GULF WAR ILLNESS

The Relationship Between Traumatic Brain Injury and Rates of Chronic Symptomatic Illness in 202 Gulf War Veterans.

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Mil Med. 2018 Nov 1;183(11-12):e571-e579. doi: 10.1093/milmed/usy109. PMID: 29788089.

Introduction: Although not a "signature injury" of Operation Desert Shield/Desert Storm (i.e., Gulf War, GW), some GW veterans have a history traumatic brain injury (TBI). For example, a previous study found that 12.2% of the GW veterans from the Fort Devens Cohort Study had self-reported TBIs. The present study sought to build upon this finding by examining the relationship between TBI and chronic symptomatic illness in a different sample of GW veterans.

Materials and Methods: Participants were 202 GW veterans recruited from 2014 to 2018 at the San Francisco Veterans Affairs Medical Center as part of a VA-funded study on the effects of predicted exposure to low levels of sarin and cyclosarin on brain structure and function. The Ohio State University TBI identification method was used to determine lifetime history of TBI. The Kansas Gulf War Military History and Health Questionnaire was used to assess symptoms and to determine cases of Kansas Gulf War Illness (GWI) and Centers for Disease Control and Prevention (CDC) Chronic Multisymptom Illness (CMI).

Results: Nearly half (47%) the sample had a history of TBI, but only 7% of the TBIs were sustained in injuries that occurred during the GW. Most of the TBIs were sustained in injuries that occurred prior to (73%) or after (34%) the GW. History of TBI was not associated with higher rates of symptomatic illness when it was narrowly defined (i.e., Kansas GWI cases or cases of severe CMI). History of TBI was only associated with higher rates of symptomatic illness when it is broadly defined (i.e., CDC CMI or mild-moderate CMI). There was suggestive evidence that veterans who sustained TBIs during the GW (only seven in the present sample) have poorer functional outcomes compared with GW veterans with non-GW related TBIs.

Conclusions: While TBIs were uncommon during the GW, many GW veterans sustained TBIs prior or after the GW. Because TBI and GWI/CMI share some overlapping symptoms, history of TBI may appear to be associated with increased rates of chronic symptomatic illness in GW veterans if chronic symptomatic illness is defined broadly (i.e., CDC CMI or mild-moderate CMI). History of pre-GW TBI did not affect the veterans' response to exposures/experiences from the GW; however, there was suggestive evidence that veterans who sustained TBIs during the GW may have poorer functional outcomes that GW veterans without TBI or even GW veterans with non-GW-related TBIs. Future, better powered studies with randomly and systematically select participants from the larger population of GW veterans will need to confirm this finding.

CHRONIC FATIGUE SYNDROME

Blood Volume Status in ME/CFS Correlates With the Presence or Absence of Orthostatic Symptoms: Preliminary Results.

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Front Pediatr. 2018 Nov 15;6:352. doi: 10.3389/fped.2018.00352. PMCID: PMC6262290. PMID: 30525014. eCollection 2018.

Introduction: Conflicting data have been published on the reduction of circulating blood volume in adults with Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). The aim of the present study was to compare blood volumes based on the presence or absence of orthostatic symptoms.

Methods and Results: Twenty consecutive adults with ME/CFS participated in the study. All underwent dual isotope blood volume measurement and were evaluated for a clinical suspicion of orthostatic intolerance (OI). The mean age was 34 (10) years, and median duration of disease was 7.5 (6-10) years. The mean (SD) absolute blood volume was 59 (8) ml/kg, a value -11 (7) ml/kg below the reference blood volume. Of the 12 patients, 4 had no OI and 8 had a clinical suspicion of OI. In 8 patients with OI, absolute blood volumes were significantly lower than for the 4 without OI (56 [2] vs. 66 [5]; p < 0.05) as were the differences between the measured and the reference blood volume (-14 [2]; vs. -4 [3]; p < 0.02).

Conclusions: Adults with ME/CFS had a significantly lower blood volume if they had a clinical suspicion of OI compared to those without a clinical suspicion of OI, as well as a significantly lower blood volume compared to the expected value. The data suggest that accounting for symptoms of OI could enhance the detection of the subset with reduced blood volume.

