GULF WAR ILLNESS

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

CHRONIC FATIGUE SYNDROME

Psychometric properties of the PROMIS® Fatigue Short Form 7a among adults with myalgic encephalomyelitis/chronic fatigue syndrome.

Yang M[1,2], Keller S[3], Lin JS[4].

Qual Life Res. **2019 Sep 10**. doi: 10.1007/s11136-019-02289-4. PMID: 31506915. [Epub ahead of print]

PURPOSE: To evaluate the psychometric properties of the Patient-Reported Outcome Measurement Information System® Fatigue Short Form 7a (PROMIS F-SF) among people with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS).

METHODS: Analyses were conducted using data from the Multi-Site Clinical Assessment of ME/CFS study, which recruited participants from seven ME/CFS specialty clinics across the US. Baseline and follow-up data from ME/CFS participants and healthy controls were used. Ceiling/Floor effects, internal consistency reliability, differential item functioning (DIF), known-groups validity, and responsiveness were examined.

RESULTS: The final sample comprised 549 ME/CFS participants at baseline, 386 of whom also had follow-up. At baseline, the sample mean of PROMIS F-SF T-score was 68.6 (US general population mean T-score of 50 and standard deviation of 10). The PROMIS F-SF demonstrated good internal consistency reliability (Cronbach's $\alpha = 0.84$) and minimal floor/ceiling effects. No DIF was detected by age or sex for any item. This instrument also showed good known-groups validity with medium-to-large effect sizes ($\eta^2 = 0.08$-0.69), with a monotonic increase of the fatigue T-score across ME/CFS participant groups with low, medium, and high functional impairment as measured by three different variables ($p < 0.01$), and with significantly higher fatigue T-scores among ME/CFS participants than healthy controls ($p < 0.0001$). Acceptable responsiveness was found with small-to-medium effect sizes (Guyatt's Responsiveness Statistic = 0.28-0.54).

CONCLUSIONS: Study findings support the reliability and validity of PROMIS F-SF as a measure of fatigue for ME/CFS and lend support to the drug development tool submission for qualifying this measure to evaluate therapeutic effect in ME/CFS clinical trials.

Inflammatory proteins are altered in chronic fatigue syndrome-A systematic review and meta-analysis.

Strawbridge R[1], Sartor ML[2], Scott F[2], Cleare AJ[2].

Neurosci Biobehav Rev. **2019 Aug 26**;107:69-83. doi: 10.1016/j.neubiorev.2019.08.011. PMID: 31465778. [Epub ahead of print]

Immune dysfunction has been posited as a key element in the aetiology of chronic fatigue syndrome (CFS) since the illness was first conceived. However, systematic reviews have yet to quantitatively synthesise inflammatory biomarkers across the literature. We undertook a systematic review and meta-analysis to quantify available data on circulating inflammatory proteins, examining studies recruiting patients with a CFS diagnosis and a non-affected control group. Results were meta-analysed from 42 studies. Patients with CFS had significantly elevated tumour necrosis factor (ES = 0.274, $p < 0.001$), interleukin-2 (ES = 0.203, $p = 0.006$), interleukin-4 (ES = 0.373, $p = 0.004$), transforming growth factor-β (ES = 0.967, $p < 0.001$) and c-reactive protein (ES = 0.622, $p = 0.019$). 12 proteins did not differ between groups. These data provide some support for an inflammatory component in CFS, although inconsistency of results indicates that inflammation is unlikely to be a primary feature in all those suffering from this disorder. It is hoped that further work will elucidate whether there are subgroups of patients with clinically-relevant inflammatory dysfunction, and whether inflammatory cytokines may provide a prognostic biomarker or moderate treatment effects.

HEADACHE and MIGRAINE

Non-invasive vagus nerve stimulation (nVNS) for the preventive treatment of episodic migraine: The multicentre, double-blind, randomised, sham-controlled PREMIUM trial.

