GULF WAR ILLNESS

No Updates this Week for Gulf War Illness or Chronic Multisymptom Illness.

CHRONIC FATIGUE SYNDROME

Cardiovascular characteristics of chronic fatigue syndrome.

Bozzini S[1], Albergati A[2,3], Capelli E[4], Lorusso L[5], Gazzaruso C[1,3,6], Pelissero G[3], Falcone C[1,3,7].

Biomed Rep. **2018 Jan**;8(1):26-30. doi: 10.3892/br.2017.1024. PMID: 29399336. Epub 2017 Nov 28.

Patients with chronic fatigue syndrome (CFS) commonly exhibit orthostatic intolerance. Abnormal sympathetic predominance in the autonomic cardiovascular response to gravitational stimuli was previously described in numerous studies. The aim of the current study was to describe cardiological and clinical characteristics of Italian patients with CFS. All of the patients were of Caucasian ethnicity and had been referred to our center, the Cardiology Department of the University Hospital of Pavia (Pavia, Italy) with suspected CFS. A total of 44 patients with suspected CFS were included in the present study and the diagnosis was confirmed in 19 patients according to recent clinical guidelines. The characteristics at baseline of the population confirm findings from various previous reports regarding the prevalence in females with a female to male ratio of 4:1, the age of onset of the pathology and the presence of previous infection by the Epstein-Barr virus, cytomegalovirus and other human herpesviruses. Despite the current data indicating that the majority of the cardiological parameters investigated are not significantly different in patients with and without CFS, a significant association between the disease and low levels of blood pressure was identified. Other pilot studies revealed a higher prevalence of hypotension and orthostatic intolerance in patients with CFS. Furthermore, many of the CFS symptoms, including fatigue, vertigo, decreased concentration, tremors and nausea, may be explained by hypotension.

Rethinking childhood adversity in chronic fatigue syndrome.

Clark JE[1], Davidson SL[1], Maclachlan L[1], Newton JL[2], Watson S[1,3].

Fatigue. **2017 Oct 10**;6(1):20-29. doi: 10.1080/21641846.2018.1384095. PMCID: PMC5774185. eCollection 2018.

Background: Previous studies have consistently shown increased rates of childhood adversity in chronic fatigue syndrome (CFS). However, such aetiopathogenic studies of CFS are potentially confounded by co-morbidity and misdiagnosis particularly with depression.

Purpose: We examined the relationship between rates of childhood adversity using two complimentary approaches (1) a sample of CFS patients who had no lifetime history of depression and (2) a modelling approach.

Methods: Childhood trauma questionnaire (CTQ) administered to a sample of 52 participants with chronic fatigue syndrome and 19 controls who did not meet criteria for a psychiatric disorder (confirmed using the Structured Clinical Interview for DSM-IV). Subsequently, Mediation Analysis (Baye's Rules) was used to establish the risk childhood adversity poses for CFS with and without depression.

Results: In a cohort of CFS patients with depression comprehensively excluded, CTQ scores were markedly lower than in all previous studies and, in contrast to these previous studies, not increased compared with healthy controls. Post-hoc analysis showed that CTQ scores correlated with the number of depressive symptoms during the lifetime worst period of low mood. The probability of developing CFS given a history of childhood trauma is 4%, a two-fold increased risk compared to the general population. However, much of this risk is mediated by the concomitant development of major depression.

Conclusions: The data suggests that previous studies showing a relationship between childhood adversity and CFS may be attributable to the confounding effects of co-morbid or misdiagnosed depressive disorder.

Abbreviations: CFS: Chronic fatigue syndrome; CTQ: Childhood trauma questionnaire; MDD: Major depressive disorder; CA: Childhood adversity; *P*: Probability.

CHRONIC FATIGUE SYNDROME (Continued)

Improvement of severe myalgic encephalomyelitis/chronic fatigue syndrome symptoms following surgical treatment of cervical spinal stenosis.

Rowe PC[1], Marden CL[2], Heinlein S[3], Edwards CC 2nd[4].