CHRONIC FATIGUE SYNDROME (Continued)

Physical Activity and Sleep in Chronic Fatigue Syndrome and Fibromyalgia Syndrome: Associations with Symptom Severity in the General Population Cohort LifeLines.

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Pain Res Manag. 2018 Nov 4;2018:5801510. doi: 10.1155/2018/5801510. PMCID: PMC6247578. PMID: 30533166. eCollection 2018.

Objective: The aim of the current study was to compare physical activity and sleep duration between patients with chronic fatigue syndrome (CFS), patients with fibromyalgia syndrome (FMS), and controls and to examine the association between physical activity level and sleep duration with symptom severity within these patient groups.

Methods: This study used data of LifeLines, a general population cohort in which 1.0% (*n*=943, 63.7% female, age 44.9 (SD 11.6) years) reported CFS, 3.0% (*n*=2,714; 91.6% female; age 48.4 (SD 10.7) years) <u>reported FMS</u>, and 95.7% (*n*=87,532; 57.9% female; age 44.3 (SD 12.4) years) reported neither CFS nor FMS. Physical activity, sleep duration, and symptom severity were assessed by questionnaires and analysed using ANCOVA and regression analyses, adjusted for age, sex, body mass index, smoking, and educational level.

Results: Patients with CFS and FMS had significantly lower physical activity scores (8834 ± 5967 and 8813 ± 5549 MET * minutes) than controls (9541 ± 5533 ; p < 0.001). Patients with CFS had the longest sleep duration (466 ± 86 minutes) compared to patients with FMS and controls (450 ± 67 and 446 ± 56 ; p < 0.001). A linear association between physical activity, sleep duration, and symptom severity was only found in controls, in whom higher physical total activity scores and longer sleep duration were associated with a lower symptom severity. In contrast, quadratic associations were found in all groups: both relatively low and high physical activity scores and relatively short and long sleep duration were associated with higher symptom severity in CFS, FMS, and controls.

Conclusion: This study indicates that patients with CFS or FMS sleep longer and are less physically active than controls on average. Both low and high levels of physical activity and short and long sleep duration are associated with higher symptom severity, suggesting the importance of patient-tailored treatment.

Hand Grip Strength as a Clinical Biomarker for ME/CFS and Disease Severity.

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Front Neurol. 2018 Nov 27;9:992. doi: 10.3389/fneur.2018.00992. PMCID: PMC6277492. PMID: 30538664. eCollection 2018.

Background: The diagnosis of myalgic encephalomyelitis (ME/CFS) in research and clinical practice has largely relied on clinical history, which can be subjective in nature. Clinical signs are often subtle, overlap with other conditions, and are not formally included as part of diagnostic workup. The characterization of clinical signs and biomarkers is needed for better diagnosis and classification of patients and to monitor treatment response. Hand grip strength (HGS) has been used as an objective measure of muscle strength and fatigue, which is a primary symptom of ME/CFS. We assessed the potential usefulness of HGS as a diagnostic marker in ME/CFS.

Methods: We compared HGS measurements from participants in the UK ME/CFS Biobank, with groups consisting of people with ME/CFS of differing severity (n = 272), healthy (n = 136), multiple sclerosis (n = 76) controls, and others with chronic fatigue not meeting the diagnosis of ME/CFS (n = 37). We correlated the maximum and minimum of, and differences between, 3 repeated HGS measurements with parameters of disease severity, including fatigue and pain analog scales, and physical and mental component summaries from the SF-36v2TM questionnaire across recruitment groups.

Results: HGS indicators were associated with having ME/CFS, with magnitudes of association stronger in severely affected than in mild/moderately affected patients. Compared with healthy controls, being severely affected was associated with a reduction in minimum HGS of 15.3 kg (95%Cl 19.3-11.3; p < 0.001), while being mild/moderately affected was associated with a 10.5 kg (95%Cl 13.2-7.8; p < 0.001) reduction. The association persisted after adjusting for age, sex and body mass index. ME/CFS cases also showed lower values of maximum HGS and significant drops in values from the first to second and third trials, compared to other study groups. There were significant correlations between HGS indicators and clinical parameters of disease severity, including fatigue analog scale (Spearman's Rho = -0.40, p < 0.001), pain analog scale (Rho = -0.38, p < 0.001), and physical component summary (Rho = 0.42, p < 0.001).

