GULF WAR ILLNESS

Small airways disease in an Operation Desert Storm Deployer: Case report and review of the literature on respiratory health and inhalational exposures from Gulf War I.

Weiler BA[1], Colby TV[2], Floreth TJ[3], Hines SE[1,4].

Am J Ind Med. **2018 Aug 16**. doi: 10.1002/ajim.22893. PMID: 30117179. [Epub ahead of print]

Constrictive Bronchiolitis (CB) has been reported in US Operation Iraqi Freedom/Enduring Freedom (OIF/OEF) deployers but not in those from prior US conflicts. A 62-year old presented with progressive dyspnea 13 years after deployment to the Persian Gulf in 1991-1992, where he was exposed to burning oil well fire emissions, dust storms, and other potential airborne hazards. In 2014, after a chest computed tomography (CT) scan demonstrated diffuse mosaic attenuation, he underwent surgical lung biopsy, which revealed CB. Deployers from both GWI and OIF/OEF share many exposures. As respiratory symptoms are a feature associated with Gulf War medically unexplained illness, there may be a role for renewed interest in evaluating GWI Veterans with unexplained respiratory symptoms for conditions such as CB, which may result from exposures relevant to deployers from both conflicts.

CHRONIC FATIGUE SYNDROME

The expression signature of very long non-coding RNA in myalgic encephalomyelitis/chronic fatigue syndrome.

Yang CA[1,2,3,4], Bauer S[5], Ho YC[3], Sotzny F[5], Chang JG[1,3,4], Scheibenbogen C[6].

J Transl Med. **2018 Aug 17**;16(1):231. doi: 10.1186/s12967-018-1600-x. PMID: 30119681.

BACKGROUND: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a chronic debilitating disease with huge social-economic impact. It has been suggested that immune dysregulation, nitrooxidative stress, and metabolic impairment might contribute to disease pathogenesis. However, the etiology of ME/CFS remains largely unclear, and diagnostic/prognostic disease markers are lacking. Several long noncoding RNAs (lncRNA, > 200 bp) have been reported to play roles in immunological diseases or in stress responses.

METHODS: In our study, we examined the expression signature of 10 very long lncRNAs (> 5 kb, CR933609, His-RNA, AK124742, GNAS1-AS, EmX2OS, MIAT, TUG1, NEAT1, MALAT1, NTT) in the peripheral blood mononuclear cells of 44 ME/CFS patients.

RESULTS: LncRNAs NTT, MIAT and EmX2OS levels were found to be significantly elevated in ME/CFS patients as compared with healthy controls. Furthermore, NTT and EmX2OS levels increased with disease severity. Stimulation of human monocytic cell line THP-1 and glioma cell line KALS1 with H_2O_2 (oxidative stress) and poly (I:C) (double strand RNA, representing viral activation) increased the expression levels of NTT and MIAT.

CONCLUSIONS: Our study revealed a ME/CFS-associated very long lncRNA expression signature, which might reflect the regulatory response in ME/CFS patients to oxidative stress, chronic viral infection and hypoxemia. Further investigations need to be done to uncover the functions and potential diagnostic value of these lncRNAs in ME/CFS.

CHRONIC FATIGUE SYNDROME (Continued)

Longitudinal associations of lymphocyte subsets with clinical outcomes in chronic fatigue syndrome.

Mehalick ML[1], Schmaling KB[1], Sabath DE[2], Buchwald DS[3].

Fatigue. **2018**;6(2):80-91. doi: 10.1080/21641846.2018.1426371. PMCID: PMC6089525. PMID: 30112249. Epub 2018 Jan 12.

Background: Chronic fatigue syndrome (CFS) is characterized by prolonged fatigue and other physical and neurocognitive symptoms. Some studies suggest that CFS is accompanied by disruptions in the number and function of various lymphocytes. However, it is not clear which lymphocytes might influence CFS symptoms.

Purpose: To determine if patient reported fatigue symptoms and physical functioning scores significantly changed across time with lymphocyte counts as evidence of a relation among chronic fatigue symptoms and the immune response.

