Research Advisory Committee on Gulf War Veterans' Illnesses (RACGWVI) — PubMed Research Citations for October, November, December 2023

Prepared by Staff of the RACGWVI

RACGWVI: Gulf War Illness — PubMed Citations for October, November, December 2023

The following is a list of published research projects that focus on Gulf War Illness (GWI) for the months of October, November, December 2023.

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

Brain Behav Immun. 2023 Oct:113:248-258. doi: 10.1016/j.bbi.2023.07.003. Epub 2023 Jul 10.

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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.

Association of Atherosclerotic Cardiovascular Disease, Hypertension, Diabetes, and Hyperlipidemia With Gulf War Illness Among Gulf War Veterans

J Am Heart Assoc. 2023 Oct 3;12(19):e029575. doi: 10.1161/JAHA.123.029575. Epub 2023 Sep 29.

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Abstract

Background Approximately 30% of the 700 000 Gulf War veterans report a chronic symptom-based illness of varying severity referred to as Gulf War illness (GWI). Toxic deployment-related exposures have been implicated in the cause of GWI, some of which contribute to metabolic dysregulation and lipid abnormalities. As this cohort ages, the relationship between GWI and atherosclerotic cardiovascular disease (ASCVD) is a growing concern. We evaluated associations between GWI and ASCVD, diabetes, hyperlipidemia, and hypertension in veterans of the Gulf War (1990-1991). Methods and Results Analysis of survey data collected in 2014 to 2016 from a national sample of deployed Gulf War veterans (n=942) and Veterans Health Administration electronic health record data (n=669). Multivariable logistic regression models tested for associations of GWI with self-reported ASCVD, diabetes, hyperlipidemia, and hypertension, controlling for confounding factors. Separate models tested for GWI associations with ASCVD and risk factors documented in the electronic health record. GWI was associated with self-reported hypertension (adjusted odds ratio [aOR], 1.67 [95% CI, 1.18-2.36]), hyperlipidemia (aOR, 1.46 [95% CI, 1.03-2.05]), and ASCVD (aOR, 2.65 [95% CI, 1.56-4.51]). In the subset of veterans with electronic health record data, GWI was associated with documented diabetes (aOR, 2.34 [95% CI, 1.43-3.82]) and hypertension (aOR, 2.84 [95% CI, 1.92-4.20]). Hyperlipidemia and hypertension served as partial mediators of the association between GWI and self-reported ASCVD. Conclusions Gulf War veterans with GWI had higher odds of hyperlipidemia, hypertension, diabetes, and ASCVD compared with Gulf War veterans without GWI. Further examination of the mechanisms underlying this association, including a possible shared exposure-related mechanism, is necessary.

Cognitive decrements in 1991 Gulf War veterans: associations with Gulf War illness and neurotoxicant exposures in the Boston Biorepository, Recruitment, and Integrative Network (BBRAIN) cohorts

Environ Health. 2023 Oct 4;22(1):68. doi: 10.1186/s12940-023-01018-2.

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Abstract

Background: During deployment, veterans of the 1991 Gulf War (GW) were exposed to multiple war-related toxicants. Roughly a third of these veterans continue to exhibit neurotoxicant induced symptoms of Gulf War Illness (GWI), a multi-faceted condition that includes fatigue, pain and cognitive decrements. When studied empirically, both deployed veterans with exposures and those who meet the criteria for GWI are more likely to show deficits in the area of neuropsychological functioning. Although studies have shown cognitive impairments in small sample sizes, it is necessary to revisit these findings with larger samples and newer cohorts to see if other areas of deficit emerge with more power to detect such differences. A group of researchers and clinicians with expertise in the area of GWI have identified common data elements (CDE) for use in research samples to compare data sets. At the same time, a subgroup of researchers created a new repository to share these cognitive data and biospecimens within the GWI research community.

Methods: The present study aimed to compare cognitive measures of attention, executive functioning, and verbal memory in a large sample of GWI cases and healthy GW veteran controls using neuropsychological tests recommended in the CDEs. We additionally subdivided samples based on the specific neurotoxicant exposures related to cognitive deficits and compared exposed versus non-exposed veterans regardless of case criteria status. The total sample utilized cognitive testing outcomes from the newly collated Boston, Biorepository, Recruitment, and Integrative Network (BBRAIN) for GWI.