Discussion: HGS is markedly reduced in ME/CFS, particularly in patients with more severe disease, and may indicate muscle and fatigue related symptoms. HGS is a potential diagnostic tool in ME/CFS, and could also be used to enhance patient phenotyping and as an outcome measure following interventions.

HEADACHE and MIGRAINE

Associations Between Migraine and Type 2 Diabetes in Women: Findings From the E3N Cohort Study.

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JAMA Neurol. 2018 Dec 17. doi: 10.1001/jamaneurol.2018.3960. PMID: 30556831. [Epub ahead of print]

Importance: Little is known about the associations between migraine and type 2 diabetes and the temporality of the association between these 2 diseases.

Objective: To evaluate the association between migraine and type 2 diabetes incidence as well as the evolution of the prevalence of active migraine before and after type 2 diabetes diagnosis.

Design, Setting, and Participants: We used data from the E3N cohort study, a French prospective population-based study initiated in 1990 on a cohort of women born between 1925 and 1950. The E3N study participants are insured by a health insurance plan that mostly covers teachers. From the eligible women in the E3N study, we included those who completed the 2002 follow-up questionnaire with information available on migraine. We then excluded prevalent cases of type 2 diabetes, leaving a final sample of women who were followed up between 2004 and 2014. All potential occurrences of type 2 diabetes were identified through a drug reimbursement database. Statistical analyses were performed in March 2018.

Exposures: Self-reported migraine occurrence.

Main Outcomes and Measures: Pharmacologically treated type 2 diabetes.

Results: From the 98 995 women in the study, 76 403 women completed the 2002 follow-up survey. Of these, 2156 were excluded because they had type 2 diabetes, leaving 74 247 women. Participants had a mean (SD) age of 61 (6) years at baseline, and all were free of type 2 diabetes. During 10 years of follow-up, 2372 incident type 2 diabetes cases occurred. A lower risk of type 2 diabetes was observed for women with active migraine compared with women with no migraine history (univariate hazard ratio, 0.80 [95% CI, 0.67-0.96], multivariable-adjusted hazard ratio, 0.70 [95% CI, 0.58-0.85]). We also observed a linear decrease in active migraine prevalence from 22% (95% CI, 16%-27%) to 11% (95% CI, 10%-12%) during the 24 years prior to diabetes diagnosis, after adjustment for potential type 2 diabetes risk factors. A plateau of migraine prevalence around 11% was then observed for 22 years after diagnosis.

Conclusions and Relevance: We observed a lower risk of developing type 2 diabetes for women with active migraine and a decrease in active migraine prevalence prior to diabetes diagnosis. Further targeted research should focus on understanding the mechanisms involved in explaining these findings.

Cortical abnormalities in episodic migraine: A multi-center 3T MRI study.

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Cephalalgia. 2018 Dec 10:333102418795163. doi: 10.1177/0333102418795163. PMID: 30525946. [Epub ahead of print]

BACKGROUND: Several previous studies have investigated cortical abnormalities, specifically cortical thickness, in patients with migraine, with variable results. The relatively small sample sizes of most previous studies may partially explain these inconsistencies.

OBJECTIVE: To investigate differences of cortical thickness between control subjects and migraineurs in a large cohort.

METHODS: Three Tesla MRI data of 131 patients (38 with and 93 without aura) and 115 control subjects were analysed. A vertex-wise linear model was applied controlling for age, gender and MRI scanner to investigate differences between groups and determine the impact of clinical factors on cortical thickness measures.

RESULTS: Migraineurs showed areas of thinned cortex compared with controls bilaterally in the central sulcus, in the left middle-frontal gyrus, in left visual cortices and the right occipito-temporal gyrus. Frequency of migraine attacks and the duration of the disorder had a significant impact on cortical thickness in the sensorimotor cortex and middle-frontal gyrus. Patients without aura showed thinner cortex than controls bilaterally in the central sulcus and in the middle frontal gyrus, in the left primary visual cortices, in the left supramarginal gyrus and in the right cuneus. Patients with aura showed clusters of thinner cortex bilaterally in the subparietal sulcus (between the precuneus and posterior cingulate cortex), in the left intraparietal sulcus and in the right anterior cingulate.