Methods: The current longitudinal, naturalistic study assessed the cellular expression of three lymphocyte subtypes -- natural killer (NK) cells (CD3-CD16+ and CD3-CD56+) and naïve T cells (CD4+CD45RA+) -- to determine whether changes in lymphocytes at 4 time points across 18 months were associated with clinical outcomes, including CFS symptoms, physical functioning, and vitality, among patients with chronic fatigue. Latent growth curve models were used to examine the longitudinal relationship between lymphocytes and clinical outcomes.

Results: Ninety-three patients with Fukuda-based CFS and seven with non-CFS fatigue provided study data. Results indicated that higher proportions of naïve T cells and lower proportions of NK cells were associated with worse physical functioning, whereas higher proportions of NK cells (CD3-CD16+) and lower proportions of naïve T cells were associated with fewer CFS symptoms.

Conclusion: These findings suggest that lymphocytes are modestly related to clinical outcomes over time.

Biopsychosocial predictors and trajectories of work participation after transdiagnostic occupational rehabilitation of participants with mental and somatic disorders: a cohort study.

Hara KW[1,2,3,4], Bjørngaard JH[5,6], Jacobsen HB[7,8,9], Borchgrevink PC[7,10,8], Johnsen R[5], Stiles TC[11], Brage S[12], Woodhouse A[5,7,10].

BMC Public Health. **2018 Aug 15**;18(1):1014. doi: 10.1186/s12889-018-5803-0. PMID: 30111291.

BACKGROUND: Group-based transdiagnostic occupational rehabilitation programs including participants with mental and somatic disorders have emerged in clinical practice. Knowledge is sparse on subsequent participation in competitive work. This study aimed to investigate trajectories for (re)entry to work for predefined subgroups in a diagnostically heterogeneous sample of sick-listed participants after completing occupational rehabilitation.

METHODS: A cohort of 212 participants aged 18-69 on long-term sick leave (> 8 weeks) with chronic pain, chronic fatigue and/or common mental disorders was followed for one year after completing a 3½-week rehabilitation intervention based on Acceptance and Commitment Therapy. Self-reported, clinical and registry data were used to study the associations between predefined biopsychosocial predictors and trajectories for (re)entry to competitive work (≥ 1 day per week on average over 8 weeks). Generalized estimating equations analysis was used to investigate trajectories.

RESULTS: For all biopsychosocial subgroups (re)entry to work increased over time. Baseline employment, partial sick leave and higher expectation of return to work (RTW) predicted higher probability of having (re)entered work at any given time after discharge. The odds of increasing reentry over time (statistical interaction with time) was weaker for the group receiving the benefit work assessment allowance compared with those receiving sickness benefit (OR = 0.92, p = 0.048) or for those on partial sick leave compared with full sick leave (OR 0.77, p < 0.001), but higher for those who at baseline had reported having a poor economy versus not (OR 1.16, p = 0.010) or reduced emotional functioning compared with not (OR 1.11, p = 0.012). Health factors did not differentiate substantially between trajectories.

CONCLUSIONS: Work participation after completing a transdiagnostic occupational rehabilitation intervention was investigated. Individual and system factors related to work differentiated trajectories for (re)entry to work, while individual health factors did not. Having a mental disorder did not indicate a worse prognosis for (re)entry to work following the intervention. Future trials within occupational rehabilitation are recommended to pivot their focus to work-related factors, and to lesser extent target diagnostic group.

HEADACHE and MIGRAINE

Fremanezumab for preventive treatment of migraine: Functional status on headache-free days.

VanderPluym J[1], Dodick DW[2], Lipton RB[2], Ma Y [2], Loupe PS[2], Bigal ME[2].

Neurology. **2018 Aug 17**. pii: 10.1212/01.wnl.0000544321.19316.40. doi: 10.1212/01.wnl.0000544321.19316.40. PMID: 30120138. [Epub ahead of print]

OBJECTIVE: To evaluate the effect of fremanezumab on the functional status on headache-free days in phase 2 episodic migraine (EM) and chronic migraine (CM) studies.

