

GULF WAR ILLNESS

[Dizziness, Vertigo, and Mental Health Comorbidity in Gulf War Veterans.](#)

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J Am Acad Audiol. **2018 Nov 14**. doi: 10.3766/jaaa.17122. PMID: 30424834. [Epub ahead of print]

BACKGROUND: Gulf War Illness (GWI) is a chronic condition involving symptoms across multiple body systems. Previous research has implicated the vestibular system as a potential underlying factor in the symptoms experienced by veterans with GWI, due in part to exposure to potentially ototoxic chemicals and events.

PURPOSE: To characterize the presence of vertigo and dizziness symptoms in a sample of veterans with GWI using validated self-report instruments, accounting for mental health comorbidities.

RESEARCH DESIGN: This is a case series, follow-up, prospective interview of clinical veterans; results presented are purely descriptive.

STUDY SAMPLE: Our sample of 50 veterans was a follow-up to a case series of clinical Gulf War veterans evaluated at the War Related Illness and Injury Study Center.

DATA COLLECTION AND ANALYSIS: Veterans participated in a 70-min phone interview where the following questionnaires were administered: Vertigo Symptom Scale (VSS), Patient Health Questionnaire (depression scale), Patient Health Questionnaire (somatization scale), Beck Anxiety Inventory, Posttraumatic Stress Disorder (PTSD) Checklist, Defense and Veterans Brain Injury Center Traumatic Brain Injury Questionnaire, and GWI (Kansas) Questionnaire. We used descriptive (mean/median, standard deviation, interquartile range, and percentage) statistics to describe our sample and illuminate possible relationships between measures.

RESULTS: Our primary finding is a substantial report of vertigo symptoms in our sample, according to the VSS. Ninety percent of participants scored above the VSS threshold (>12), suggesting "severe dizziness." The most commonly endorsed symptom on the VSS was "headache or pressure in the head."

CONCLUSIONS: We conclude that there is significant burden of vertigo symptoms in veterans with GWI, suggesting a need for objective tests of vestibular function in this population. Furthermore, the relationship between symptoms of vertigo and dizziness, vestibular function, and PTSD warrants further exploration using objective measures.

CHRONIC FATIGUE SYNDROME

[Evaluation of four clinical laboratory parameters for the diagnosis of myalgic encephalomyelitis.](#)

[De Meirleir KL](#)¹, [Mijatovic T](#)², [Subramanian K](#)³, [Schlauch KA](#)⁴, [Lombardi VC](#)⁵.

J Transl Med. **2018 Nov 21**;16(1):322. doi: 10.1186/s12967-018-1696-z. PMID: 30463572.

BACKGROUND: Myalgic encephalomyelitis (ME) is a complex and debilitating disease that often initially presents with flu-like symptoms, accompanied by incapacitating fatigue. Currently, there are no objective biomarkers or laboratory tests that can be used to unequivocally diagnosis ME; therefore, a diagnosis is made when a patient meets series of a costly and subjective inclusion and exclusion criteria. The purpose of the present study was to evaluate the utility of four clinical parameters in diagnosing ME.

METHODS: In the present study, we utilized logistic regression and classification and regression tree analysis to conduct a retrospective investigation of four clinical laboratory in 140 ME cases and 140 healthy controls.

RESULTS: Correlations between the covariates ranged between [- 0.26, 0.61]. The best model included the serum levels of the soluble form of CD14 (sCD14), serum levels of prostaglandin E2 (PGE₂), and serum levels of interleukin 8, with coefficients 0.002, 0.249, and 0.005, respectively, and p-values of 3×10^{-7} , 1×10^{-5} , and 3×10^{-3} , respectively.

CONCLUSIONS: Our findings show that these parameters may help physicians in their diagnosis of ME and may additionally shed light on the pathophysiology of this disease.

CHRONIC FATIGUE SYNDROME (Continued)

[Low omega-3 index and polyunsaturated fatty acid status in patients with chronic fatigue syndrome/myalgic encephalomyelitis.](#)

[Castro-Marrero J](#)¹, [Zaragoza MC](#)², [Domingo JC](#)³, [Martinez-Martinez A](#)⁴, [Alegre J](#)⁴, [von Schacky C](#)⁵.