CONCLUSION: These results indicate cortical abnormalities in specific brain regions in migraineurs. Some of the observed abnormalities may reflect a genetic susceptibility towards developing migraine attacks, while others are probably a consequence of repeated head pain attacks.

HEADACHE and MIGRAINE (Continued)

Illness Perception and Job Satisfaction in Patients Suffering from Migraine Headaches: Trait Anxiety and Depressive Symptoms as Potential Mediators.

Rogante E¹, Sarubbi S¹, Lamis DA², Canzonetta V³, Sparagna A³, De Angelis V⁴, Erbuto D³, Martelletti P⁴, Pompili M³. Headache. **2018 Dec 13**. doi: 10.1111/head.13461. PMID: 30548860. [Epub ahead of print]

BACKGROUND AND OBJECTIVES: Migraine headache is the seventh leading cause of disability worldwide causing adverse outcomes in many aspects of an individual's life. Many psychological aspects affect chronic migraine (CM): illness perception, anxiety, depressive symptoms, and job satisfaction. This observational study aimed to examine the association among illness perception, anxiety, depressive symptoms, and job satisfaction, connected to migraine and its features.

METHODS: Ninety-eight individuals with CM treated with OnabotulinumtoxinA were recruited from the Regional Referral Headache Centre of Sant'Andrea Hospital in Rome. They completed 4 questionnaires (Brief Illness Perception Quality of Life, Enjoyment and Satisfaction Questionnaire, State-Trait Anxiety Inventory, Beck Depression Inventory-II) and a socio-anamnestic form.

RESULTS: This cross-sectional study examined 2 mediational models. The first one demonstrated an indirect mediating effect of trait anxiety on the association between illness perception and job satisfaction (ab = -0.217, 95% CI [-0.37, -0.09]). In the second model, depressive symptoms mediated the association between illness perception and job satisfaction (ab = -0.186, 95% CI [-0.33, -0.04]).

CONCLUSIONS: In our study, levels of anxiety and depressive symptoms showed a mediational effect on the association between illness perception and job fulfillment. It is important to develop interventions aimed at improving the quality of life of individuals with CM and to increase knowledge about headache and psychological consequences.

<u>Disruption of periaqueductal grey-default mode network functional connectivity predicts</u> persistent post-traumatic headache in mild traumatic brain injury.

J Neurol Neurosurg Psychiatry. 2018 Dec 15. pii: jnnp-2018-318886. doi: 10.1136/jnnp-2018-318886. PMID: 30554137. [Epub ahead of print]

OBJECTIVE: Post-traumatic headache (PTH) is one of the most frequent and persistent physical symptoms following mild traumatic brain injury (mTBI) and develop in more than 50% of this population. This study aimed to investigate the periaqueductal grey (PAG)-seeded functional connectivity (FC) in patients with mTBI with acute post-traumatic headache (APTH) and further examine whether the FC can be used as a neural biomarker to identify patients developing chronic pain 3 months postinjury.

METHODS: 70 patients with mTBI underwent neuropsychological measurements and MRI scans within 7 days postinjury and 56 (80%) of patients were followed up at 3 months. 46 healthy controls completed the same protocol on recruitment to the study. PAG-seeded resting-state FC analysis was measured in 54 patients with mTBI with APTH, in comparison with 46 healthy volunteers.

RESULTS: The mTBI+APTH group presented significantly reduced PAG-seeded FC within the default mode network (DMN), compared with healthy volunteers group. The connectivity strength can also predict patients' complaints on the impact of headache on their lives. Crucially, the initial FC strength between the PAG-right precuneus as well as the PAG-right inferior parietal lobule became the important predictor to identify patients with mTBI developing persistent PTH 3 months postinjury.

