neuroprotection following these toxic exposures. We hope that the extract and the neuronal processes influenced will open new avenues of research regarding treatment of Gulf War Illness and neurodegenerative disorders.

## Gulf war toxicant-induced effects on the hippocampal dendritic arbor are reversed by treatment with a Withania somnifera extract

Front Neurosci. 2024 Feb 21:18:1368667. doi: 10.3389/fnins.2024.1368667. eCollection 2024.

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### Abstract

Gulf War Illness (GWI) is a multi-symptom disorder that manifests with fatigue, sleep disturbances, mood-cognition pathologies, and musculoskeletal symptoms. GWI affects at least 25% of the military personnel that served in Operations Desert Shield and Desert Storm from 1990 to 1991. We modeled Gulf War toxicant exposure in C57BL/6J mice by combined exposure to pyridostigmine bromide (an anti-sarin drug), chlorpyrifos (an organophosphate insecticide), and DEET (an insect repellent) for 10 days followed by oral treatment with Withania somnifera root extract for 21 days beginning at 12 weeks post-exposure. W. somnifera, commonly referred to as ashwagandha, has been used in traditional Ayurvedic medicine for centuries to improve memory and reduce inflammation, and its roots contain bioactive molecules which share functional groups with modern pain, cancer, and anti-inflammatory drugs. Previously, we observed that GWI mice displayed chronic reductions in dendritic arbor and loss of spines in granule cells of the dentate gyrus of the hippocampus at 14 weeks post-exposure. Here, we examined the effects of treatment with W. somnifera root extract on chronic dendrite and spine morphology in dentate granule cells of the mouse hippocampus following Gulf War toxicant exposure. GWI mice showed approximately 25% decreases in dendritic length ($p < 0.0001$) and overall dendritic spine density with significant reductions in thin and mushroom spines. GWI mice treated with the Ayurvedic W. somnifera extract exhibited dendritic lengths and spine densities near normal levels. These findings demonstrate the efficacy of the Ayurvedic treatment for neuroprotection following these toxic exposures. We hope that the extract and the neuronal processes influenced will open new avenues of research regarding treatment of Gulf War Illness and neurodegenerative disorders.

## Improving care for veterans' environmental exposure concerns: applications of the consolidated framework for implementation research in program evaluation

BMC Health Serv Res. 2024 Feb 23;24(1):241. doi: 10.1186/s12913-024-10614-y.

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### Abstract

**Background:** Healthcare systems, like the US Department of Veterans Affairs (VA), need policies and procedures for delivering care to special populations including those with environmental exposure concerns. Despite being common and pervasive, especially among Veterans, environmental exposures are largely overlooked by healthcare providers. To successfully implement care for Veterans with military environmental exposure concerns, an understanding of contextual factors impeding care on the provider (e.g., knowledge and beliefs) and organizational (e.g., leadership's priorities) level is needed. Our goal was to conduct an operational needs assessment of providers to examine provider educational needs regarding Veterans' military environmental exposure concerns.

**Methods:** In 2020, we surveyed 2,775 VA medical and behavioral health providers. Our cross-sectional assessment was informed by the Consolidated Framework for Implementation Research (CFIR) and assessed barriers and facilitators to the uptake and application of knowledge regarding interdisciplinary care for environmental exposure concerns. The web-based survey was emailed to providers across the United States representing a variety of disciplines and practice settings to reflect the interdisciplinary approach to care for environmental exposures. We used bivariate statistics to investigate the intervention setting, inner setting, and individual characteristics of providers regarding care for environmental exposure concerns.

**Results:** Approximately one-third of VA medical and behavioral health clinicians report low to no knowledge of environmental exposure concerns. We find 88% of medical and 91% of behavioral health providers report they are ready to learn more about environmental exposures. Half of medical and behavioral health providers report they have access to information on environmental exposures and less than half report care for environmental exposures is a priority where they practice.

**Conclusions:** Our findings suggest interdisciplinary providers' knowledge of and discussion with Veterans about environmental exposures may be influenced by contextual factors at the organizational level. Considering individual-level factors and organizational culture is important to consider when supporting care for environmental exposures. Since this needs assessment, VA established targeted programs to improve care related to military environmental exposures in response to legislation; future exploration of these same variables or contextual factors is warranted.

## Predictors of Mortality in Veterans with Amyotrophic Lateral Sclerosis: Respiratory Status and Speech Disorder at Presentation

Med Sci Monit. 2024 Feb 27:30:e943288. doi: 10.12659/MSM.943288.