METHODS: Functional status data were collected prospectively via the electronic headache diary on all headache-free days by patients answering questions regarding work/school/household chore performance, speed of work completion, concentration, and feeling of fatigue. Individuals with EM receiving monthly doses of fremanezumab 225 mg (n = 96) or 675 mg (n = 97) or placebo (n = 104) were compared. Individuals with CM receiving fremanezumab 675 mg followed by monthly 225 mg (n = 88) and 900 mg (n = 86) were also independently compared to those receiving placebo (n = 89).

RESULTS: In patients with EM, compared to patients receiving placebo, those receiving fremanezumab experienced an increased number of headache-free days with normal function in work/school/household chore performance and concentration/mental fatigue measures compared to their baseline over the entire treatment period (all $p < 0.005$). An increased number of headache-free days with normal functional performance for some measures was also found in the CM group in those treated with fremanezumab.

CONCLUSION: There was an increased number of headache-free days with normal functional performance on all measures for the patients with EM and some measures for patients with CM in the fremanezumab-treated groups. Further research is required to confirm these findings in a prospective study and to clarify the underlying mechanism(s).

CLINICALTRIALSGOV IDENTIFIER: NCT02025556 and NCT02021773.

CLASSIFICATION OF EVIDENCE: This study provides Class II evidence that for patients with migraine, fremanezumab increases normal functional performance on headache-free days.

Thyrotropin levels and severity of symptoms in migraine patients of tertiary headache center.

Starikova NL[1], Baidina TV[1], Kalashnikova TP[1].

Cephalalgia. **2018 Aug 13**:333102418794941. doi: 10.1177/0333102418794941. PMID: 30103617. [Epub ahead of print]

Background: The role of thyroid regulation in migraine is poorly understood, and data is contradictory. Objective To study the possible association of clinical features of migraine with patients' thyroid function.

Patients and methods: One hundred and thirty migraine patients of a tertiary headache center took part in an open-label, cross-sectional comparative study. The Migraine Disability Assessment questionnaire, Spielberger State-Trait Anxiety Inventory, Beck Depression Inventory, Vanderbilt's Questionnaire of Pain Management, Gothenburg Quality of Life Questionnaire and Migraine-Specific Quality of Life questionnaire were used. The effectiveness of the attacks' therapy was assessed according to the Migraine Assessment of Current Therapy questionnaire. Levels of thyrotropine (thyroid stimulating hormone), thyroxine, and triiodothyronine were studied by standard immune chemiluminescent method using the Immulite-2000 set.

Results: An inverse correlation between levels of thyroid stimulating hormone in serum and duration of headache attacks was revealed. The effectiveness of abortive therapy for attacks showed a statistically significant positive correlation with thyroid stimulating hormone level. Quality of life measured by a general quality of life questionnaire, as well as the functional and social indices of a migraine-specific questionnaire, showed direct correlation with serum thyroid stimulating hormone.

Conclusion: These results show an association of a more severe clinical course of migraine with lower thyroid stimulating hormone levels.

HEADACHE and MIGRAINE (Continued)

Measures of Functioning in Patients With Episodic Migraine: Findings From a Double-Blind, Randomized, Placebo-Controlled Phase 2b Trial With Galcanezumab.

Ayer DW[1], Skljarevski V[1], Ford JH[1], Nyhuis AW[1], Lipton RB[2], Aurora SK[1].

Headache. **2018 Aug 14**. doi: 10.1111/head.13383. PMID: 30106172. [Epub ahead of print]

Objective - To evaluate 12-week changes from baseline of 2 disease-specific patient-reported outcome (PRO) measures in adults with migraine treated with galcanezumab, an investigational humanized antibody binding calcitonin gene-related peptide (CGRP), or placebo.

Background - Preventing headache-related functional impairment is an important goal of migraine preventive treatment and a measurement target for PROs. Understanding which drugs have the potential to improve patient functioning in addition to preventing migraine headaches is vital to lessening patient burden.

Design/Methods - This Phase 2b double-blind, randomized, placebo-controlled study enrolled adults with episodic migraine. Galcanezumab (120 mg subcutaneous injection; n = 60) or placebo (n = 127) was administered every 28 days for 12 weeks. Post hoc secondary analyses were conducted for those who completed 12 weeks of treatment on 2 PROs: The Migraine-Specific Quality of Life Questionnaire (MSQ) v2.1 and the Headache Impact Test™ (HIT-6).