Results: Participants included 411 GW veterans, 312 GWI (cases) and 99 healthy veterans (controls). Veterans with GWI showed significantly poorer attention, executive functioning, learning, and short-and-long term verbal memory than those without GWI. Further, GW veterans with exposures to acetylcholinesterase inhibiting pesticides and nerve gas agents, had worse performance on executive function tasks. Veterans with exposure to oil well fires had worse

performance on verbal memory and those with pyridostigmine bromide anti-nerve gas pill exposures had better verbal memory and worse performance on an attention task compared to unexposed veterans.

Conclusions: This study replicates prior results regarding the utility of the currently recommended CDEs in determining impairments in cognitive functioning in veterans with GWI in a new widely-available repository cohort and provides further evidence of cognitive decrements in GW veterans related to war-related neurotoxicant exposures.

First Annual PACT Act Research Symposium on Veterans Health: A Colorado PACT Act Collaboration (CoPAC) Initiative

Mil Med. 2023 Oct 13:usad391. doi: 10.1093/milmed/usad391. Online ahead of print.

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Abstract

In response to the Sergeant First Class Heath Robinson Honoring our Promise to Address Comprehensive Toxics (PACT) Act being signed into law, several research groups in Colorado organized the First Annual PACT Act Research Symposium for Veteran Health. The 2-day symposium was interested in research relevant to military exposures with a primary focus on respiratory and mental health. Information on the PACT Act, data sources in the Department of Veteran Affairs and DOD, and research opportunities at the Veteran Affairs were presented. The morning session centered on respiratory health, highlighting research conducted over the last two decades regarding deployment-related respiratory diseases. Despite the high prevalence of mental health disorders among Veterans, information presented during the afternoon sessions on mental health highlighted the dearth of research to date regarding psychological health and military-related exposures. Policymakers, clinicians, and researchers were encouraged to adopt a life-course approach when conceptualizing physical and psychological exposures. On the second day of meetings, a smaller group of participants discussed next steps in military exposure research, as well as priorities for future research. Per the latter, recommendations for future research were made

regarding the need for more precise exposure characterization, longitudinal data collection, and efforts to increase understanding regarding disease pathogenesis, as well as the impact of exposures across multiple organs. Such efforts will require interdisciplinary collaboration.

Ketamine produces antidepressant effects by inhibiting histone deacetylases and upregulating hippocampal BDNF levels in a DFP-based rat model of Gulf War Illness

J Pharmacol Exp Ther. 2023 Oct 20:JPET-AR-2023-001824. doi: 10.1124/jpet.123.001824. Online ahead of print.

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Abstract

Approximately one-third of Gulf War veterans suffer from Gulf War Illness (GWI), which encompass mood disorders and depressive symptoms. Deployment-related exposure to organophosphate (OP) 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 FDA 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 signal BDNF upregulations in GWI. Male Sprague-Dawley rats were injected once-daily with diisopropyl fluorophosphate (DFP, 0.5 mg/kg s.c., 5-d). At 6-m following DFP exposure, KET (10 mg/kg, i.p.) was injected and brains were dissected 24-h later. Western blotting was utilized for protein expression and epigenetic studies utilized chromatin immunoprecipitation methods. Dil staining was conducted for assessing dendritic spines. Our results indicated that an antidepressant dose of KET inhibited the upregulation of 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 involves the inhibition of HDAC expression, upregulation of BDNF, and dendritic modifications that together ameliorates the pathological synaptic plasticity and exerts an antidepressant effect in DFP rats. Significance Statement Our research 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 BDNF 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.

Nonsuicidal self-injury methods among U.S. Veterans: Latent class analysis and associations with psychosocial outcomes

Psychiatry Res. 2023 Nov:329:115558. doi: 10.1016/j.psychres.2023.115558. Epub 2023 Oct 22.

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Abstract

Nonsuicidal self-injury (NSSI) is a debilitating concern among U.S. veterans, with wall/object-punching commonly endorsed as an NSSI method. We examined how this behavior relates to other NSSI methods and psychosocial outcomes. We conducted a latent class analysis (LCA) of NSSI methods among 1,138 Gulf War Era veterans, (77.9% male), 21.7% of whom endorsed lifetime NSSI. We categorized classes based on their associations with age, sex, combat and military sexual assault exposure, then examined the association of class membership with psychosocial indicators. LCA results supported four classes: 1) High punching/banging NSSI (2.5%); 2) Multimethod NSSI methods (6.3%); 3) High-risk, multimethod NSSI (3.1%); and 4) Low-risk NSSI (88.1%). Psychosocial indicators (suicide attempt, ideation, possible depressive or posttraumatic stress disorders, poor psychosocial functioning) were worse for members of the NSSI classes versus those in the low-risk group. A subset of U.S. veterans may engage in NSSI primarily via punching/banging methods. All patterns of NSSI engagement were associated with negative psychosocial outcomes relative to those in the low-risk class of the behavior.