J Transl Med. **2018 Feb 2**;16(1):21. doi: 10.1186/s12967-018-1397-7. PMID: 29391028.

BACKGROUND: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a potentially disabling disorder. Little is known about the contributors to severe forms of the illness. We describe three consecutive patients with severe ME/CFS whose symptoms improved after recognition and surgical management of their cervical spinal stenosis.

METHODS: All patients satisfied clinical criteria for ME/CFS and orthostatic intolerance, and were later found to have cervical spinal stenosis. Overall function was assessed before and after surgery using the Karnofsky score and the SF-36 physical function subscale score.

RESULTS: Neurological findings included > 3+ deep tendon reflexes in 2 of 3, a positive Hoffman sign in 2 of 3, tremor in 2 of 3, and absent gag reflex in 1 of 3. The cervical spine canal diameter in the three patients ranged from 6 to 8.5 mm. One had congenital cervical stenosis with superimposed spondylosis, and two had single- or two-level spondylosis. Anterior cervical disc replacement surgery in two patients and a hybrid anterior cervical disc fusion and disc replacement in the third was associated with a marked improvement in myelopathic symptoms, resolution of lightheadedness and hemodynamic dysfunction, improvement in activity levels, and improvement in global ME/CFS symptoms.

CONCLUSIONS: The prompt post-surgical restoration of more normal function suggests that cervical spine stenosis contributed to the pathogenesis of refractory ME/CFS and orthostatic symptoms. The improvements following surgery emphasize the importance of a careful search for myelopathic examination findings in those with ME/CFS, especially when individuals with severe impairment are not responding to treatment.

HEADACHE and MIGRAINE

A Genome-Wide Association Study Finds Genetic Associations with Broadly-Defined Headache in UK Biobank (N=223,773).

Meng W[1], Adams MJ[2], Hebert HL[3], Deary IJ[4], McIntosh AM[5], Smith BH[3].

EBioMedicine. **2018 Jan 31**. pii: S2352-3964(18)30028-8. doi: 10.1016/j.ebiom.2018.01.023. PMID: 29397368. [Epub ahead of print]

BACKGROUND: Headache is the most common neurological symptom and a leading cause of years lived with disability. We sought to identify the genetic variants associated with a broadly-defined headache phenotype in 223,773 subjects from the UK Biobank cohort.

METHODS: We defined headache based on a specific question answered by the UK Biobank participants. We performed a genome-wide association study of headache as a single entity, using 74,461 cases and 149,312 controls.

RESULTS: We identified 3343 SNPs which reached the genome-wide significance level of $P<5\times10^{-8}$. The SNPs were located in 28 loci, with the top SNP of rs11172113 in the LRP1 gene having a P value of 4.92×10^{-47}. Of the 28 loci, 14 have previously been associated with migraine. Among 14 new loci, rs77804065 with a P value of 5.87×10^{-15} in the LINC02210-CRHR1 gene was the top SNP. Significant relationships between multiple brain tissues and genetic associations were identified through tissue expression analysis. We also identified significant positive genetic correlations between headache and many psychological traits.

CONCLUSIONS: Our results suggest that brain function is closely related to broadly-defined headache. In addition, we found that many psychological traits have genetic correlations with headache.

HEADACHE and MIGRAINE (Continued)

Activation of pial and dural macrophages and dendritic cells by CSD (67 chrs).

Schain AJ[1,2], Melo-Carrillo A[1,2], Borsook D[2,3], Grutzendler J[4], Strassman AM[1,2], Burstein R[1,2].

Ann Neurol. **2018 Feb 2**. doi: 10.1002/ana.25169. PMID: 29394508. [Epub ahead of print]

OBJECTIVE: Cortical spreading depression (CSD) has long been implicated in migraine attacks with aura. The process by which CSD, a cortical event that occurs within the blood brain barrier (BBB), results in nociceptor activation outside the BBB is likely mediated by multiple molecules and cells. The objective of this study was to determine whether CSD activates immune cells inside the BBB (pia), outside the BBB (dura), or in both, and if so, when.