Diener HC[1], Goadsby PJ[2], Ashina M[3], Al-Karagholi MA[3], Sinclair A[4], Mitsikostas D[5], Magis D[6], Pozo-Rosich P[7,8], Sieira PI[9], Làinez MJ[10], Gaul C[11], Silver N[12], Hoffmann J[2], Marin J[2], Liebler E[13], Ferrari MD[14]; PREMIUM Study Group.

Cephalalgia. **2019 Sep 15**:333102419876920. doi: 10.1177/0333102419876920. PMID: 31522546. [Epub ahead of print]

INTRODUCTION: Non-invasive vagus nerve stimulation (nVNS; gammaCore®) has the potential to prevent migraine days in patients with migraine on the basis of mechanistic rationale and pilot clinical data.

METHODS: This multicentre study included a 4-week run-in period, a 12-week double-blind period of randomised treatment with nVNS or sham, and a 24-week open-label period of nVNS. Patients were to administer two 120-second stimulations bilaterally to the neck three times daily (6-8 hours apart).

RESULTS: Of 477 enrolled patients, 332 comprised the intent-to-treat (ITT) population. Mean reductions in migraine days per month (primary outcome) were 2.26 for nVNS (n = 165; baseline, 7.9 days) and 1.80 for sham (n = 167; baseline, 8.1 days) ($p = 0.15$). Results were similar across other outcomes. Upon observation of suboptimal adherence rates, post hoc analysis of patients with ≥ 67% adherence per month demonstrated significant differences between nVNS (n = 138) and sham (n = 140) for outcomes including reduction in migraine days (2.27 vs. 1.53; $p = 0.043$); therapeutic gains were greater in patients with aura than in those without aura. Most nVNS device-related adverse events were mild and transient, with application site discomfort being the most common.

CONCLUSIONS: Preventive nVNS treatment in episodic migraine was not superior to sham stimulation in the ITT population. The "sham" device inadvertently provided a level of active vagus nerve stimulation. Post hoc analysis showed significant effects of nVNS in treatment-adherent patients. Study identification and registration: PREMIUM; NCT02378844; https://clinicaltrials.gov/ct2/show/NCT02378844.

Two-step deep neural network for segmentation of deep white matter hyperintensities in migraineurs.

Hong J[1], Park BY[1], Lee MJ[2], Chung CS[2], Cha J[3], Park H[4].

Comput Methods Programs Biomed. **2019 Sep 5**;183:105065. doi: 10.1016/j.cmpb.2019.105065. PMID: 31522090. [Epub ahead of print]

BACKGROUND AND OBJECTIVE: Patients with migraine show an increased presence of white matter hyperintensities (WMHs), especially deep WMHs. Segmentation of small, deep WMHs is a critical issue in managing migraine care. Here, we aim to develop a novel approach to segmenting deep WMHs using deep neural networks based on the U-Net.

METHODS: 148 non-elderly subjects with migraine were recruited for this study. Our model consists of two networks: the first identifies potential deep WMH candidates, and the second reduces the false positives within the candidates. The first network for initial segmentation includes four down-sampling layers and four up-sampling layers to sort the candidates. The second network for false positive reduction uses a smaller field-of-view and depth than the first network to increase utilization of local information.

RESULTS: Our proposed model segments deep WMHs with a high true positive rate of 0.88, a low false discovery rate of 0.13, and F_1 score of 0.88 tested with ten-fold cross-validation. Our model was automatic and performed better than existing models based on conventional machine learning.

CONCLUSION: We developed a novel segmentation framework tailored for deep WMHs using U-Net. Our algorithm is open-access to promote future research in quantifying deep WMHs and might contribute to the effective management of WMHs in migraineurs.

HEADACHE and MIGRAINE (Continued)

OnabotulinumtoxinA Wear-off Phenomenon in the Treatment of Chronic Migraine.

Masters-Israilov A[1], Robbins MS[2].