Neuropathological Outcomes of Traumatic Brain Injury and Alcohol Use in Males and Females: Studies Using Pre-Clinical Rodent and Clinical Human Specimens

J Neurotrauma. 2023 Nov;40(21-22):2410-2426. doi: 10.1089/neu.2023.0074. Epub 2023 Jul 26.

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Abstract

Traumatic brain injury (TBI) and alcohol misuse are inextricably linked and can increase the risk for development of neurodegenerative diseases, particularly in military veterans and contact sport athletes. Proteinopathy (defects in protein degradation) is considered an underlying factor in neurodegenerative diseases. Whether it contributes to TBI/alcohol-mediated neurodegeneration is unexplored, however. Our recent studies have identified ISGylation, a conjugated form of ISG15 (Interferon-Stimulated Gene 15) and inducer of proteinopathy, as a potential mechanistic link underlying TBI-mediated neurodegeneration and proteinopathy in veterans. In the current study, a rat model of combined TBI and alcohol use was utilized to investigate the same relationship. Here, we report sustained induction of Interferon β (IFNβ), changes in TAR DNA Binding 43 (TDP-43) ISGylation levels, TDP-43 proteinopathy (C-terminal fragmentation [CTF]), and neurodegeneration in the ventral horns of the lumbar spinal cords (LSCs) and/or motor cortices (MCs) of female rats post-TBI in a time-dependent manner. In males, these findings mostly remained non-significant, although moderate alcohol use appears to decrease neurodegeneration in males (but not females) post-TBI. We, however, do not claim that moderate alcohol consumption is beneficial for preventing TBI-mediated neurodegeneration. We have previously demonstrated that ISGylation is increased in the LSCs of veterans with TBI/ALS (amyotrophic lateral sclerosis). Here, we show increased ISGylation of TDP-43 in the LSCs of TBI/ALS-afflicted female veterans compared with male veterans. Knowing that ISGylation induces proteinopathy, we suggest targeting ISGylation may prevent proteinopathy-mediated neurodegeneration post-TBI, particularly in women; however, causal studies are required to confirm this claim.

Military Environmental Exposures

Am J Nurs. 2023 Nov 1;123(11):47-52. doi: 10.1097/01.NAJ.0000995364.07542.c5.

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Abstract

The passage of the PACT Act of 2022 expanded the services veterans receive through the U.S. Department of Veterans Affairs (VA), ensuring they now qualify for benefits if they've been exposed to certain toxins during their military service. This significant expansion of VA benefits also highlights the need for nurses and other health providers working outside the VA system-who care for millions of veterans-to be well-informed about their patients' military experiences and any potential environmental exposures and health impacts. In this article, the author raises awareness of military environmental exposures and offers guidance about exposure-informed care.

Bioenergetic function is decreased in peripheral blood mononuclear cells of veterans with Gulf War Illness

PLoS One. 2023 Nov 1;18(11):e0287412. doi: 10.1371/journal.pone.0287412. eCollection 2023.