METHODS: Investigating cellular events in the meninges shortly after CSD, we used in-vivo 2-photon imaging to identify changes in macrophages and dendritic cells (DC) that reside in the pia, arachnoid, and dura, and their anatomical relationship to TRPV1 axons.

RESULTS: We found that activated meningeal macrophages retract their processes and become circular, and that activated meningeal DC stop migrating. We found that CSD activates pial macrophages instantaneously, pial, subarachnoid and dural DC 6-12 minutes later, and dural macrophages 20 minutes later. Dural macrophages and DC can appear in close proximity to TRPV1-positive axons.

INTERPRETATION: The findings suggest that activation of pial macrophages may be more relevant to cases where aura and migraine begin simultaneously, that activation of dural macrophages may be more relevant to cases where headache begins 20-30 minutes after aura, and that activation of dural macrophages may be mediated by activation of migratory DC in the SAS and dura. The anatomical relationship between TRPV1-positive meningeal nociceptors, and dural macrophages and dendritic cells support a role for these immune cells in the modulation of head pain.

Migraine and the risk of incident hypertension among women.

Rist PM[1], Winter AC[2], Buring JE[1], Sesso HD[1], Kurth T[1,3].

Cephalalgia**. 2018 Jan 1**:333102418756865. doi: 10.1177/0333102418756865. PMID: 29388437. [Epub ahead of print]

Background Few studies have examined whether migraine is associated with an increased risk of incident hypertension. Methods We performed a prospective cohort study among 29,040 women without hypertension at baseline. Women were classified as having active migraine with aura, active migraine without aura, a past history of migraine, or no history of migraine. Incident hypertension was defined as new physician diagnosis or newly self-reported systolic or diastolic blood pressure ≥140 mmHg or ≥90 mmHg respectively. Cox proportional hazards models were used to evaluate the association between migraine and incident hypertension. Results During a mean follow-up of 12.2 years, 15,176 incident hypertension cases occurred. Compared to those with no history of migraine, women who experience migraine with aura had a 9% increase in their risk of developing hypertension (95% CI: 1.02, 1.18); women who experience migraine without aura had a 21% increase in their risk of developing hypertension (95% CI: 1.14, 1.28); and women with a past history of migraine had a 15% increase in their risk of developing hypertension (95% CI: 1.07, 1.23). Conclusions Women with migraine have a higher relative risk of developing hypertension compared to women without migraine.

HEADACHE and MIGRAINE (Continued)

Migraine and risk of cardiovascular diseases: Danish population based matched cohort study.

Adelborg K[1], Szépligeti SK[2], Holland-Bill L[2], Ehrenstein V[2], Horváth-Puhó E[2], Henderson VW[2,3,4], Sørensen HT[2,3].

BMJ. **2018 Jan 31**;360:k96. doi: 10.1136/bmj.k96. PMID: 29386181.

OBJECTIVE: To examine the risks of myocardial infarction, stroke (ischaemic and haemorrhagic), peripheral artery disease, venous thromboembolism, atrial fibrillation or atrial flutter, and heart failure in patients with migraine and in a general population comparison cohort.

DESIGN: Nationwide, population based cohort study.

SETTING: All Danish hospitals and hospital outpatient clinics from 1995 to 2013.

PARTICIPANTS: 51 032 patients with migraine and 510 320 people from the general population matched on age, sex, and calendar year.

MAIN OUTCOME MEASURES: Comorbidity adjusted hazard ratios of cardiovascular outcomes based on Cox regression analysis.