Prostaglandins Leukot Essent Fatty Acids. **2018 Dec**;139:20-24. doi: 10.1016/j.plefa.2018.11.006. PMID: 30471769. Epub 2018 Nov 9.

BACKGROUND: Several studies have suggested that low levels of omega-3 fatty acids (n-3 PUFAs) including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are associated with cardiovascular risk, major depression, sleep problems, inflammation and other health-related issues. So far, however, erythrocyte PUFA status in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) has not been established. This study aimed to determine whether n-3 PUFA content and omega-3 index are associated with measures in CFS/ME patients.

PATIENTS AND METHODS: PUFA levels and omega-3 index were measured in 31 Spanish CFS/ME patients using the HS-Omega-3 Index method. Demographic and clinical characteristics and self-reported outcome measures were also recorded.

RESULTS: A low mean omega-3 index (5.75%) was observed in 92.6% of the sample. Omega-3 index was inversely correlated with the AA/EPA ratio ($p = 0.00002$) and the BMI ($p = 0.0106$). In contrast, the AA/EPA ratio was positively associated with the BMI ($p = 0.0038$). No association for FIS-40 and PSQI measures was found ($p > 0.05$).

CONCLUSION: The low omega-3 index found in our CFS/ME patients may indicate increased risks for cardiovascular health, which should be further investigated. A low omega-3 index also suggests a pro-inflammatory state in these patients. Attempts should be made to increase the omega-3 index in CFS/ME patients, based on intervention trials assessing a potential therapeutic value.

[The development and initial validation of the Fatigue Sensitivity Questionnaire.](#)

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Cogn Behav Ther. **2018 Nov 20**:1-11. doi: 10.1080/16506073.2018.1533580. PMID: 30457446. [Epub ahead of print]

Currently, there is poor understanding of fatigue and the possible psychological conditions that may underlie chronic fatigue. Although substantial work has been directed to better clinically address fatigue, no work has explored individual differences in expectations or perceptions of the negative consequences associated with fatigue-related symptoms. The goals of this study were to (a) develop and (b) validate a measure of expectations or perceptions of the negative consequences associated with fatigue-related symptoms (e.g. fatigue sensitivity) across two independent samples ($N = 1,827$; 73.1% female; $M_{age} = 21.68$; $SD = 4.54$) of young adults. Results supported a 10-item measure of fatigue sensitivity, entitled the Fatigue Sensitivity Questionnaire (FSQ). The FSQ demonstrated unidimensionality, excellent internal consistency, and strong convergent and discriminant validity. Overall, the 10-item scale offers a single score that can be employed to measure fatigue sensitivity. Clinically, the FSQ may be a brief, informative, and easily disseminated measure in better understanding and capturing expectations or perceptions about the negative consequences of fatigue. As a research tool, the use of the FSQ may provide broader understanding of vulnerability factors that may influence fatigue-related health outcomes. Future research is needed to test the validity of the FSQ in other samples.

HEADACHE and MIGRAINE

[Acute migraine therapy with external trigeminal neurostimulation \(ACME\): A randomized controlled trial.](#)

[Chou DE](#)¹, [Shnayderman Yugrakh M](#)¹, [Winegarner D](#)², [Rowe V](#)², [Kuruville D](#)³, [Schoenen J](#)⁴.

Cephalalgia. **2018 Nov 17**:333102418811573. doi: 10.1177/0333102418811573. PMID: 30449151. [Epub ahead of print]

OBJECTIVE: To assess the safety and efficacy of external trigeminal nerve stimulation for acute pain relief during migraine attacks with or without aura via a sham-controlled trial.

METHODS: This was a double-blind, randomized, sham-controlled study conducted across three headache centers in the United States. Adult patients who were experiencing an acute migraine attack with or without aura were recruited on site and randomly assigned 1:1 to receive either verum or sham external trigeminal nerve stimulation treatment (CEFALY Technology) for 1 hour. Pain intensity was scored using a visual analogue scale (0 = no pain to 10 = maximum pain). The primary outcome measure was the mean change in pain intensity at 1 hour compared to baseline.