Results - Analysis of covariance revealed significant differences in least square mean changes from baseline between galcanezumab and placebo for all MSQ domains including total mean change placebo of 18.63, galcanezumab of 27.36 (95% CI 2.449, 15.008; P-value of .0067); Role Function-Restrictive mean change placebo of 22.40, galcanezumab of 31.92 (95% CI 2.636, 16.518; P-value of .0071); Role Function-Preventive mean change placebo of 13.43, galcanezumab of 19.76 (95% CI 0.476, 12.185; P-value of .0342); and Emotional Function mean change placebo of 16.88, galcanezumab of 26.61 (95% CI 2.789, 16.674; P-value of .0063). At baseline, mean number of migraine headache days (MHDs) did not correlate with MSQ total scores or HIT-6. At 12 weeks post-treatment, MHD correlated with MSQ and HIT-6 scores (all P < .0001). Change in MHD was associated with change in MSQ domains and change in HIT-6 scores (all P < .0001).

Conclusions - In comparison with placebo, treatment with galcanezumab was associated with significant functional improvements as reflected by changes in MSQ scores. Change in MHD was associated with improvements in MSQ and reductions in HIT-6 scores, indicating the clinical importance of these changes in relation to PROs that measure function.

Prevalence of restless legs syndrome in individuals with migraine: a systematic review and meta-analysis of observational studies.

Yang X[1], Liu B[1], Yang B[2], Li S[3], Wang F[1], Li K[1], Hu F[4], Ren H[1], Xu Z[5].

Neurol Sci. **2018 Aug 17**. doi: 10.1007/s10072-018-3527-7. PMID: 30116981. [Epub ahead of print]

OBJECTIVE: Recent studies have shown an association between migraine and restless legs syndrome (RLS), but RLS prevalence among individuals with migraine differs substantially across studies. The present work aimed to comprehensively assess available evidence to estimate RLS prevalence among individuals with migraine and non-migraine controls.

METHOD: Web of Science, PubMed, Embase, Chinese National Knowledge Infrastructure, Wanfang, and SinoMed databases were searched for observational and case-control studies of RLS prevalence among individuals with migraine. Eligible studies were meta-analyzed using Stata 12.0 software.

RESULTS: Pooled RLS prevalence in migraine was 19%, and the prevalence was lower in Asia (16%) than outside Asia (21%). Pooled RLS prevalence was 18.8% among individuals with migraine with aura, and 18.5% among individuals with migraine without aura; the RLS prevalence in migraine with aura (MA) was higher than that of migraine without aura (MO) (OR 1.17, 95%CI 1.01-1.34; p = 0.037). Pooled RLS prevalence in a case-control study was significantly higher among individuals with migraine (17.9%) than among non-migraine controls (7.1%) (OR 2.65, 95%CI 2.26-3.10; p < 0.001).

CONCLUSION: Our meta-analysis provides the first reliable pooled estimate of RLS prevalence among individuals with migraine, and it provides strong evidence that RLS risk is higher among individuals with migraine than among controls.

HEADACHE and MIGRAINE (Continued)

Efficacy and safety of DFN-11 (sumatriptan injection, 3 mg) in adults with episodic migraine: an 8-week open-label extension study.

Landy S[1], Munjal S[2], Brand-Schieber E[3], Rapoport AM[4].

J Headache Pain. **2018 Aug 15**;19(1):70. doi: 10.1186/s10194-018-0882-y. PMID: 30112725.

BACKGROUND: DFN-11, a 3 mg sumatriptan subcutaneous (SC) autoinjector for acute treatment of migraine, has not been assessed previously in multiple attacks. The objective of this study was to evaluate the efficacy, tolerability, and safety of DFN-11 in the acute treatment of multiple migraine attacks.

METHODS: This was an 8-week open-label extension of multicenter, randomized, double-blind, placebo-controlled US study. Subjects averaging 2 to 6 episodic migraine attacks per month were randomized to DFN-11 or placebo to treat a single attack of moderate-to-severe intensity and then entered the extension study to assess the efficacy, tolerability, and safety of DFN-11 in multiple attacks of any pain intensity.