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Abstract

Gulf War Illness (GWI) is a major health problem for approximately 250,000 Gulf War (GW) veterans, but the etiology of GWI is unclear. We hypothesized that mitochondrial dysfunction is an important contributor to GWI, based on the similarity of some GWI symptoms to those occurring in some mitochondrial diseases; the plausibility that certain pollutants to which GW veterans were exposed affect mitochondria; mitochondrial effects observed in studies in laboratory models of GWI; and previous evidence of mitochondrial outcomes in studies in GW veterans. A primary role of mitochondria is generation of energy via oxidative phosphorylation. However, direct assessment of mitochondrial respiration, reflecting oxidative phosphorylation, has not been carried out in veterans with GWI. In this case-control observational study, we tested multiple measures of mitochondrial function and integrity in a cohort of 114 GW veterans, 80 with and 34 without GWI as assessed by the Kansas definition. In circulating white blood cells, we analyzed multiple measures of mitochondrial respiration and extracellular acidification, a proxy for non-aerobic energy generation; mitochondrial DNA (mtDNA) copy number; mtDNA damage; and nuclear DNA damage. We also collected detailed survey data on demographics; deployment; self-reported exposure to pesticides, pyridostigmine bromide, and chemical and biological warfare agents; and current biometrics, health and activity levels. We observed a 9% increase in mtDNA content in blood in veterans with GWI, but did not detect differences in DNA damage. Basal and ATP-linked oxygen consumption were respectively 42% and 47% higher in veterans without GWI, after adjustment for mtDNA amount. We did not find evidence for a compensatory increase in anaerobic energy generation: extracellular acidification was also lower in GWI (12% lower at baseline). A subset of 27 and 26 veterans returned for second and third visits, allowing us to measure stability of mitochondrial parameters over time. mtDNA CN, mtDNA damage, ATP-linked OCR, and spare respiratory capacity were moderately replicable over time, with intraclass correlation coefficients of 0.43, 0.44, 0.50, and 0.57, respectively. Other measures showed higher visit-to-visit variability. Many measurements showed lower replicability over time among veterans with GWI compared to veterans without GWI. Finally, we found a strong association between recalled exposure to pesticides, pyridostigmine bromide, and chemical and biological warfare agents and GWI ($p < 0.01$, $p < 0.01$, and $p < 0.0001$, respectively). Our results demonstrate decreased mitochondrial respiratory function as well as decreased glycolytic activity, both of which are consistent with decreased energy availability, in peripheral blood mononuclear cells in veterans with GWI.

Bioenergetic function is decreased in peripheral blood mononuclear cells of veterans with Gulf War Illness

PLoS One. 2023 Nov 1;18(11):e0287412. doi: 10.1371/journal.pone.0287412. eCollection 2023.

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Abstract

Gulf War Illness (GWI) is a major health problem for approximately 250,000 Gulf War (GW) veterans, but the etiology of GWI is unclear. We hypothesized that mitochondrial dysfunction is an important contributor to GWI, based on the similarity of some GWI symptoms to those occurring in some mitochondrial diseases; the plausibility that certain pollutants to which GW veterans were exposed affect mitochondria; mitochondrial effects observed in studies in laboratory models of GWI; and previous evidence of mitochondrial outcomes in studies in GW veterans. A primary role of mitochondria is generation of energy via oxidative phosphorylation. However, direct assessment of mitochondrial respiration, reflecting oxidative phosphorylation, has not been carried out in veterans with GWI. In this case-control observational study, we tested multiple measures of mitochondrial function and integrity in a cohort of 114 GW veterans, 80 with and 34 without GWI as assessed by the Kansas definition. In circulating white blood cells, we analyzed multiple measures of mitochondrial respiration and extracellular acidification, a proxy for non-aerobic energy generation; mitochondrial DNA (mtDNA) copy number; mtDNA damage; and nuclear DNA damage. We also collected detailed survey data on demographics; deployment; self-reported exposure to pesticides, pyridostigmine bromide, and chemical and biological warfare agents; and current biometrics, health and activity levels. We observed a 9% increase in mtDNA content in blood in veterans with GWI, but did not detect differences in DNA damage. Basal and ATP-linked oxygen consumption were respectively 42% and 47% higher in veterans without GWI, after adjustment for mtDNA amount. We did not find evidence for a compensatory increase in anaerobic energy generation: extracellular acidification was also lower in GWI (12% lower at baseline). A subset of 27 and 26 veterans returned for second and third visits, allowing us to measure stability of mitochondrial parameters over time. mtDNA CN, mtDNA damage, ATP-linked OCR, and spare respiratory capacity were moderately replicable over time, with intraclass correlation coefficients of 0.43, 0.44, 0.50, and 0.57, respectively. Other measures showed higher visit-to-visit variability. Many measurements showed lower replicability over time among veterans with GWI compared to veterans without GWI. Finally, we found a strong association between recalled exposure to pesticides, pyridostigmine bromide, and chemical and biological warfare agents and GWI ($p < 0.01$, $p < 0.01$, and $p < 0.0001$, respectively). Our results demonstrate decreased mitochondrial respiratory function as well as decreased glycolytic activity, both of which are consistent with decreased energy availability, in peripheral blood mononuclear cells in veterans with GWI.