RESULTS: A total of 109 participants were screened between February 1, 2016 and March 31, 2017. Of these, 106 patients were randomized and included in the intention-to-treat analysis (verum: n = 52; sham: n = 54). The primary outcome measure was significantly more reduced in the verum group than in the sham group: -3.46 ± 2.32 versus -1.78 ± 1.89 ($p < 0.0001$), or -59% versus -30% ($p < 0.0001$). With regards to migraine subgroups, there was a significant difference in pain reduction between verum and sham for 'migraine without aura' attacks: mean visual analogue scale reduction at 1 hour was -3.3 ± 2.4 for the verum group versus -1.7 ± 1.9 for the sham group ($p = 0.0006$). For 'migraine with aura' attacks, pain reduction was numerically greater for verum versus sham, but did not reach significance: mean visual analogue scale reduction at 1 hour was -4.3 ± 1.8 for the verum group versus -2.6 ± 1.9 for the sham group ($p = 0.060$). No serious adverse events were reported and five minor adverse events occurred in the verum group.

CONCLUSION: One-hour treatment with external trigeminal nerve stimulation resulted in significant headache pain relief compared to sham stimulation and was well tolerated, suggesting it may be a safe and effective acute treatment for migraine attacks.

STUDY PROTOCOL: ClinicalTrials.gov Identifier: [NCT02590939](#).

[Analysis of Initial Nonresponders to Galcanezumab in Patients With Episodic or Chronic Migraine: Results From the EVOLVE-1, EVOLVE-2, and REGAIN Randomized, Double-Blind, Placebo-Controlled Studies.](#)

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Headache. **2018 Nov 21**. doi: 10.1111/head.13443. PMID: 30462830. [Epub ahead of print]

OBJECTIVE: To examine the likelihood of response with continued galcanezumab treatment in patients with episodic or chronic migraine without initial clinical improvement.

BACKGROUND: A percentage of patients with migraine may require additional time on pharmacotherapy but discontinue treatment prematurely. Additionally, recognizing when continued treatment is unlikely to provide improvement limits unnecessary exposure.

METHODS: Post hoc analysis of response after continued galcanezumab treatment was conducted in a subset of patients with episodic (N = 879) and chronic (N = 555) migraine who did not achieve "good" early improvement (episodic, $\geq 50\%$ reduction in baseline migraine headache days [MHD] and chronic, $\geq 30\%$ reduction) after 1 month of dosing (NR-1; episodic, n = 450 and chronic, n = 306). This subset was categorized by level of reduction in MHD during 1 month of treatment: "modest" ($>30\%$ to $<50\%$ fewer MHD for episodic and $>10\%$ to $<30\%$ fewer MHD for chronic), "limited" (episodic only; $>10\%$ to $\leq 30\%$ fewer MHD), or "minimal/no" early improvement ($\leq 10\%$ fewer MHD to $\leq 10\%$ more MHD), or "worsening" ($>10\%$ more MHD). The percentages of patients having "better" ($\geq 75\%$ fewer MHD for episodic and $\geq 50\%$ for chronic), "good," or "little-to-no" ($\leq 10\%$ fewer MHD) response during the remaining treatment period were calculated for each category. Similarly, the subset of NR-1 patients who did not achieve "good" early improvement after 2 months of treatment (NR-2; episodic, n = 290 and chronic, n = 240) were categorized by level of their average monthly reduction across 1 and 2 months using similar categories.

RESULTS: Of NR-1 patients with episodic migraine having "modest" early improvement, 62% (96/155) achieved "good" and 20% (31/155) achieved "better" responses with continued treatment. A percentage of patients with "limited" (43%; 46/108) or "minimal/no" (34%; 29/85) early improvement, or "worsening" (20%; 20/102) achieved a "good" response after continued treatment. A percentage of NR-1 patients with chronic migraine having "modest" early improvement achieved "good" (38%; 44/116) and "better" (13%; 15/116) responses with continued treatment. A "good" response was achieved for a percentage of patients with "minimal/no" early improvement (17%; 23/133). Similar patterns were observed for the NR-2 subset, though percentages were lower.