Headache. **2019 Sep 16**. doi: 10.1111/head.13638. PMID: 31524289. [Epub ahead of print]

OBJECTIVE: To evaluate the frequency and features of onabotulinumtoxinA (onabotA) wear-off in chronic migraine (CM).

BACKGROUND: Clinical experience suggests that patients with CM frequently perceive onabotA treatment duration <12 weeks, but this phenomenon has not been well explored.

METHODS: This study was a retrospective chart review of patients (n = 143) with CM initiated on onabotA over a 2-year period. Wear-off was considered present with the phrase documented, a quantitative headache day increase, or increased use of abortive medications, bridging therapies or emergency department visits in the 6 weeks preceding the subsequent administration.

RESULTS: Wear-off was present in 90/143 patients (62.9%). Age, sex, medication overuse, psychiatric comorbidity, injector training level, and mean days between injections did not differ between the wear-off and no wear-off groups. Mean units injected per session in the wear-off group until first documented wear-off were significantly less vs no wear-off group (166.0 ± 13.1 vs 173.4 ± 10.3, P = .0005). Wear-off most commonly occurred 2-4 weeks before the next injection (43.3%) and after the very first injection (40.0%). Intramuscular ketorolac injections (33.3%) and peripheral nerve blocks (25.6%) were the most common bridge therapies used in the wear-off period.

CONCLUSIONS: Most patients with CM receiving onabotA experience wear-off. Clinicians may consider increasing the units used from the treatment onset to reduce the frequent need for bridging therapies.

A Biomarker for Discriminating Between Migraine With and Without Aura: Machine Learning on Functional Connectivity on Resting-State EEGs.

Frid A[1], Shor M[2], Shifrin A[3,2], Yarnitsky D[3,2], Granovsky Y[3,2].

Ann Biomed Eng. **2019 Sep 13**. doi: 10.1007/s10439-019-02357-3. PMID: 31520332. [Epub ahead of print]

Advanced analyses of electroencephalography (EEG) are rapidly becoming an important tool in understanding the brain's processing of pain. To date, it appears that none have been explored as a way of distinguishing between migraine patients with aura (MWA) vs. those without aura (MWoA). In this work, we apply a mixture of predictive, e.g., classification methods and attribute-selection techniques, and traditional explanatory, e.g., statistical, analyses on functional connectivity measures extracted from EEG signal acquired from at-rest participants (N = 52) during their interictal period and tested them against the distinction between MWA and MWoA. We show that a functional connectivity metric of EEG data obtained during resting state can serve as a sole biomarker to differentiate between MWA and MWoA. Using the proposed analysis, we not only have been able to present high classification results (average classification of 84.62%) but also to discuss the underlying neurophysiological mechanisms upon which our technique is based. Additionally, a more traditional statistical analysis on the selected features reveals that MWoA patients show higher than average connectivity in the Theta band (p = 0.03) at rest than MWAs. We propose that our data-driven analysis pipeline can be used for resting-EEG analysis in any clinical context.

HEADACHE and MIGRAINE (Continued)

Efficacy of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers in the Preventative Treatment of Episodic Migraine in Adults.

Dorosch T[1], Ganzer CA[2], Lin M[3], Seifan A[4].

Curr Pain Headache Rep. **2019 Sep 12**;23(11):85. doi: 10.1007/s11916-019-0823-8. PMID: 31515634.

PURPOSE OF REVIEW: Systematic review of angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers (ARB) in the prophylactic treatment of adults with migraine. To identify gaps in research and provide guidance for future clinical trials.