Gut microbiota in pathophysiology, diagnosis, and therapeutics of inflammatory bowel disease

Intest Res. 2023 Nov 8. doi: 10.5217/ir.2023.00080. Online ahead of print.

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Abstract

Inflammatory bowel disease (IBD) is a multifactorial disease, which is thought to be an interplay between genetic, environment, microbiota, and immune-mediated factors. Dysbiosis in the gut microbial composition, caused by antibiotics and diet, is closely related to the initiation and progression of IBD. Differences in gut microbiota composition between IBD patients and healthy individuals have been found, with reduced biodiversity of commensal microbes and colonization of opportunistic microbes in IBD patients. Gut microbiota can, therefore, potentially be used for diagnosing and prognosticating IBD, and predicting its treatment response. Currently, there are no curative therapies for IBD. Microbiota-based interventions, including probiotics, prebiotics, synbiotics, and fecal microbiota transplantation, have been recognized as promising therapeutic strategies. Clinical studies and studies done in animal models have provided sufficient evidence that microbiota-based interventions may improve inflammation, the remission rate, and microscopic aspects of IBD. Further studies are required to better understand the mechanisms of action of such interventions. This will help in enhancing their effectiveness and developing personalized therapies. The present review summarizes the relationship between gut microbiota and IBD immunopathogenesis. It also discusses the use of gut microbiota as a noninvasive biomarker and potential therapeutic option.

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

Clin Exp Ophthalmol. 2023 Nov 12. doi: 10.1111/ceo.14313. Online ahead of print.

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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.

Prevalence and risk factors of post-acute sequelae of COVID-19 among United States Veterans

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Abstract

Purpose: To better understand Post-Acute Sequelae of COVID-19 (PASC) in the Veteran population, this study aims to determine the prevalence of PASC and identify risk factors associated with its development.

Methods: This retrospective cohort study included 363,825 Veterans that tested positive for COVID-19 between February 1, 2020, and September 30, 2022. The primary outcome was the development of PASC 30-180 days following an acute infection with SARS-CoV-2. Multivariate logistic regression was utilized to examine factors associated with PASC.

Results: Of the 363,825 Veterans included in the analysis, 164,315 (45%) displayed symptoms of PASC. The Veterans in this analysis were predominantly male, non-Hispanic White, under the age of 65 years old, and lived in an urban residence. The strongest predictors for PASC included Non-Hispanic Black or African American race compared to Non-Hispanic White race (aOR=1.14), being between the ages of 50 and 64 compared to ages 50 and below (aOR=1.80), diabetes (aOR=8.46), and severe acute infection (aOR=1.42).

Conclusion: Results demonstrate potential health inequities for vulnerable individuals, as well as increased risk for individuals with pre-existing comorbidities. The prevalence of PASC provides estimates for future health care utilization. The risk factors identified can aid public health interventions to reduce the burden of PASC.

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

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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.

The effect of disease misclassification on the ability to detect a gene-environment interaction: implications of the specificity of case definitions for research on Gulf War illness

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Abstract

Background: Since 1997, research on Gulf War illness (GWI) has predominantly used 3 case definitions-the original Research definition, the CDC definition, and modifications of the Kansas definition-but they have not been compared against an objective standard.

Methods: All 3 case definitions were measured in the U.S. Military Health Survey by a computer-assisted telephone interview in a random sample (n = 6,497) of the 1991 deployed U.S. military force. The interview asked whether participants had heard nerve agent alarms during the conflict. A random subsample (n = 1,698) provided DNA for genotyping the PON1 Q192R polymorphism.

Results: The CDC and the Modified Kansas definition without exclusions were satisfied by 41.7% and 39.0% of the deployed force, respectively, and were highly overlapping. The Research definition, a subset of the others, was satisfied by 13.6%. The majority of veterans meeting CDC and Modified Kansas endorsed fewer and milder symptoms; whereas, those meeting Research endorsed more symptoms of greater severity. The group meeting Research was more highly enriched with the PON1 192R risk allele than those meeting CDC and Modified Kansas, and Research had twice the power to detect the previously described gene-environment interaction between hearing alarms and RR homozygosity (adjusted relative excess risk due to interaction [aRERI] = 7.69; 95% CI 2.71-19.13) than CDC (aRERI = 2.92; 95% CI 0.96-6.38) or Modified Kansas without exclusions (aRERI = 3.84; 95% CI 1.30-8.52) or with exclusions (aRERI = 3.42; 95% CI 1.20-7.56). The lower power of CDC and Modified Kansas relative to Research was due to greater false-positive disease misclassification from lower diagnostic specificity.