RESULTS: Overall, 234 subjects enrolled in the open-label period, and 29 (12.4%) discontinued early. A total of 848 migraine episodes were treated with 1042 doses of open-label DFN-11 and subjects treated a mean (SD) of 3.9 (2.3) attacks. At 2 h postdose in attacks 1 (N = 216), 2 (N = 186), 3 (N = 142) and 4 (N = 110), respectively, pain freedom rates were 57.6%, 64.6%, 61.6%, and 66.3%; pain relief rates were 83.4%, 88.4%, 84.1%, and 81.7%; most bothersome symptom (MBS)-free rates were 69.0%, 76.5%, 77.7%, and 74.7%; nausea-free rates were 78.1%, 84.6%, 86.5%, and 85.7%; photophobia-free rates were 75.3%, 76.4%, 72.3%, and 77.5%; and phonophobia-free rates were 75.2%, 77.5%, 73.6%, and 76.0%. Overall, 40.6% (89/219) of subjects reported treatment-emergent adverse events (TEAE), the most common of which were associated with the injection site: swelling (12.8%), pain (11.4%), irritation (6.4%), and bruising (6.4%). Most subjects (65.2%, 58/89) had mild TEAEs; severe TEAEs were reported by 1 subject (treatment-related jaw tightness). Five subjects (2.1%) discontinued due to adverse events, which included mild throat tightness (n = 2), moderate hernia pain (n = 1), moderate hypersensitivity (n = 1), and 1 subject with mild nausea and moderate injection site swelling. There were no serious TEAEs and no new or unexpected safety findings.

CONCLUSION: DFN-11 was effective, tolerable, and safe in the acute treatment of 4 migraine attacks over 8 weeks, with consistent responses on pain and associated symptoms. Most TEAEs were mild, with a very low incidence of triptan-related TEAEs. DFN-11 is potentially an effective and safe alternative for the acute treatment of migraine.

TRIAL REGISTRATION: ClinicalTrials.gov, NCT02569853 . Registered 07 October 2015.

CHRONIC PAIN

The prevalence and awareness of sleep apnea in patients suffering chronic pain: an assessment using the STOP-Bang sleep apnea questionnaire.

Tentindo GS[1], Fishman SM[2], Li CS[3], Wang Q[4], Brass SD[5,6].

Nat Sci Sleep. **2018 Aug 1**;10:217-224. doi: 10.2147/NSS.S167658. PMCID: PMC6078087. PMID: 30123015. eCollection 2018.

Purpose: Some patient subsets are at higher risk of sleep apnea, including patients with chronic pain. However, it is unclear whether patients and their caregivers are aware of the possibly increased risk of sleep apnea in this population. Chronic pain is often treated with opioids which may decrease both the central respiratory drive and the patency of the upper airway, potentially contributing to this sleep disorder. Using a self-reporting questionnaire approach in the chronic pain population, this study surveyed patient and caregiver awareness surrounding the risk of sleep apnea. In addition, we looked at the influence of opioid therapy on the prevalence of sleep apnea.

Participants and methods: Consecutive patients presenting to a pain clinic were invited to participate anonymously in a survey that included the STOP-Bang sleep apnea questionnaire, which assesses patients' knowledge, testing, diagnosis, or treatment of sleep apnea and whether their caregivers had discussed with them their increased risk of sleep apnea and opioid use.

Results: Among 305 participating patients, 58.2% (n=173) screened positive for sleep apnea. Among the 202 patients on opioid therapy, 59.2% (116/202) were STOP-Bang positive (score ≥3). However, only 37.5% (n=72/173) of these patients had discussed their risk of sleep apnea with a caregiver and only 30.7% (n=59) underwent testing. Against expectation, opioids did not increase the prevalence of sleep apnea in our study population.

Conclusion: Chronic pain patients had a high risk of sleep apnea, regardless of opioid prescription. Most patients were unaware of their increased risk and denied undergoing the necessary testing. Greater attention to screening, testing, and education for sleep apnea needs to be paid in chronic pain patients, especially given the potentially dangerous ramifications of opioid-induced sleep apnea.