RECENT FINDINGS: A search was completed using PubMed, MEDLINE, Embase, and the Cochrane Library January 1, 1990 through December 31, 2017. The following are keywords used in the search: migraine, migraine prophylaxis/prevention, renin-angiotensin-aldosterone system, RAAS, ACE inhibitors, angiotensin-converting enzyme inhibitors: quinapril, perindopril, ramipril, captopril, enalapril, lisinopril, benazepril, fosinopril. Angiotensin receptor blockers, ARB, angiotensin II receptor antagonists: candesartan cilexetil, irbesartan, olmesartan, valsartan, losartan, azilsartan medoxomil, telmisartan, and eprosartan. The search included randomized controlled trials (RCT), systemic reviews and open-label studies of ACE inhibitors and ARB for the prevention of migraine attacks in adults 18-70 years old. Of 2461 retrieved articles, 18 included RCT, meta-analysis, systemic reviews, or guidelines published on ACE inhibitors or ARB in the prevention of migraine. Three RCT with telmisartan 80 mg, candesartan 16 mg, and enalapril 10 mg, and two open-label trials with lisinopril 5 mg and ramipril 5 mg found a high number of responders with greater than 50 % reduction in migraine attack frequency when compared to a 4-week baseline period. Candesartan was superior to placebo while telmisartan and enalapril were not. Lipophilic ACE inhibitors and ARBs can be effective prophylactic agents for reduction of migraine frequency in adults. Based on the limited number of published trials and small sample size, they are not recommended as first-line prophylactic agents. However, in populations with co-morbidities such as hypertension, they may be useful as first- or second-line prophylactics. Additional trials following the International Headache Society's guidelines on RCT are warranted.

Electrographic indices in migraine patients: A systematic review and meta-analysis.

Lee S[1], Gong M[2], Lai RWC[1], Liu FZ[3], Lam MHS[4], Chang D[5], Xia Y[6], Liu T[2], Tse G[7], Li KHC[8].

Electrocardiol. **2019 Jun 1**;57:63-68. doi: 10.1016/j.jelectrocard.2019.05.018. PMID: 31514014. [Epub ahead of print]

BACKGROUND AND AIM: Migraine patients can exhibit autonomic dysregulation, in turn leading to cardiac conduction and repolarization abnormalities. This systematic review and meta-analysis evaluated the electrocardiographic changes in migraineurs.

METHOD: PubMed and Embase databases were searched for human studies using the search terms 'migraine' and 'electrocardiogram' until 15th December 2018, identifying 108 and 131 studies.

RESULTS: Thirteen studies involving 667 migraineurs and 208 normal subjects included (mean age=30.7, total male percentage=19.8%) were included. A longer mean QTc interval (standard mean difference=7.89, 95% confidence interval=[3.29, 12.49], p=0.0008) and higher frequency of QTc prolongation (risk ratio [RR]=6.23, [2.86-13.58], p<0.00001), but no difference in PR-interval (SMD=4.33, [-3.90-12.56], p=0.30) were observed during migraine attacks compared to pain-free periods. P-wave dispersion was higher in migraine patients compared to controls (mean difference=3.62, [1.03-6.21], p=0.006). RR-interval were statistically indistinguishable between migraine patients and controls (SMD=0.08, [-0.65-0.81], p=0.83), or between migraineurs with and without aura (SMD=-0.03, [-0.44-0.38], p=0.89). Deep breathing ratio was significantly lower in migraineurs compared to controls (SMD=-0.27, 95% CI=[-0.46, -0.08], p=0.006) but similar between migraineurs with and without aura (SMD=-0.04, [-0.27-0.19], p=0.74). No significant difference in Valsalva ratio is found between migraineurs and controls (SMD=0.10, [-0.32-0.53], p=0.63) or between migraineurs with and without aura (SMD=-0.17, [-0.40-0.06], p=0.14). Root mean square of successive differences (RMSSD) (SMD=-0.07, [-1.10-0.95], p=0.89) and standard deviation of NN intervals (SDNN) (SMD=-0.10, [-0.61-0.41], p=0.71) did not significantly differ between migraine patients and controls.

CONCLUSION: Electrocardiographic alterations are observed in migraine patients compared to controls, especially during migraine attacks.

HEADACHE and MIGRAINE (Continued)

Probiotics for the Prophylaxis of Migraine: A Systematic Review of Randomized Placebo Controlled Trials.

Naghibi MM[1], Day R[2], Stone S[3], Harper A[4].