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### Abstract

**BACKGROUND** There is a lack of accurate models to predict amyotrophic lateral sclerosis (ALS) disease course and outcomes. As a result, risk assessment and counseling, the timing of interventions, and their stratification in clinical trials are difficult. This study aimed to evaluate the association between symptoms at presentation and mortality. MATERIAL AND METHODS A single veterans hospital reviewed the electronic records of 105 veterans with ALS who were periodically followed in our ALS clinic between 2010 and 2021. A survival decision tree (≤3 or >3 years) was generated based on the statistical median survival of our data. The variables known to influence survival when alive were compared to patients who died. RESULTS The (mean±SD) age at onset was 62±11 years, M/F ratio 101: 4, and 90% were non-Hispanic whites. The initial score for the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) was 31±8.3. Dysarthria and shortness of breath (SOB) were present on initial presentation in 52 (49.5%) and 32 (30.5%) patients, respectively. Deaths occurred in 80 (76.2%) patients during the study period. The main cause of death was respiratory disease (failure and pneumonia, n=43 53.75%). Patients survived for >3 years on initial presentation with normal respiration and speech, compared to ≤3 years of survival in patients with dysarthria and SOB, irrespective of age. CONCLUSIONS This study suggests that for veterans with ALS, the main predictors of shorter survival were respiratory status and speech disorder on initial presentation to the clinic.

## Migraine Prevalence, Environmental Risk, and Comorbidities in Men and Women Veterans

JAMA Netw Open. 2024 Mar 4;7(3):e242299. doi: 10.1001/jamanetworkopen.2024.2299.

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### Abstract

**Importance:** Migraine is a prevalent and debilitating condition that substantially impacts quality of life. Investigating migraine prevalence, associated comorbidities, and potential military service exposures in veterans, focusing on gender differences, is crucial for targeted interventions and management strategies.

**Objective:** To determine the prevalence of migraine, associated health comorbidities, and potential military service and environmental exposures among men and women US veterans using a large-scale epidemiological sample from the Million Veteran Program (MVP).

**Design, setting, and participants:** This cross-sectional study analyzed self-report survey data from the MVP, a large epidemiological sample of US veterans that was started in 2011 and has ongoing enrollment. Eligible participants were selected from the MVP database in 2023. The study included 491 604 veterans to examine migraine prevalence, health comorbidities, demographic characteristics, military service history, and environmental exposures. Data were analyzed from December 2022 to July 2023.

**Exposures:** Military service and environmental factors, such as chemical or biological warfare exposure, were considered.

**Main outcomes and measures:** The primary outcome was migraine prevalence among men and women veterans, assessed through self-reported diagnoses. Secondary outcomes included the association between migraine and health comorbidities, demographic characteristics, military service history, and environmental exposures.

**Results:** Of the 491 604 veterans included in this study, 450 625 (91.8%) were men and 40 979 (8.2%) were women. The lifetime prevalence of migraine was significantly higher in women (12 324 of 40 979 [30.1%]) than in men (36 816 of 450 625 [8.2%]). Migraine prevalence varied by race and ethnicity, with the highest prevalence in Hispanic or Latinx women (1213 of 3495 [34.7%]). Veterans with migraine reported worse general health, higher levels of pain, increased pain interference with work, a higher likelihood of psychiatric and neurological health conditions, and greater lifetime opioid use. Specific aspects of military service, including service post-September 2001 and deployment in Operation Enduring Freedom and Operation Iraqi Freedom, and environmental

factors, including Agent Orange, chemical and biological welfare, and antinerve agent pills history, were significantly associated with migraine prevalence.

**Conclusions and relevance:** In this cross-sectional study of migraine, the results highlighted gender differences in migraine prevalence and associated health comorbidities among US veterans. The findings emphasized the need for interdisciplinary approaches to migraine management, increased awareness and education efforts, and population-based screening strategies, particularly for women and Hispanic veterans who are at greater risk. Our findings encourage further research into tailored interventions for specific subpopulations and the impact of military service and environmental exposures on migraine and related health conditions.

## Prevalence of Burn Pit Associated Symptoms Among US Veterans Who Utilize Non-VA Private Healthcare

J Occup Environ Med. 2024 Mar 6. doi: 10.1097/JOM.0000000000003085. Online ahead of print.

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**Abstract**

**Objective:** Do the 3.5 million US veterans, who primarily utilize private healthcare, have similar burn pit exposure and disease compared to the VA Burn Pit registry.

**Methods:** Online volunteer survey of Gulf War and Post-9/11 veterans.

**Results:** Burn pit exposure had significantly higher odds of extremity numbness, aching pain and burning, asthma, COPD, interstitial lung disease, constrictive bronchiolitis, pleuritis, and pulmonary fibrosis. Chi-square did not reveal a difference in burn pit exposure and cancer diagnoses.

**Conclusions:** These data demonstrate increased risk of neurological symptoms associated with burn pit exposure, that are not covered in the 2022 federal Promise to Address Comprehensive Toxics (PACT) Act. Additional data will allow for the continued review and consideration for future medical benefits.