RESULTS: Higher absolute risks were observed among patients with incident migraine than in the general population across most outcomes and follow-up periods. After 19 years of follow-up, the cumulative incidences per 1000 people for the migraine cohort compared with the general population were 25 *v* 17 for myocardial infarction, 45 *v* 25 for ischaemic stroke, 11 *v* 6 for haemorrhagic stroke, 13 *v* 11 for peripheral artery disease, 27 *v* 18 for venous thromboembolism, 47 *v* 34 for atrial fibrillation or atrial flutter, and 19 *v* 18 for heart failure. Correspondingly, migraine was positively associated with myocardial infarction (adjusted hazard ratio 1.49, 95% confidence interval 1.36 to 1.64), ischaemic stroke (2.26, 2.11 to 2.41), and haemorrhagic stroke (1.94, 1.68 to 2.23), as well as venous thromboembolism (1.59, 1.45 to 1.74) and atrial fibrillation or atrial flutter (1.25, 1.16 to 1.36). No meaningful association was found with peripheral artery disease (adjusted hazard ratio 1.12, 0.96 to 1.30) or heart failure (1.04, 0.93 to 1.16). The associations, particularly for stroke outcomes, were stronger during the short term (0-1 years) after diagnosis than the long term (up to 19 years), in patients with aura than in those without aura, and in women than in men. In a subcohort of patients, the associations persisted after additional multivariable adjustment for body mass index and smoking.

CONCLUSIONS: Migraine was associated with increased risks of myocardial infarction, ischaemic stroke, haemorrhagic stroke, venous thromboembolism, and atrial fibrillation or atrial flutter. Migraine may be an important risk factor for most cardiovascular diseases.

CHRONIC PAIN

Evidence that dry eye is a comorbid pain condition in a U.S. veteran population.

Lee CJ[1,2], Levitt RC[1,3,4,5], Felix ER[1,6], Sarantopoulos CD[3], Galor A[1,2].

Pain Rep. **2017 Nov 20**;2(6):e629. doi: 10.1097/PR9.0000000000000629. PMCID: PMC5741329. eCollection 2017 Nov.

Introduction: Recent evidence suggests that dry eye (DE) may be comorbid with other chronic pain conditions.

Objectives: To evaluate DE as a comorbid condition in the U.S. veteran population.

Methods: Retrospective review of veterans seen in the Veterans Administration Healthcare System (Veteran Affairs) between January 1, 2010, and December 31, 2014. Dry eye and nonocular pain disorders were ascertained by *International Classification of Diseases, Ninth Revision (ICD-9)* codes. Dry eye was further separated into *ICD-9* codes representing tear film dysfunction or ocular pain. χ^2 and logistic regression analyses were used to examine frequency and risk of DE, ocular pain, and tear film dysfunction by pain disorders.

Results: Of 3,265,894 veterans, 959,881 had a DE diagnosis (29.4%). Dry eye frequency increased with the number of pain conditions reported ($P < 0.0005$). Ocular pain was most strongly associated with headache (odds ratio [OR] 2.98; 95% confidence interval [CI] 2.95-3.01), tension headache (OR 2.64; 95% CI 2.58-2.71), migraine (OR 2.58; 95% CI 2.54-2.61), temporomandibular joint dysfunction (OR 2.39; 95% CI 2.34-2.44), pelvic pain (OR 2.30; 95% CI 2.24-2.37), central pain syndrome (OR 2.24; 95% CI 1.94-2.60), and fibromyalgia/muscle pain (OR 2.23; 95% CI 2.20-2.26), all $P < 0.0005$. Tear film dysfunction was most closely associated with osteoarthritis (OR 1.97; 95% CI 1.96-1.98) and postherpetic neuralgia (OR 1.95; 95% CI 1.90-2.00), both $P < 0.0005$.

Conclusions: Dry eye, including both ocular pain and tear film dysfunction, is comorbid with pain conditions in this nationwide population, implying common mechanisms.

CHRONIC PAIN (Continued)

Meta-analysis of cognitive performance in fibromyalgia.

Bell T[1], Trost Z[1], Buelow MT[2], Clay O[1], Younger J[3], Moore D[4], Crowe M[1].

J Clin Exp Neuropsychol. **2018 Feb 1**:1-17. doi: 10.1080/13803395.2017.1422699. PMID: 29388512. [Epub ahead of print]

INTRODUCTION: Fibromyalgia is a condition with symptoms of pain, physical function difficulties, and emotional problems, but is also characterized by complaints of poor cognition (often called "FibroFog"). Over the last two decades, a number of studies have examined cognitive differences between individuals with and without fibromyalgia. The purpose of the current study was to conduct a quantitative synthesis of these differences across multiple cognitive domains.