J Clin Med. **2019 Sep 11**;8(9). pii: E1441. doi: 10.3390/jcm8091441. PMID: 31514352.

Migraine is a common and disabling neurological condition with a complex etiology. Recent advances in the understanding of the gut microbiome have shown the role of gut micro-organisms in disease outcomes for distant organs-including the brain. Interventions targeting the gut microbiome have been shown to be effective in multiple neurological diagnoses, but there is little research into the role of the microbiome in migraine. This systematic review seeks to assess the current research landscape of randomized placebo controlled trials utilizing probiotic interventions as migraine prophylaxis. Searches were conducted of scientific databases including PubMed, MEDLINE, and the Cochrane Library, following PRISMA guidelines. Of 68 screened studies, 2 were eligible for analysis. Due to methodological differences, meta-analysis was not possible. Qualitative comparison of the studies demonstrated a dichotomy of results-one trial reported no significant change in migraine frequency and intensity, while the second trial reported highly significant improvements. No clear 'gold standard' currently exists for microbiome research, let alone for migraine-related microbiome research. The heterogeneity of outcome measures used in the two trials included in this systematic review shows the need for a standardization of outcome measures, therefore a series of recommendations for future probiotic-migraine research are included.

Cognition and Cognitive Impairment in Migraine.

Gil-Gouveia R[1,2], Martins IP[3,4].

Curr Pain Headache Rep. **2019 Sep 11**;23(11):84. doi: 10.1007/s11916-019-0824-7. PMID: 31511992.

BACKGROUND: Migraine is a complex neurological disorder that affects a significant percentage of the human species, from all geographic areas and cultures. Cognitive symptoms and dysfunctions are interim and disabling components of this disorder and may be related to the brain processes underlying the pathophysiology. Yet they are often undervalued by clinicians. In this review, we present the different types of cognitive dysfunctions associated with migraine and the mechanisms that are potentially causing them.

FINDINGS: While reversible attack-related cognitive dysfunction seems extremely consistent and likely related to functional cortical and subcortical brain changes occurring during attacks, interictal cognitive dysfunction is less consistent and might become more relevant as attack frequency and disease complexity increase. Migraine traits do not seem a predisposition to long-term cognitive decline. Cognitive dysfunction is a frequent manifestation of migraine attacks and may be specific to this disorder; it is important to understand if it could be useful in migraine diagnosis. Attack-related cognitive dysfunction is clinically relevant and contributes to disability, so it should be perceived as a therapeutic target. While there is no evidence to support that migraine increases the risk of long-term or persistent cognitive dysfunction, the fact that it occurs during the attacks and may persist in subjects with frequent or complicated attacks should prompt the understanding of the mechanisms related to its pathophysiology for it may also clarify the processes underlying migraine.

CHRONIC PAIN

Yoga for Chronic Non-Malignant Pain Management: A Review of Clinical Effectiveness, Cost-Effectiveness and Guidelines [Internet].

Editors: **Gray C**, **McCormack S**.

2019 July, Ottawa (ON): Canadian Agency for Drugs and Technologies in Health. CADTH Rapid Response Reports. PMID: 31525007.

Excerpt: Chronic pain serves no biological purpose in contrast with acute pain, which warns of disease or injury, and is characterized by significant emotional distress or functional disability.[1] Definitions of chronic pain vary across classification systems.[1] The World Health Organization defines recurrent or persistent pain as chronic if it lasts longer than three months in duration,[2] whereas the American Psychological Association considers pain lasting longer than six months as chronic.[3] Chronic pain affects millions of Canadians. The prevalence of chronic pain not associated with cancer (also called non-malignant) among Canadian adults has been estimated between 19% and 29%.[1] Treatments for chronic pain tend to be only partially effective, and unrelieved pain costs Canada approximately $43 to $60 billion dollars per year in health care expenditures and lost productivity.[4] In Canada, opioids are commonly prescribed to treat chronic non-malignant pain. Alternative strategies are being sought due to the side effects of opioids (e.g., nausea, constipation, respiratory depression), potential for addiction and misuse, and uncertain long-term effectiveness for the treatment of chronic non-cancer pain.[5] Complementary and alternative medicine therapies are commonly sought to overcome the limitations of pharmacological treatments.[6] Yoga, which consists of physical postures, breathing techniques, relaxation, and meditation, has been proposed as a potential intervention for chronic non-malignant pain in adults as it is thought to target the physical and psychological aspects of pain.[6] The objective of this report is to summarize the evidence concerning the clinical effectiveness, cost-effectiveness, and guidelines regarding yoga for chronic non-malignant pain in adults.