HEADACHE and MIGRAINE (Continued)

[Lifestyle modifications as therapy for medication refractory post-traumatic headache \(PTHA\) in the military population of Okinawa.](#)

[Baker VB](#)¹, [Eliassen KM](#)², [Hack NK](#)³.

J Headache Pain. **2018 Nov 22**;19(1):113. doi: 10.1186/s10194-018-0943-2. PMID: 30466384.

OBJECTIVE: Our aim was 1) to reduce disability, as characterized by headache frequency, duration and severity in patients with post-traumatic headache (PTHA), 2) to reduce the number of medical boards and work limitations in patients with post traumatic headache, and 3) to reduce use of medical resources and clinic visits related to headache or migraine.

BACKGROUND: Modifiable risk factors for PTHA include stressful life event, sleep disturbances, and medication overuse. Cognitive-behavioral strategies, biofeedback, and relaxation therapy may have an important role in treatment and preventing progression to chronic post-traumatic headache (CPTHA). There is limited literature and a known practice gap for implementation of these techniques.

DESIGN/METHODS: An IRB approved project focused on patients who were seen for PTHA and CPTHA. 1) Intervention consisted of lifestyle teaching, cognitive-behavioral therapy and biofeedback, supplemented by decreasing polypharmacy. 2) Patients were followed for 2 years and a retrospective review was conducted for 2 years prior to presentation. 3) Outcome measures included reduction in migraine intensity or frequency, improved quality of life, duty status, and decreased utilization of clinic visits.

RESULTS: Over the course of one year, 221 patients were treated for migraines in the Naval Okinawa Neurology Clinic. Of these, 22 active duty service members and 3 Dependents suffered a mild TBI prior to onset. After intervention, there was a 36% decrease in PTHA frequency, 56% decrease in headache severity and 60% of patients had improved quality of life as compared to the 2 years prior to intervention. Twenty-four percent had reduction in polypharmacy. Appointment frequency for migraine decreased from an average of 6.8 to 2.6 per year.

CONCLUSIONS: An implemented program geared towards reducing polypharmacy was shown to improve safety, quality of life and reduce hospitalizations from the burden of migraines. Our systematic approach resulted in quality of life improvements and decreased use of medical resources.

TRIAL REGISTRATION: Authors received the approval of NAVMED West, Okinawa Naval Hospital Institutional Review Board on January 13th, 2016. QI.2016.0021.

CHRONIC PAIN

[The mediating effect of sleep disturbance on the relationship between non-malignant chronic pain and suicide death.](#)

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Pain Pract. **2018 Nov 21**. doi: 10.1111/papr.12750. PMID: 30462885. [Epub ahead of print]

IMPORTANCE: Few studies have examined the relationship between non-malignant chronic pain (NMCP) and suicide death and even fewer have specifically explored what role sleep disturbance might play in the association between NMCP and suicide death.

OBJECTIVE: To assess whether sleep disturbance mediates the relationship between NMCP and suicide death.

DESIGN: This case-control study included 2,674 individuals who died by suicide between 2000-2013 (cases) and 267,400 matched individuals (controls).

SETTING: Eight Mental Health Research Network (MHRN)-affiliated healthcare systems.

PARTICIPANTS: All cases and matched controls were health plan members for at least 10 months during the year prior to the index date.

MAIN OUTCOMES AND MEASURES: Sociodemographic data and diagnosis codes for NMCP and sleep disorders were extracted from the MHRN's Virtual Data Warehouse. Suicide mortality was identified using ICD-10 codes from official government mortality records matched to health system records.

RESULTS: After accounting for covariates, there was a significant relationship between NMCP and sleep disturbance; those who were diagnosed with NMCP were more likely to develop subsequent sleep disturbance. Similarly, sleep disturbance was significantly associated with suicide death. Finally, a significant indirect effect of NMCP on suicide death, through sleep disturbance, and a non-significant direct effect of NMCP on suicide death provide support for a fully mediated model.