METHOD: Following Cochrane guidelines, we identified 37 eligible studies for analysis where persons with fibromyalgia (total n = 964) were compared to participants from age-matched control groups without fibromyalgia (total n = 1025) on a range of neuropsychological measures. Group differences between persons with fibromyalgia and healthy controls were examined for cognitive domains including processing speed, long- and short-term memory, and executive functions (inhibitory control, set shifting, updating, and accessing). Random-effect meta-analyses were conducted to determine effect sizes for these differences in cognitive performance.

RESULTS: Fibromyalgia was significantly and negatively associated with performance on all domains of cognitive function. The largest effect size was found for inhibitory control (g = 0.61), followed by memory (g = 0.51 for short-term, 0.50 for long-term memory). The smallest cognitive difference between those with fibromyalgia and controls was for set shifting (g = 0.30).

CONCLUSION: These findings support the hypothesis that the self-reported cognitive impact of fibromyalgia is also found in objective neuropsychological measures. Routine screening for cognitive dysfunction in those with fibromyalgia may be warranted in addition to assessment of the traditional fibromyalgia symptoms.

Untangling chronic pain and post-concussion symptoms: the significance of depression.

Snell DL[1,2], Martin R[3], Macleod AD[1], Surgenor LJ[4], Siegert RJ[5], Hay-Smith EJC[3], Melzer T[6,7,8], Hooper GJ[2], Anderson T[6,7,8].

Brain Inj. **2018 Feb 1**:1-10. doi: 10.1080/02699052.2018.1432894. PMID: 29388838. [Epub ahead of print]

OBJECTIVES: Post-concussion-like symptoms (PCS) are common in patients without a history of brain injury, such as those with chronic pain (CP). This exploratory study examined neuro-cognitive and psychological functioning in patients with PCS following mild traumatic brain injury (mTBI) or CP, to assess unique and overlapping phenomenology.

METHODS: In this case-control study, participants (n = 102) with chronic symptoms after mTBI (n = 45) were matched with mTBI recovered (n = 31) and CP groups (n = 26), on age, gender, ethnicity and education. Psychological status, cognitive functioning, health symptoms, beliefs and behaviours were examined.

RESULTS: Participants who had not recovered from an mTBI and participants with CP did not differ in terms of PCS symptoms, quality of life, distress or illness behaviours, however, the CP group endorsed fewer subjective cognitive problems, more negative expectations about recovery and more distress ($p < 0.05$). On cognitive testing participants who had not recovered from an mTBI demonstrated greater difficulties with attention ($p < 0.01$) although differences disappeared when depression was controlled in the analyses.

CONCLUSIONS: Unique patterns associated with each condition were evident though caution is required in attributing PCS and cognitive symptoms to a brain injury in people with mTBI presenting with chronic pain and/or depression. Psychological constructs such as illness and recovery beliefs appear to be important to consider in the development of treatment interventions.

OTHER RESEARCH OF INTEREST

Evaluation of the Department of Veterans Affairs Mental Health Services

A Consensus Study Report of The National Academies of Sciences, Engineering, and Medicine.

Released **January 31, 2018**. *Evaluation of the Department of Veterans Affairs Mental Health Services.* Washington, DC: The National Academies Press. doi: https://doi.org/10.17226/24915.

Report at a Glance: Key Findings and Recommendations (HTML). Press Release (HTML)

Approximately 4 million U.S. service members took part in the wars in Afghanistan and Iraq. Shortly after troops started returning from their deployments, some active-duty service members and veterans began experiencing mental health problems. Given the stressors associated with war, it is not surprising that some service members developed such mental health conditions as posttraumatic stress disorder, depression, and substance use disorder. Subsequent epidemiologic studies conducted on military and veteran populations that served in the operations in Afghanistan and Iraq provided scientific evidence that those who fought were in fact being diagnosed with mental illnesses and experiencing mental health–related outcomes—in particular, suicide—at a higher rate than the general population.