IRRITABLE BOWEL SYNDROME

Development of an Index Score for Intestinal Inflammation-Associated Dysbiosis Using Real-World Stool Test Results.

Chen L[1], Reynolds C[2], David R[3], Peace Brewer A[4].

Dig Dis Sci. **2019 Sep 16**. doi: 10.1007/s10620-019-05828-8. PMID: 31529411. [Epub ahead of print]

BACKGROUND: Gut microbiota play an important role in human health. However, the application of gut microbiome in regular clinical practice is limited by interindividual variations and complexity of test results.

HYPOTHESIS: It is possible to address interindividual variation by using large data-based exploratory-pattern analysis.

METHODS: The current study was conducted using a large data set (n = 173,221) of nonselective incoming patients' test results from a stool test. The data set included assays for the detection of 24 selected commensal microorganisms and multiple biomarkers in feces. Patients were grouped based on their levels of inflammation biomarkers such as calprotectin, eosinophil protein X, and IgA. Group mean values of biomarkers and commensal microbes were used in an exploratory-pattern analysis for association from which an index score for intestinal inflammation-associated dysbiosis (IAD) was developed. The IAD score was evaluated in one questionnaire-based study (n = 7263) and one prospective case series study (n = 122) with patients of inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), and celiac disease.

RESULTS: We identified a microbial profile strongly associated with fecal inflammation biomarkers. Developed on the pattern of the microbial profile, the IAD score demonstrated a strong association with fecal inflammation biomarkers and was significantly different between patients with IBD and those with IBS or celiac disease.

CONCLUSION: Using real-world data, we have developed a method to predict gut dysbiosis associated with different GI disease conditions. It may help clinicians simplify the process of interpreting gut microbial status and provide gut health assessment and treatment evaluation.

IRRITABLE BOWEL SYNDROME (Continued)

Low FODMAP diet significantly improves IBS symptoms: an Irish retrospective cohort study.

Nawawi KNM[1,2], Belov M[3], Goulding C[4].

Eur J Nutr. **2019 Sep 13**. doi: 10.1007/s00394-019-02074-6. PMID: 31520160. [Epub ahead of print]

INTRODUCTION: There is growing evidence that a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) improves symptoms in irritable bowel syndrome (IBS) patients. We aimed to retrospectively investigate the effects of this diet in Irish IBS cohort over a 12-month follow-up period, including after re-introduction of the high FODMAP foods.

METHODS: All the tertiary referrals seen by an FODMAP-trained dietician were reviewed (2013-2016). Patients were evaluated for IBS symptoms by a questionnaire (four-point Likert scale). Subsequently, advice regarding the low FODMAP diet was given. Symptoms' response was assessed at 3-, 6-, and 12-month follow-up, by use of the same questionnaire. Re-introduction of high FODMAP foods was aimed to commence at the subsequent follow-up.