CONCLUSIONS AND RELEVANCE: There is a need for clinicians to screen for both sleep disturbance and suicidal ideation in NMCP patients and for health systems to implement more widespread behavioral treatments that address comorbid sleep problems and NMCP.

CHRONIC PAIN (Continued)

[The association between multisite musculoskeletal pain and cardiac autonomic modulation during work, leisure and sleep - a cross-sectional study.](#)

[de Oliveira Sato T](#)¹, [Hallman DM](#)², [Kristiansen J](#)³, [Holtermann A](#)^{3,4}.

BMC Musculoskelet Disord. **2018 Nov 20**;19(1):405. doi: 10.1186/s12891-018-2312-3. PMID: 30458750.

BACKGROUND: The prevention and rehabilitation of multisite musculoskeletal pain would benefit from studies aiming to understand its underlying mechanism. Autonomic imbalance is a suggested mechanism for multisite pain, but hardly been studied during normal daily living. Therefore, the aim of the study is to investigate the association between multisite musculoskeletal pain and cardiac autonomic modulation during work, leisure and sleep.

METHODS: This study is based on data from the "Danish Physical activity cohort with objective measurements" among 568 blue-collar workers. Pain intensity scales were dichotomized according to the median of each scale, and the number of pain sites was calculated. No site was regarded as the pain-free, one site was considered as single-site musculoskeletal pain and pain in two or more sites was regarded as multisite musculoskeletal pain. Heart rate variability (HRV) was measured by an electrocardiogram system (ActiHeart) and physical activity using accelerometers (Actigraph). Crude and adjusted linear mixed models were applied to investigate the association between groups and cardiac autonomic regulation during work, leisure and sleep.

RESULTS: There was no significant difference between groups and no significant interaction between groups and domains in the crude or adjusted models for any HRV index. Significant differences between domains were found in the crude and adjusted model for all indices, except SDNN; sleep time showed higher values than leisure and work time, except for LF and LF/HF, which were higher during work.

CONCLUSION: This cross-sectional study showed that multisite musculoskeletal pain is not associated with imbalanced cardiac autonomic regulation during work, leisure and sleep time.

[No moderating impact of a medically unexplained etiology on the relationship between psychological profile and chronic pain.](#)

[McNaughton DT](#)¹, [Hush JM](#)², [Beath AP](#)², [Dear BF](#)², [Jones MP](#)².

J Psychosom Res. **2018 Dec**;115:87-93. doi: 10.1016/j.jpsychores.2018.10.017. PMID: 30470323. Epub 2018 Oct 30.

OBJECTIVES: The objective of the present study was to test the moderating impact of an unknown pain etiology on the relationship between psychological factors and chronic pain intensity and disability.

METHODS: N = 471 chronic pain sufferers presented to an online Cognitive Behavioral Therapy randomized control trial, known as the Pain Course. Participants' etiology was classified as medically unexplained or medically explained via interview and self-reported data. Standardized psychological measures at baseline were used in a non-hierarchical cluster analysis, which allocated chronic pain participants into mutually exclusive groups.

RESULTS: Four distinct clusters were identified: Psychologically healthy, mild psychological distress, high psychological distress, and average. The profile with high psychological distress experienced the greatest pain intensity (mean: 6.44 (SD = 1.66)) and disability (mean: 17.53 (SD: 3.65)). This relationship was not moderated by preceding pain etiology being medically explained or unexplained ($\chi^2(3) = 0.45$, $p = 0.93$ and $\chi^2(3) = 7.07$, $p = 0.07$ respectively).

CONCLUSION: These findings indicate that an unknown pain etiology has little role in altering the relationship between psychological factors and pain disability in individuals experiencing chronic pain. This suggests that the psychological association with pain disability and intensity experienced by people with medically unexplained symptoms is similar to people with medically explained symptoms.

CHRONIC PAIN (Continued)

[Resilience to Pain: A Peripheral Component Identified using induced Pluripotent Stem Cells and Dynamic Clamp.](#)

[Mis MA](#)^{1,2}, [Yang Y](#)^{1,2}, [Tanaka BS](#)^{1,2}, [Gomis-Perez C](#)^{1,2}, [Liu S](#)^{1,2}, [Dib-Hajj F](#)^{1,2}, [Adi T](#)^{1,2}, [Garcia-Milian R](#)³, [Schulman BR](#)^{1,2}, [Dib-Hajj SD](#)^{1,2}, [Waxman SG](#)^{4,2}.