Media reports also brought to the nation's attention problems that veterans were having obtaining timely health care appointments and high-quality care through the Department of Veterans Affairs (VA) health system (that is, the Veterans Health Administration, VHA). Addressing the health needs of the large influx of veterans presented a substantial challenge to the VHA. In the National Defense Authorization Act of 2013, Congress included a mandate for the National Academies of Sciences, Engineering, and Medicine (the National Academies) to conduct a study to assess the VHA's mental health care services and provide recommendations to assist the VHA with improving its services. The report that follows details the work of the National Academies' study committee that was appointed to carry out this task.

Ensuring Timely Access to Quality Care for US Veterans.

Daley J[1].

JAMA. **2018 Jan 17**. doi: 10.1001/jama.2017.20743. PMID: 29344616. [Epub ahead of print]

Link to full text of this JAMA Viewpoint article.

The Department of Veterans Affairs (VA) is among the most comprehensive systems of assistance for veterans in the world. The VA provides services to veterans honorably discharged from the military during both war and peace times. The largest of these services is the Veterans Health Administration (VHA), which has a long history of providing health care services to veterans who were either injured or became ill during their service to their country ("service-connected veterans"), and to veterans who are economically disadvantaged and must pass a means test to qualify for VHA care.

For much of its modern history, dating from 1921, VHA has been distinguished by the high quality of care its facilities and staff provide. A recent study concluded that the quality of care in VHA is equal to and, in some cases, better than many non-VHA facilities in the United States.[1] Opportunities still exist for VHA to improve its patient-centered care metrics, but its process of care measures in inpatient and outpatient care compare well with more than 4000 non-VHA hospitals on the CMS Hospital Compare website. The VHA is also an important resource for the training and education of physicians, nurses, and other allied personnel. Since the VA formed mutually advantageous collaborations with academic medical centers 60 years ago, well-trained specialists introduce new diagnostic and treatment techniques to the VHA. In its research programs, the VHA supports basic science and applied research in advancing the care of older patients, palliative care, posttraumatic stress disorder, depression, substance use disorders involving alcohol and opioids, prosthetics development, suicide prevention, and the care of multiple complex injuries, to name only a few.

The VHA has not been without its critics. Members of Congress and other groups such as the Veterans Service Organizations (VSOs), journalists, and the family members of veterans keep a focused and vigilant eye on the quality of care. In 1985, allegations of poor care and suboptimal health outcomes compared with non-VHA hospitals led to the development of new quality measurement and reporting systems, new transparency and accountability tools for review by internal and external stakeholders, and a major restructuring of how VHA facilities were managed and evaluated by VHA leadership…. [Continues in JAMA Viewpoint.]

OTHER RESEARCH OF INTEREST (Continued)

Effect of Prolonged Exposure Therapy Delivered Over 2 Weeks vs 8 Weeks vs Present-Centered Therapy on PTSD Symptom Severity in Military Personnel: A Randomized Clinical Trial.

Foa EB[1], McLean CP[1,2], Zang Y[1], Rosenfield D[3], Yadin E[1], Yarvis JS[4], Mintz J[5,6], Young-McCaughan S[5], Borah EV[5,7], Dondanville KA[5], Fina BA[5], Hall-Clark BN[5], Lichner T[1], Litz BT[8,9], Roache J[5], Wright EC[5,10], Peterson AL[5,11,12]; STRONG STAR Consortium.

JAMA. **2018 Jan 23**;319(4):354-364. doi: 10.1001/jama.2017.21242. PMID: 29362795.

Comment in: A Window Into the Evolution of Trauma-Focused Psychotherapies for Posttraumatic Stress Disorder. [**JAMA. 2018**]

Importance: Effective and efficient treatment is needed for posttraumatic stress disorder (PTSD) in active duty military personnel.

Objective: To examine the effects of massed prolonged exposure therapy (massed therapy), spaced prolonged exposure therapy (spaced therapy), present-centered therapy (PCT), and a minimal-contact control (MCC) on PTSD severity.