CONCLUSIONS: Patients with mTBI+APTH exhibited significant PAG-related FC differences mainly within the DMN. These regions extended beyond traditional pain processing areas and may reflect the diminished top-down attention regulation of pain perception through antinociceptive descending modulation network. The disrupted PAG-DMN FC may be used as an early imaging biomarker to identify patients at risk of developing persistent PTH.

CHRONIC PAIN

<u>The Influence of Race and Gender on Nursing Care Decisions: A Pain Management Intervention.</u>

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Pain Manag Nurs. 2018 Jun;19(3):238-245. doi: 10.1016/j.pmn.2017.10.015. PMID: 29501358. Epub 2018 Mar 1.

BACKGROUND: Understanding whether a patient's race or gender and/or the nurse's race or gender influence how nurses form care decisions can contribute to exploration of methods that can positively affect disparate treatment.

AIMS: This research examined how the variables of race and gender of both the nurse and the patient influence nurses' decision making about pain management.

DESIGN: A randomized four-group post-test-only experimental design was used to examine the variables and variable interactions.

SETTINGS: An investigator-developed case vignette tool hosted online was used to obtain data about nursing pain management decisions. The vignette intervention was developed to simulate four exact patient scenarios that differed only by patient race and gender. Participants/Subjects: A quota sample of 400 nurses was recruited using a self-selected face-to-face recruitment technique.

METHODS: A four-way between-groups analysis of variance assessed whether the gender of the nurse, race of the nurse, gender of the patient, or race of the patient made any differences in the dose intensity of pain medications selected by the nurse sample.

RESULTS: No significant interactions were noted between any combinations of the four independent variables. A significant main effect was noted in medication intensity for nurse gender (F[1,384] = 9.75, p = .002).

CONCLUSIONS: Data trends suggested that gender stereotypes about how patients managed pain played a role in dose intensity decisions because female patients on average were given higher doses of pain medication than male patients were by all the nurses in the study. Further research is needed in this complex area of study.

The temporal relationship between pain intensity and pain interference and incident dementia.

Ezzati A¹, Wang C², Katz MJ¹, Derby CA¹, Zammit AR¹, Zimmerman ME¹, Pavlovic JM¹, Sliwinski MJ³, Lipton RB¹.

Curr Alzheimer Res. 2018 Dec 12. doi: 10.2174/1567205016666181212162424. PMID: 30543173. [Epub ahead of print]

BACKGROUND: Chronic pain is common among older adults and is associated with cognitive dysfunction based on cross-sectional studies. However, the longitudinal association between chronic pain and incident dementia in community-based samples is unknown.

OBJECTIVE: We aimed to evaluate the associations of pain intensity and pain interference with incident dementia in a community-based sample of older adults.

METHODS: Participants were 1,114 individuals 70 years of age or older from Einstein Aging Study (EAS), a longitudinal cohort study of community-dwelling older adults in the Bronx County, NY. The primary outcome measure was incident dementia, diagnosed using DSM-IV criteria. Pain intensity and interference in the month prior to first annual visit were measured using items from the SF-36 questionnaire. Pain intensity and pain interference were assessed as predictors of time to incident dementia using Cox proportionate hazards models while controlling for potential confounders.

RESULTS: Among participants, 114 individuals developed dementia over an average 4.4 years (SD=3.1) of follow-up. Models showed that pain intensity had no significant effect on time to developing dementia, whereas higher levels of pain interference were associated with a higher risk of dementia. In the model that included both pain intensity and interference as predictors of incident dementia, the pain interference had a significant effect on incident dementia, and pain intensity remained non-significant.

CONCLUSION: As a potential remediable risk factor, the mechanisms linking pain interference to cognitive decline merit further exploration.

OTHER RESEARCH OF INTEREST

Military-related risk factors in female veterans and risk of dementia.

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Neurology. 2018 Dec 12. pii: 10.1212/WNL.00000000000006778. doi: 10.1212/WNL.0000000000006778. PMID:30541865. [Epub ahead of print]

OBJECTIVE: To determine whether diagnoses of traumatic brain injury (TBI), posttraumatic stress disorder (PTSD), and depression, alone or in combination, increase dementia risk among older female veterans.