CHRONIC PAIN (Continued)

Do fragments and glycosylated isoforms of alpha-1-antitrypsin in CSF mirror spinal pathophysiological mechanisms in chronic peripheral neuropathic pain? An exploratory, discovery phase study.

Bäckryd E[1], Edström S[2], Gerdle B[2], Ghafouri B[2].

BMC Neurol. **2018 Aug 16**;18(1):116. doi: 10.1186/s12883-018-1116-2. PMID: 30115020.

BACKGROUND: Post-translational modifications (PTMs) generate a tremendous protein diversity from the ~ 20,000 protein-coding genes of the human genome. In chronic pain conditions, exposure to pathological processes in the central nervous system could lead to disease-specific PTMs detectable in the cerebrospinal fluid (CSF). In a previous hypothesis-generating study, we reported that seven out of 260 CSF proteins highly discriminated between neuropathic pain patients and healthy controls: one isoform of angiotensinogen (AG), two isoforms of alpha-1-antitrypsin (AT), three isoforms of haptoglobin (HG), and one isoform of pigment epithelium-derived factor (PEDF). The present study had three aims: (1) To examine the multivariate inter-correlations between all identified isoforms of these seven proteins; (2) Based on the results of the first aim, to characterize PTMs in a subset of interesting proteins; (3) To regress clinical pain data using the 260 proteins as predictors, thereby testing the hypothesis that the above-mentioned seven discriminating proteins and/or the characterized isoforms/fragments of aim (2) would be among the proteins having the highest predictive power for clinical pain data.

METHODS: CSF samples from 11 neuropathic pain patients and 11 healthy controls were used for biochemical analysis of protein isoforms. PTM characterization was performed using enzymatic reaction assay and mass spectrometry. Multivariate data analysis (principal component analysis and orthogonal partial least square regression) was applied on the quantified protein isoforms.

RESULTS: We identified 5 isoforms of AG, 18 isoforms of AT, 5 isoforms of HG, and 5 isoforms of PEDF. Fragments and glycosylated isoforms of AT were studied in depth. When regressing the pain intensity data of patients, three isoforms of AT, two isoforms of PEDF, and one isoform of angiotensinogen "reappeared" as major results, i.e., they were major findings both when comparing patients with healthy controls and when regressing pain intensity in patients.

CONCLUSIONS: Altered levels of fragments and/or glycosylated isoforms of alpha-1-antitrypsin might mirror pathophysiological processes in the spinal cord of neuropathic pain patients. In particular, we suggest that a putative disease-specific combination of the levels of two different N-truncated fragments of alpha-1-antitrypsin might be interesting for future CSF and/or plasma biomarker investigations in chronic neuropathic pain.

The Chinese Medicine Wu-Tou Decoction Relieves Neuropathic Pain by Inhibiting Hippocampal Microglia Activation.

Zhu C[1], Xu Q[1], Mao Z[1], Lin N[2].

Sci Rep. **2018 Aug 16**;8(1):12292. doi: 10.1038/s41598-018-30006-7. PMID: 30115941.

The comorbidity between the nociceptive and mental syndromes adds to the refractoriness of neuropathic pain (NP). Wu-Tou decoction (WTD) has been prescribed for chronic pain for thousands of years in China. Recently, we reported that WTD was helpful for hippocampus and co-curative for the nociceptive, depressive and anxiety behaviors in the spinal cord ligation (SNL) mice. However, the mechanism underlying the rescue of hippocampus, as well as the roles hippocampus assumed in co-curation remain unexplored. In this study, we validated that in SNL mice, the long-lasting damages to limbic system were mainly limited to hippocampus. In addition, hippocampal neurons were proven sensitive to harms induced by microglia and rescued by WTD, which in sum indicated hippocampal microglia as the critical modulator of co-curation. To validate this hypothesis the hippocampal microglia were mal-activated in shamed mice, in which the atrophy of hippocampus and the development of NP syndromes were consolidated and proven rescued by WTD. On the contrary, in the SNL mice, the failure to control hippocampal microglia was sufficient to void all the rescues mediated by WTD. In sum, our study points out that the effective modulation of microglia in hippocampus is of pivotal importance for the co-curation by WTD.