RESULTS: A total of 164 patients were identified. Thirty-seven patients were excluded due to failure to attend for follow-up. Hundred and twenty-seven patients (77% patients, of which 85% were female) completed the initial 3-month follow-up. Forty-five percent (74/164) and twenty-five percent (41/164) of the patients had continued follow-up at 6 and 12 months, respectively. Of the 127 patients who returned for follow-up, their commonest baseline symptoms were lethargy (92%), bloating (91%), flatulence (91%), and abdominal pain (89%). All symptoms were significantly improved at the initial follow-up ($p < 0.0001$ for all). Most patients (66%) were satisfied with their overall symptoms control. In patients who had a longer follow-up duration, all symptoms remained significantly improved compared to the baseline ($p < 0.0001$ for combined symptoms at 6 and 12 months). After re-introduction of the high FODMAP foods, all patients maintained their symptomatic response ($n = 14/14$ and $n = 7/7$ at 6- and 12-month follow-up, respectively). The best symptoms' improvement was seen in those who were fully adherent to the FODMAP diet.

CONCLUSION: In this Irish retrospective cohort study, the low FODMAP diet significantly improved all IBS symptoms at 3-, 6-, and 12-month follow-up. Following the re-introduction of the high FODMAP foods in a subgroup of patients, they were able to maintain their long-term symptomatic response up to 9 months. The low FODMAP diet might be continued for longer than 3 months; however, further studies are needed to assess the long-term safety of this diet.

Effect of Repeated Consumption of Partially Hydrolyzed Guar Gum on Fecal Characteristics and Gut Microbiota: A Randomized, Double-Blind, Placebo-Controlled, and Parallel-Group Clinical Trial.

Yasukawa Z[1,2], Inoue R[3], Ozeki M[4,5], Okubo T[6,7], Takagi T[8], Honda A[9], Naito Y[10].

Nutrients. **2019 Sep 10**;11(9). pii: E2170. doi: 10.3390/nu11092170. PMCID: PMC6769658. PMID: 31509971.

Partially hydrolyzed guar gum (PHGG) is a water-soluble dietary fiber and is used in solid and liquid food to regulate gut function. The aim of this study was to investigate effects of PHGG on bowel movements (stool form and frequency), plasma bile acids, quality of life, and gut microbiota of healthy volunteers with a tendency toward diarrhea, i.e., irritable bowel syndrome diarrhea (IBS-D)-like symptoms. A randomized, double-blind, placebo-controlled, and parallel trial was performed on 44 healthy volunteers (22 males, 22 females, 41.9 ± 6.3 years old (average ± SD)) with minimum 7 bowel movements every week, wherein above 50% of their stool was between the Bristol stool scale (BSS) value of 5 and 6. Intake of the PHGG for 3 months significantly improved stool form, evaluated using BSS, and had no effects on stool frequency. BSS was significantly normalized in the group consuming the PHGG compared with the placebo. Comprehensive fecal microbiome analysis by the 16S rRNA-sequence method detected significant changes in the ratio of some bacteria, such as an increase of *Bifidobacterium* ($p < 0.05$) in the PHGG group. Our results suggest that intake of PHGG improves human stool form via regulating intestinal microbiota.

OTHER RESEARCH OF INTEREST

Cardiovascular Disease among Female Veterans of the 1991 Gulf War Era.

Coughlin SS[1,2], Heboyan V[3], Sullivan K[4], Krengel M[5], Wilson CC[6], Iobst S[7], Klimas N[8,9].

J Environ Health Sci. **2019**;5(1):24-25. doi: 10.15436/2378-6841.19.2455. PMCID: PMC6688166. PMID: 31403084. Epub 2019 Mar 29.

Introduction: Recent clinical studies have identified exercise-induced transient postural tachycardia and abnormal heart-rate variability in patients with Gulf War Illness (GWI) (Rayhan et al. 2013; Garner et al. 2018; Blanchard et al. 2018). Altered heart rate variability may reflect autonomic dysfunction and atrophy in the cardio-regulatory regions of the brainstem (Rayhan et al. 2013). However, the long-term cardiovascular effects of abnormal autonomic nervous system functioning in patients with GWI are unknown (Blanchard et al. 2018). In additional clinical research studies, veterans with GWI have been found to have higher levels of cytokines such as interleukins (Coughlin 2017), which are inflammatory factors associated with increased risk of coronary heart disease and other chronic diseases (Lampert et al. 2006).