J Neurosci. **2018 Nov 20**. pii: 2433-18. doi: 10.1523/JNEUROSCI.2433-18.2018. PMID: 30459225. [Epub ahead of print]

Pain is a complex process that involves both detection in the peripheral nervous system and perception in the central nervous system. Individual-to-individual differences in pain are well-documented, but not well-understood. Here we capitalized on inherited erythromelalgia (IEM), a well-characterized human genetic model of chronic pain, and studied a unique family containing related IEM subjects with the same disease-causing Nav1.7 mutation, which is known to make dorsal root ganglion (DRG) neurons hyperexcitable, but different pain profiles (affected son with severe pain, affected mother with moderate pain and an unaffected father). We show, first, that at least in some cases, relative sensitivity to pain can be modeled in subject-specific iPSC-derived sensory neurons *in vitro*; second, that in some cases, mechanisms operating in peripheral sensory neurons contribute to inter-individual differences in pain; and third, using Whole Exome Sequencing (WES) and dynamic clamp we show that it is possible to pinpoint a specific variant of another gene, *KCNQ* in this particular kindred, that modulates the excitability of iPSC-derived sensory neurons in this family. While different gene variants may modulate DRG neuron excitability and thereby contribute to inter-individual differences in pain in other families, this study shows that subject-specific iPSCs can be used to model inter-individual differences in pain. We further provide proof-of-principle that iPSCs, WES, and dynamic clamp can be used to investigate peripheral mechanisms and pinpoint specific gene variants that modulate pain signaling and contribute to inter-individual differences in pain.

SIGNIFICANCE STATEMENT: Individual-to-individual differences in pain are well-documented, but not well-understood. In this study we show, first, that at least in some cases, relative sensitivity to pain can be modeled in subject-specific iPSC-derived sensory neurons *in vitro*; second, that in some cases, mechanisms operating in peripheral sensory neurons contribute to inter-individual differences in pain; and third, using Whole Exome Sequencing (WES) and dynamic clamp we show that it is possible to pinpoint a specific gene variant that modulates pain signaling and contributes to inter-individual differences in pain.

OTHER RESEARCH OF INTEREST

[Somatic APP gene recombination in Alzheimer's disease and normal neurons.](#)

[Lee MH](#)¹, [Siddoway B](#)¹, [Kaesler GE](#)^{1,2}, [Segota](#)¹, [Rivera R](#)¹, [Romanow WJ](#)¹, [Liu CS](#)^{1,2}, [Park C](#)^{1,2}, [Kennedy G](#)¹, [Long T](#)¹, [Chun J](#)³.

Nature. **2018 Nov 21**. doi: 10.1038/s41586-018-0718-6. PMID: 30464338. [Epub ahead of print]

The diversity and complexity of the human brain are widely assumed to be encoded within a constant genome. Somatic gene recombination, which changes germline DNA sequences to increase molecular diversity, could theoretically alter this code but has not been documented in the brain, to our knowledge. Here we describe recombination of the Alzheimer's disease-related gene APP, which encodes amyloid precursor protein, in human neurons, occurring mosaically as thousands of variant 'genomic cDNAs' (gencDNAs). gencDNAs lacked introns and ranged from full-length cDNA copies of expressed, brain-specific RNA splice variants to myriad smaller forms that contained intra-exonic junctions, insertions, deletions, and/or single nucleotide variations. DNA *in situ* hybridization identified gencDNAs within single neurons that were distinct from wild-type loci and absent from non-neuronal cells. Mechanistic studies supported neuronal 'retro-insertion' of RNA to produce gencDNAs; this process involved transcription, DNA breaks, reverse transcriptase activity, and age. Neurons from individuals with sporadic Alzheimer's disease showed increased gencDNA diversity, including eleven mutations known to be associated with familial Alzheimer's disease that were absent from healthy neurons. Neuronal gene recombination may allow 'recording' of neural activity for selective 'playback' of preferred gene variants whose expression bypasses splicing; this has implications for cellular diversity, learning and memory, plasticity, and diseases of the human brain.