OTHER RESEARCH OF INTEREST

The Gulf War Era Cohort and Biorepository: A Longitudinal Research Resource of Veterans of the 1990-1991 Gulf War Era.

Khalil L[1], McNeil RB[1,2], Sims KJ[1], Felder KA[1], Hauser ER[1,3,4], Goldstein KM[5,6], Voils CI[7,8], Klimas NG[9,10], Brophy MT[1,11], Thomas CM[1], Whitley RL[1], Dursa EK[1,2,12], Helmer DA[1,3,4,13,14], Provenzale DT[1,5,15].

Am J Epidemiol. **2018 Jul 30**. doi: 10.1093/aje/kwy147. PMID: 30060060. [Epub ahead of print]

The United States Department of Veterans Affairs Gulf War Era Cohort and Biorepository (GWECB) is a nationally representative longitudinal cohort of United States Veterans who served during the 1990-1991 Gulf War era. The GWECB combines survey data, such as demographic, health behavior, and environmental exposure data; medical records; and a linked biorepository of blood specimens that can support a broad range of future research regarding health concerns unique to Veterans of this era. To build this resource, the Veterans Affairs Cooperative Studies Program initiated a pilot study (2014-2016) to establish the GWECB and evaluate the processes required to build and maintain the resource. Participants (n=1,275) consented to future sharing of their data and biospecimens for research purposes. We describe the pilot study, including recruitment and enrollment procedures, data collection and management, quality control, and challenges experienced. The GWECB data available to investigators under approved sharing mechanisms, and the procedures for accessing them, are extensively detailed. The study's consenting documents and a website link for the research survey are provided. Our hope is that new research drawing on the GWECB data and biospecimens will result in effective treatments and improved approaches to address the health concerns of Gulf War Era Veterans.

Disability Rating, Age at Death, and Cause of Death in U.S. Veterans with Service-Connected Conditions.

Maynard C[1,2], Trivedi R[3,4], Nelson K[1,2,5], Fihn SD[1,2,5,6].

Mil Med. **2018 Mar 26**. doi: 10.1093/milmed/usy040. PMID: 29590473. [Epub ahead of print]

Introduction: The association between disability and cause of death in Veterans with service-connected disabilities has not been studied. The objective of this study was to compare age at death, military service and disability characteristics, including disability rating, and cause of death by year of birth. We also examined cause of death for specific service-connected conditions.

Materials and methods: This study used information from the VETSNET file, which is a snapshot of selected items from the Veterans Benefits Administration corporate database. We also used the National Death Index (NDI) for Veterans which is part of the VA Suicide Data Repository. In VETSNET, there were 758,324 Veterans who had a service-connected condition and died between the years 2004 and 2014. Using the scrambled social security number to link the two files resulted in 605,493 (80%) deceased Veterans. Age at death, sex, and underlying cause of death were obtained from the NDI for Veterans and military service characteristics and types of disability were acquired from VETSNET. We constructed age categories corresponding to period of service; birth years 1938 and earlier corresponded to Korea and World War II ("oldest"), birth years 1939-1957 to the Vietnam era ("middle"), and birth years 1958 and later to post Vietnam, Gulf War, and the more recent conflicts in Iraq and Afghanistan ("youngest").

Results: Sixty-two percent were in the oldest age category, 34% in the middle group, and 4% in the youngest one. The overall age at death was 75 ± 13 yr. Only 1.6% of decedents were women; among women 25% were in the youngest age group, while among men only 4% were in the youngest group. Most decedents were enlisted personnel, and 60% served in the U.S. Army. Nearly 61% had a disability rating of >50% and for the middle age group 54% had a disability rating of 100%. The most common service-connected conditions were tinnitus, hearing loss, and post-traumatic stress disorder (PTSD). In the oldest group, nearly half of deaths were due to cancer or cardiovascular conditions and <2% were due to external causes. In the youngest group, cardiovascular disease and cancer accounted for about 1/3 of deaths, whereas external causes or deaths due to accidents, suicide, or assault accounted for nearly 33% of deaths. For Veterans with service-connected PTSD or major depression; 6.5% of deaths were due to external causes whereas for Veterans without these conditions, only 3.1% were due to external causes.