Design, Setting, and Participants: Randomized clinical trial conducted at Fort Hood, Texas, from January 2011 through July 2016 and enrolling 370 military personnel with PTSD who had returned from Iraq, Afghanistan, or both. Final follow-up was July 11, 2016.

Interventions: Prolonged exposure therapy, cognitive behavioral therapy involving exposure to trauma memories/reminders, administered as massed therapy (n = 110; 10 sessions over 2 weeks) or spaced therapy (n = 109; 10 sessions over 8 weeks); PCT, a non-trauma-focused therapy involving identifying/discussing daily stressors (n = 107; 10 sessions over 8 weeks); or MCC, telephone calls from therapists (n = 40; once weekly for 4 weeks).

Main Outcomes and Measures: Outcomes were assessed before and after treatment and at 2-week, 12-week, and 6-month follow-up. Primary outcome was interviewer-assessed PTSD symptom severity, measured by the PTSD Symptom Scale-Interview (PSS-I; range, 0-51; higher scores indicate greater PTSD severity; MCID, 3.18), used to assess efficacy of massed therapy at 2 weeks posttreatment vs MCC at week 4; noninferiority of massed therapy vs spaced therapy at 2 weeks and 12 weeks posttreatment (noninferiority margin, 50% [2.3 points on PSS I, with 1-sided $\alpha = .05$]); and efficacy of spaced therapy vs PCT at posttreatment.

Results: Among 370 randomized participants, data were analyzed for 366 (mean age, 32.7 [SD, 7.3] years; 44 women [12.0%]; mean baseline PSS-I score, 25.49 [6.36]), and 216 (59.0%) completed the study. At 2 weeks posttreatment, mean PSS-I score was 17.62 (mean decrease from baseline, 7.13) for massed therapy and 21.41 (mean decrease, 3.43) for MCC (difference in decrease, 3.70 [95% CI,0.72 to 6.68]; P = .02). At 2 weeks posttreatment, mean PSS-I score was 18.03 for spaced therapy (decrease, 7.29; difference in means vs massed therapy, 0.79 [1-sided 95% CI, -∞ to 2.29; P = .049 for noninferiority]) and at 12 weeks posttreatment was 18.88 for massed therapy (decrease, 6.32) and 18.34 for spaced therapy (decrease, 6.97; difference, 0.55 [1-sided 95% CI, ∞ to 2.05; P = .03 for noninferiority]). At posttreatment, PSS-I scores for PCT were 18.65 (decrease, 7.31; difference in decrease vs spaced therapy, 0.10 [95% CI, -2.48 to 2.27]; P = .93).

Conclusions and Relevance: Among active duty military personnel with PTSD, massed therapy (10 sessions over 2 weeks) reduced PTSD symptom severity more than MCC at 2-week follow-up and was noninferior to spaced therapy (10 sessions over 8 weeks), and there was no significant difference between spaced therapy and PCT. The reductions in PTSD symptom severity with all treatments were relatively modest, suggesting that further research is needed to determine the clinical importance of these findings.

Trial Registration: clinicaltrials.gov Identifier: NCT01049516.

OTHER RESEARCH OF INTEREST (Continued)

Cancer risk associated with chronic diseases and disease markers: prospective cohort study.

Tu H[1], Wen CP[2,3,4], Tsai SP[5], Chow WH[1], Wen C[6], Ye Y[1], Zhao H[1], Tsai MK[2], Huang M[1], Dinney CP[7], Tsao CK[8], Wu X[9].

BMJ. **2018 Jan 31**;360:k134. doi: 10.1136/bmj.k134. PMID: 29386192.

OBJECTIVES: To assess the independent and joint associations of major chronic diseases and disease markers with cancer risk and to explore the benefit of physical activity in reducing the cancer risk associated with chronic diseases and disease markers.

DESIGN: Prospective cohort study.

SETTING: Standard medical screening program in Taiwan.

PARTICIPANTS: 405 878 participants, for whom cardiovascular disease markers (blood pressure, total cholesterol, and heart rate), diabetes, chronic kidney disease markers (proteinuria and glomerular filtration rate), pulmonary disease, and gouty arthritis marker (uric acid) were measured or diagnosed according to standard methods, were followed for an average of 8.7 years.