OTHER RESEARCH OF INTEREST (Continued)**[Association of Concussion With the Risk of Suicide: A Systematic Review and Meta-Analysis.](#)**

[Fralick M](#)^{1,2}, [Sy E](#)^{3,4}, [Hassan A](#)⁵, [Burke MJ](#)⁶, [Mostofsky E](#)^{7,1}, [Karsies T](#)⁸.

JAMA Neurol. **2018 Nov 12**. doi: 10.1001/jamaneurol.2018.3487. PMID: 30419085. [Epub ahead of print]

Importance: Concussion is the most common form of traumatic brain injury (TBI). While most patients fully recover within 1 week of injury, a subset of patients might be at a higher risk of suicide.

Objective: To assess the risk of suicide after concussion.

Data Sources: We performed a systematic search of Medline (PubMed), Embase, PsycINFO, and Published International Literature on Traumatic Stress (PILOTS) from 1963 to May 1, 2017. We also searched Google Scholar and conference proceedings and contacted experts in the field to seek additional studies.

Study Selection: Studies that quantified the risk of suicide, suicide attempt, or suicidal ideation after a concussion and/or mild TBI were included. Studies that included children and adults, including military and nonmilitary personnel, were included. Two authors independently reviewed all titles and abstracts to determine study eligibility.

Data Extraction and Synthesis: Study characteristics were extracted independently by 2 trained investigators. Study quality was assessed using the Newcastle-Ottawa Scale. Study data were pooled using random-effects meta-analysis.

Main Outcomes and Measures: The primary exposure was concussion and/or mild TBI, and the primary outcome was suicide. Secondary outcomes were suicide attempt and suicidal ideation.

Results: Data were extracted from 10 cohort studies (n = 713 706 individuals diagnosed and 6 236 010 individuals not diagnosed with concussion and/or mild TBI), 5 cross-sectional studies (n = 4420 individuals diagnosed and 11 275 individuals not diagnosed with concussion and/or mild TBI), and 2 case-control studies (n = 446 individuals diagnosed and 8267 individuals not diagnosed with concussion and/or mild TBI). Experiencing concussion and/or mild TBI was associated with a 2-fold higher risk of suicide (relative risk, 2.03 [95% CI, 1.47-2.80]; I² = 96%; P < .001). In 2 studies that provided estimates with a median follow-up of approximately 4 years, 1664 of 333 118 individuals (0.50%) and 750 of 126 114 individuals (0.59%) diagnosed with concussion and/or mild TBI died by suicide. Concussion was also associated with a higher risk of suicide attempt and suicide ideation. The heightened risk of suicide outcomes after concussion was evident in studies with and without military personnel.

Conclusions and Relevance: Experiencing concussion and/or mild TBI was associated with a higher risk of suicide. Future studies are needed to identify and develop strategies to decrease this risk.

[New NIH-DoD Limb Loss Registry.](#)

[Rubin R.](#)

JAMA. **2018 Nov 27**;320(20):2067. doi: 10.1001/jama.2018.18508. PMID: 30480712.

The National Institutes of Health (NIH) and the Department of Defense (DoD) are planning to establish the first national Limb Loss and Preservation Registry to improve rehabilitation and quality of life for active military personnel, veterans, and civilians who have lost a limb, according to a recent NIH [announcement](#).

Limb loss can be a result of injury, a surgical procedure, or a birth defect. The NIH and DoD have awarded a 5-year contract, capped at \$5 million, to the Mayo Clinic to develop and launch the registry, which is expected to become operational in 2020.

“The information housed in this database will be vital to preventing limb loss, improving amputation surgeries, refining rehabilitation approaches and guiding the development of devices for people with limb loss,” Alison Cernich, PhD, said in the announcement. Cernich directs the National Center for Medical Rehabilitation Research, part of the NIH’s Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Link to full text of article in [JAMA Health Agencies Update](#).