METHODS: This cohort study included data from 109,140 female veterans ≥55 years of age receiving care from Veterans Health Administration medical centers in the United States between October 2004 and September 2015 with at least 1 follow-up visit. TBI, PTSD, depression, and medical conditions at study baseline and incident dementia were determined according to ICD-9-CM codes. Fine-Gray proportional hazards models were used to determine the association between military-related risk factors and dementia diagnosis, accounting for the competing risk of death.

RESULTS: During follow-up (mean 4.0 years, SD 2.3), 4% of female veterans (n = 4,125) developed dementia. After adjustment for demographics and medical conditions, women with TBI, PTSD, and depression had a significant increase in risk of developing dementia compared to women without these diagnoses (TBI-adjusted subdistribution hazard ratio [adjusted sHR] 1.49, 95% confidence interval [CI] 1.01-2.20; PTSD adjusted sHR 1.78, 95% CI 1.34-2.36; and depression-adjusted sHR 1.67, 95% CI 1.55-1.80), while women with >1 diagnosis had the highest risk for dementia (adjusted sHR 2.15, 95% CI 1.84-2.51).

CONCLUSIONS: We found that women with military-related risk factors had an ≈50% to 80% increase in developing dementia relative to women without these diagnoses, while female veterans with multiple risk factors had a >2-fold risk of developing dementia. These findings highlight the need for increased screening of TBI, PTSD, and depression in older women, especially female veterans.

A usability and safety analysis of electronic health records: a multi-center study.

Ratwani RM^{1,2}, Savage E¹, Will A¹, Arnold R³, Khairat S⁴, Miller K¹, Fairbanks RJ^{1,2}, Hodgkins M⁵, Hettinger AZ^{1,2}. J Am Med Inform Assoc. **2018 Sep 1**;25(9):1197-1201. doi: 10.1093/jamia/ocy088. PMID: 29982549.

To characterize the variability in usability and safety of EHRs from two vendors across four healthcare systems (2 Epic and 2 Cerner). Twelve to 15 emergency medicine physicians participated from each site and completed six clinical scenarios. Keystroke, mouse click, and video data were collected. From the six scenarios, two diagnostic imaging, laboratory, and medication tasks were analyzed. There was wide variability in task completion time, clicks, and error rates. For certain tasks, there were an average of a nine-fold difference in time and eight-fold difference in clicks. Error rates varied by task (X-ray 16.7% to 25%, MRI: 0 to 10%, Lactate: 0% to 14.3%, Tylenol: 0 to 30%; Taper: 16.7% to 50%). The variability in time, clicks, and error rates highlights the need for improved implementation optimization. EHR implementation, in addition to vendor design and development, is critical to usable and safe products.

Alternatives for the Demilitarization of Conventional Munitions.

National Academies of Sciences, Engineering, and Medicine; Division on Engineering and Physical Sciences; Board on Army Science and Technology; Committee on Alternatives for the Demilitarization of Conventional Munitions.

December 2018. Washington, DC. The National Academies Press. https://doi.org/10.17226/25140.

Consensus Study Report: Download (PDF). Read (Online).

The U.S. military has a stockpile of approximately 400,000 tons of excess, obsolete, or unserviceable munitions. About 60,000 tons are added to the stockpile each year. Munitions include projectiles, bombs, rockets, landmines, and missiles. Open burning/open detonation (OB/OD) of these munitions has been a common disposal practice for decades, although it has decreased significantly since 2011.

OB/OD is relatively quick, procedurally straightforward, and inexpensive. However, the downside of OB and OD is that they release contaminants from the operation directly into the environment. Over time, a number of technology alternatives to OB/OD have become available and more are in research and development. Alternative technologies generally involve some type of contained destruction of the energetic materials, including contained burning or contained detonation as well as contained methods that forego combustion or detonation.

Alternatives for the Demilitarization of Conventional Munitions reviews the current conventional munitions demilitarization stockpile and analyzes existing and emerging disposal, treatment, and reuse technologies. This report identifies and evaluates any barriers to full-scale deployment of alternatives to OB/OD or non-closed loop incineration/combustion, and provides recommendations to overcome such barriers.