Conclusion: The finding of premature death due to external causes in the youngest age group as well as the finding of higher proportions of external causes in those with PTSD or major depression should be of great concern to those who care for Veterans.

OTHER RESEARCH OF INTEREST (Continued)

Association of Maternal Insecticide Levels With Autism in Offspring From a National Birth Cohort.

Brown AS[1], Cheslack-Postava K[1], Rantakokko P[1], Kiviranta H[1], Hinkka-Yli-Salomäki S[1], McKeague IW[1], Surcel HM[1], Sourander A[1].

Am J Psychiatry. **2018 Aug 16**:appiajp201817101129. doi: 10.1176/appi.ajp.2018.17101129. PMID: 30111184. [Epub ahead of print]

OBJECTIVE: Autism is a complex neurodevelopmental disorder with a largely unknown etiology. To date, few studies have investigated prenatal exposure to toxins and risk of autism by using maternal biomarkers of exposure. Persistent organic pollutants are lipophilic halogenated organic compounds and include the insecticide dichlorodiphenyltrichloroethane (DDT), as well as its metabolite p,p'-dichlorodiphenyl dichloroethylene (p,p'-DDE), and polychlorinated biphenyls (PCBs). The objective of this study was to test whether elevated maternal levels of persistent organic pollutants are associated with autism among offspring.

METHOD: The investigation was derived from the Finnish Prenatal Study of Autism, a national birth cohort study based on a nested case-control design. Cases of autism among children born between 1987 and 2005 were ascertained by national registry linkages. In cases of childhood autism and matched control subjects (778 matched case-control pairs), maternal serum specimens from early pregnancy were assayed for levels of p,p'-DDE and total levels of PCBs.

RESULTS: The odds of autism among offspring were significantly increased with maternal p,p'-DDE levels that were in the highest 75th percentile, with adjustment for maternal age, parity, and history of psychiatric disorders (odds ratio=1.32, 95% CI=1.02, 1.71). The odds of autism with intellectual disability were increased by greater than twofold with maternal p,p'-DDE levels above this threshold (odds ratio=2.21, 95% CI=1.32, 3.69). There was no association between total levels of maternal PCBs and autism.

CONCLUSIONS: These findings provide the first biomarker-based evidence that maternal exposure to insecticides is associated with autism among offspring. Although further research is necessary to replicate this finding, this study has implications for the prevention of autism and may provide a better understanding of its pathogenesis.

Retinal signs and 20-year cognitive decline in the Atherosclerosis Risk in Communities Study.

Deal JA[1], Sharrett AR[2], Rawlings AM[2], Gottesman RF[2], Bandeen-Roche K[2], Albert M[2], Knopman D[2], Selvin E[2], Wasserman BA[2], Klein B[2], Klein R[2].

Neurology. **2018 Mar 27**;90(13):e1158-e1166. doi: 10.1212/WNL.0000000000005205. PMCID: PMC5880633. PMID: 29490915. Epub 2018 Feb 28.

OBJECTIVE: To test the hypothesis that retinal vascular signs are associated with greater cognitive decline over 20 years in 12,317 men and women 50 to 73 years of age at baseline.

METHODS: A composite cognitive score was created with 3 neuropsychological tests measured at 3 time points (1990-1992 to 2011-2013). Retinal signs were measured with fundus photography (1993-1995). Differences in cognitive change by retinal signs status were estimated with linear mixed models. Cognitive scores were imputed for living participants with incomplete cognitive testing.

RESULTS: In multivariable-adjusted analyses that controlled for attrition, loss of vascular integrity (retinopathy and its components) was associated with greater 20-year decline (difference in 20-year cognitive change for moderate/severe vs no retinopathy -0.53 SD, 95% confidence interval -0.74 to -0.33). Estimated differences were similar in participants with and without diabetes mellitus and in white and black participants.

CONCLUSIONS: Retinopathy was associated with accelerated rates of 20-year cognitive decline. These findings support the exploration of more sensitive measures in the eye such as optical coherence tomography angiography, which may provide surrogate indexes of microvascular lesions relevant to cognitive decline in older adults.

###