MAIN OUTCOME MEASURES: Cancer incidence and cancer mortality.

RESULTS: A statistically significantly increased risk of incident cancer was observed for the eight diseases and markers individually (except blood pressure and pulmonary disease), with adjusted hazard ratios ranging from 1.07 to 1.44. All eight diseases and markers were statistically significantly associated with risk of cancer death, with adjusted hazard ratios ranging from 1.12 to 1.70. Chronic disease risk scores summarizing the eight diseases and markers were positively associated with cancer risk in a dose-response manner, with the highest scores associated with a 2.21-fold (95% confidence interval 1.77-fold to 2.75-fold) and 4.00-fold (2.84-fold to 5.63-fold) higher cancer incidence and cancer mortality, respectively. High chronic disease risk scores were associated with substantial years of life lost, and the highest scores were associated with 13.3 years of life lost in men and 15.9 years of life lost in women. The population attributable fractions of cancer incidence or cancer mortality from the eight chronic diseases and markers together were comparable to those from five major lifestyle factors combined (cancer incidence: 20.5% *v* 24.8%; cancer mortality: 38.9% *v* 39.7%). Among physically active (versus inactive) participants, the increased cancer risk associated with chronic diseases and markers was attenuated by 48% for cancer incidence and 27% for cancer mortality.

CONCLUSIONS: Chronic disease is an overlooked risk factor for cancer, as important as five major lifestyle factors combined. In this study, chronic diseases contributed to more than one fifth of the risk for incident cancer and more than one third of the risk for cancer death. Physical activity is associated with a nearly 40% reduction in the cancer risk associated with chronic diseases.

Detection and localization of surgically resectable cancers with a multi-analyte blood test.

Cohen JD[1,2,3,4,5], Li L[6], Wang Y[1,2,3,4], Thoburn C[3], Afsari B[7], Danilova L[7], Douville C[1,2,3,4], Javed AA[8], Wong F[1,2,3,4], Mattox A[1,2,3,4], Hruban RH[3,4,9], Wolfgang CL[8], Goggins MG[3,4,9,10,11], Dal Molin M[4], Wang TL[3,9], Roden R[3,9], Klein AP[3,4,12], Ptak J[1,2,3,4], Dobbyn L[1,2,3,4], Schaefer J[1,2,3,4], Silliman N[1,2,3,4], Popoli M[1,2,3,4], Vogelstein JT[13], Browne JD[14], Schoen RE[15,16], Brand RE[15], Tie J[17,18,19,20], Gibbs P[17,18,19,20], Wong HL[17], Mansfield AS[21], Jen J[22], Hanash SM[23], Falconi M[24], Allen PJ[25], Zhou S[1,3,4], Bettegowda C[1,2,3,4], Diaz L[1,3,4], Tomasetti C[26,6,7], Kinzler KW[27,3,4], Vogelstein B[27,2,3,4], Lennon AM[26,4,8,10,11], Papadopoulos N[27,3,4].

[978] Science. **2018 Jan 18**. pii: eaar3247. doi: 10.1126/science.aar3247. PMID: 29348365. [Epub ahead of print]

Earlier detection is key to reducing cancer deaths. Here we describe a blood test that can detect eight common cancer types through assessment of the levels of circulating proteins and mutations in cell-free DNA. We applied this test, called CancerSEEK, to 1,005 patients with non-metastatic, clinically detected cancers of the ovary, liver, stomach, pancreas, esophagus, colorectum, lung, or breast. CancerSEEK tests were positive in a median of 70% of the eight cancer types. The sensitivities ranged from 69% to 98% for the detection of five cancer types (ovary, liver, stomach, pancreas, and esophagus) for which there are no screening tests available for average-risk individuals. The specificity of CancerSEEK was > 99%: only 7 of 812 healthy controls scored positive. In addition, CancerSEEK localized the cancer to a small number of anatomic sites in a median of 83% of the patients.

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