## Bioenergetic impairment in Gulf War illness assessed via 31P-MRS

Sci Rep. 2024 Mar 28;14(1):7418. doi: 10.1038/s41598-024-57725-4.

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### Abstract

Time for post-exercise phosphocreatine-recovery (PCr-R), deemed a robust index of mitochondrial function in vivo, was previously reported to be elevated (signifying impaired ATP production) in veterans with Gulf War illness (GWI). Here we sought to replicate the finding and assess the impact of contravening previous eligibility requirements. The replication sample comprised white males. Cases reported ≥ moderate muscle-weakness to match the organ assessed to an organ affected; controls lacked recent headache or multiple symptoms. The expansion sample added cases without muscle-weakness, controls with recent headache, females, nonwhites. PCr-R, following pedal-depression-exercise, was compared in veterans with GWI versus controls (sample N = 38). In the replication sample, PCr-R results closely matched the prior report: PCr-R veterans with GWI mean(SD) = 47.7(16.5); control mean(SD) = 30.3(9.2), p = 0.017. (Prior-study PCr-R veterans with GWI mean(SD) = 46.1(17.9), control mean(SD) = 29.0(8.7), p = 0.023. Combined replication + prior samples: p = 0.001.) No case-control difference was observed in the expansion sample. In cases, PCr-R related to muscle-weakness: PCr-R = 29.9(7.1), 38.2(8.9), 47.8(15.2) for muscle-weakness rated none/low, intermediate, and high respectively (p for trend = 0.02), validating desirability of matching tissue assessed to tissue affected. In controls, headache/multiple symptoms, sex, and ethnicity each mattered (affecting PCr-R significantly). This study affirms mitochondrial/bioenergetic impairment in veterans with GWI. The importance of careful case/control selection is underscored.

## Military environmental exposures and risk of breast cancer in active-duty personnel and veterans: a scoping review

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### Abstract

**Background:** The effects of military environmental exposures (MEE) such as volatile organic compounds (VOCs), endocrine-disrupting chemicals (EDCs), tactile herbicides, airborne hazards and open burn pits (AHOBP), and depleted uranium on health are salient concerns for service members and Veterans. However, little work has been done to investigate the relationship between MEE and risk of breast cancer.

**Data sources and methods:** We conducted a scoping review on MEE, military deployment/service, and risk of breast cancer among active-duty service members and Veterans. PRISMA was used. PubMed, Embase, and citations of included articles were searched, resulting in 4,364 articles to screen: 28 articles were included.

**Results:** Most papers on military deployment and military service found a lower/equivalent risk of breast cancer when comparing rates to those without deployment or civilians. Exposure to VOCs due to military occupation or contaminated groundwater was associated with a slightly higher risk of breast cancer. Exposure to Agent Orange was not associated with an increased risk of breast cancer. Evidence regarding EDCs was limited. No paper directly measured exposure to AHOBP or depleted uranium, but deployments with known exposures to AHOBP or depleted uranium were associated with an equivalent/lower risk of breast cancer.

**Conclusions:** Women are the fastest growing population within the military, and breast cancer poses a unique risk to women Veterans who were affected by MEE during their service. Unfortunately, the literature on MEE and breast cancer is mixed and limited, in part due to the Healthy Soldier Paradox and poor classification of exposure(s).

## Recent Research Trends in Neuroinflammatory and Neurodegenerative Disorders

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### Abstract

Neuroinflammatory and neurodegenerative disorders including Alzheimer's disease (AD), Parkinson's disease (PD), traumatic brain injury (TBI) and Amyotrophic lateral sclerosis (ALS) are chronic major health disorders. The exact mechanism of the neuroimmune dysfunctions of these disease pathogeneses is currently not clearly understood. These disorders show dysregulated neuroimmune and inflammatory responses, including activation of neurons, glial cells, and neurovascular unit damage associated with excessive release of proinflammatory cytokines, chemokines, neurotoxic mediators, and infiltration of peripheral immune cells into the brain, as well as entry of inflammatory mediators through damaged neurovascular endothelial cells, blood-brain barrier and tight junction proteins. Activation of glial cells and immune cells leads to the release of many inflammatory and neurotoxic molecules that cause neuroinflammation and neurodegeneration. Gulf War Illness (GWI) and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) are chronic disorders that are also associated with neuroimmune dysfunctions. Currently, there are no effective disease-modifying therapeutic options available for these diseases. Human induced pluripotent stem cell (iPSC)-derived neurons, astrocytes, microglia, endothelial cells and pericytes are currently used for many disease models for drug discovery. This review highlights certain recent trends in neuroinflammatory responses and iPSC-derived brain cell applications in neuroinflammatory disorders.