Conclusions: The original Research case definition had greater statistical power to detect a genetic predisposition to GWI. Its greater specificity favors its use in hypothesis-driven research; whereas, the greater sensitivity of the others favor their use in clinical screening for application of future diagnostic biomarkers and clinical care.

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

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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.

Living With Toxic Wounds: The Voices and Visual Self-Representations of Gulf War Veterans

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Abstract

Operations Desert Shield and Storm occurred over 30 years ago, yet many of those who were deployed continue to experience chronic and debilitating symptoms, now recognized as Gulf War Illness (GWI). While efforts have been made to explore clinical treatments for GWI, misperceptions and skepticism about its complex nature and a lack of consensus on its etiology impede progress in this area. A critical necessity remains to better understand the experiences, needs, and concerns of veterans with GWI. In this qualitative research study, 40 Gulf War veterans were interviewed about their perceptions regarding symptoms of physical health, cognitive functioning, quality of life, and the quality of care received. In addition, they depicted their experiences through an artistic elicitation collage. Through a grounded theory method, key findings indicated that there are remaining hurdles, such as challenging symptoms, persisting unknowns about the illness, and variations in treatment quality. Veterans have mostly managed and coped with GWI, but they voice the need for acknowledgment and support. The main implication from this study is the significance of both clinical and institutional validation and recognition of the GWI experience as well as the need for specific support systems.

Treatment and life goals among veterans with Gulf War illness

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Abstract

Medically unexplained syndromes (MUS), also termed persistent physical symptoms, are both prevalent and disabling. Yet treatments for MUS are marked by high rates of patient dissatisfaction, as well as disagreement between patients and providers on the management of persistent physical symptoms. A better understanding of patient-generated goals could increase collaborative goal setting and promote person-centered care, a critical component of MUS treatment; yet research in this area is lacking. This paper aimed to develop a typology of treatment and life goals among Gulf War veterans with a medically unexplained syndrome (Gulf War Illness). We examined participants' responses to open-ended questions about treatment and life goals using Braun and Clarke's thematic analysis methodology. Results showed that treatment goals could be categorized into four overarching themes: 1) Get better/healthier, 2) Improve quality of life, 3) Improve or seek additional treatment, and 4) Don't know/Don't have any. Life goals were categorized into six overarching themes: 1) Live a fulfilling life, 2) Live a happy life, 3) Live a healthy life, 4) Be productive/financially successful, 5) Manage GWI, and 6) Don't know/Don't have any. Treatment goals were largely focused on getting better/healthier (e.g., improving symptoms), whereas life goals focused on living a fulfilling life. Implications for the treatment of Gulf War Illness and patient-provider communication are discussed. ClinicalTrials.gov Identifier: NCT02161133.

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

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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 that of 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 (GEEs) 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.

Sleep Apnea Among Gulf War Veterans: An Examination of VA Utilization Rates, Treatment Initiation, and Health Outcomes

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Abstract

Objectives: Obstructive sleep apnea (OSA) among veterans is frequently underdiagnosed and undertreated. The present study sought to: 1) characterize the prevalence and rate of treatment of OSA among VA users and non-users and 2) examine the associations between diagnosed or probable OSA and key physical and mental health outcomes.

Methods: Gulf-War I-era Veterans were recruited as part of a national survey assessing mental and physical health concerns, healthcare needs, and healthcare utilization. OSA diagnoses were self-reported while sleep apnea risk was assessed via the STOP-Bang. Veterans also completed questionnaires assessing overall health, pain, depression, PTSD, and psychosocial functioning.

Results: 1,153 veterans were included in the present analyses (Mean age = 58.81; 21.84% female). Compared to non-VA healthcare users, veterans receiving care at the VA were more likely to have been diagnosed with OSA ($p < .001$) and report receiving treatment for OSA ($p = .005$). Compared to veterans at low risk for OSA, veterans at elevated risk reported higher levels of pain ($p = .001$), depression ($p = .02$), and poorer psychosocial functioning ($p < .001$).

Conclusions: OSA diagnoses appear to be more common among VA healthcare users. Findings suggest that OSA remains underdiagnosed and associated with important physical and mental health consequences. Additional screening for OSA, especially among non-VA clinics, is warranted.