Using data from the Veterans Affairs (VA) Cooperative Studies Program 585 Gulf War Era Cohort and Biorepository (Khalil et al. 2018), this study examined the prevalence of cardiovascular disease among female veterans who served during the Gulf War or Gulf War Era.

[See full text of this article in the *J Environ Health Sci*.]

Long-term Cardiovascular Disease Risk Among Firefighters After the World Trade Center Disaster.

Cohen HW[1], Zeig-Owens R[1,2,3], Joe C[2,3], Hall CB[4], Webber MP[2,5], Weiden MD[2,6,7], Cleven KL[3], Jaber N[2], Skerker M[2,3], Yip J[2,3], Schwartz T[2,3], Prezant DJ[2,3].

JAMA Netw Open. **2019 Sep 4**;2(9):e199775. doi: 10.1001/jamanetworkopen.2019.9775. PMCID: PMC6735414. PMID: 31490535

Importance: Published studies examining the association between World Trade Center (WTC) exposure on and after September 11, 2001, and longer-term cardiovascular disease (CVD) outcomes have reported mixed findings.

Objective: To assess whether WTC exposure was associated with elevated CVD risk in Fire Department of the City of New York (FDNY) firefighters.

Design, Settings, and Participants: In this cohort study, the association between WTC exposure and the risk of CVD was assessed between September 11, 2001, and December 31, 2017, in FDNY male firefighters. Multivariable Cox regression analyses were used to estimate CVD risk in association with 2 measures of WTC exposure: arrival time to the WTC site and duration of work at the WTC site. Data analyses were conducted from May 1, 2018, to March 8, 2019.

Main Outcomes and Measures: The primary CVD outcome included myocardial infarction, stroke, unstable angina, coronary artery surgery or angioplasty, or CVD death. The secondary outcome (all CVD) included all primary outcome events or any of the following: transient ischemic attack; stable angina, defined as either use of angina medication or cardiac catheterization without intervention; cardiomyopathy; and other CVD (aortic aneurysm, peripheral arterial vascular intervention, and carotid artery surgery).

Results: There were 489 primary outcome events among 9796 male firefighters (mean [SD] age on September 11, 2001, was 40.3 [7.4] years and 7210 individuals [73.6%] were never smokers). Age-adjusted incident rates of CVD were higher for firefighters with greater WTC exposure. The multivariable adjusted hazard ratio (HR) for the primary CVD outcome was 1.44 (95% CI, 1.09-1.90) for the earliest arrival group compared with those who arrived later. Similarly, those who worked at the WTC site for 6 or more months vs those who worked less time at the site were more likely to have a CVD event (HR, 1.30; 95% CI, 1.05-1.60). Well-established CVD risk factors, including hypertension (HR, 1.41; 95% CI, 1.10-1.80), hypercholesterolemia (HR, 1.56; 95% CI, 1.28-1.91), diabetes (HR, 1.99; 95% CI, 1.33-2.98), and smoking (current: HR, 2.13; 95% CI, 1.68-2.70; former: HR, 1.55; 95% CI, 1.23-1.95), were significantly associated with CVD in the multivariable models. Analyses with the all-CVD outcome were similar.

Conclusions and Relevance: The findings of the study suggest a significant association between greater WTC exposure and long-term CVD risk. The findings appear to reinforce the importance of long-term monitoring of the health of survivors of disasters.

OTHER RESEARCH OF INTEREST (Continued)

Quantifying the Association Between Psychotherapy Content and Clinical Outcomes Using Deep Learning.

Ewbank MP[1], Cummins R[1], Tablan V[1], Bateup S[1], Catarino A[1], Martin AJ[1], Blackwell AD[1].

JAMA Psychiatry. **2019 Aug 22**. doi: 10.1001/jamapsychiatry.2019.2664. PMCID: PMC6707006. PMID: 31436785.

Importance: Compared with the treatment of physical conditions, the quality of care of mental health disorders remains poor and the rate of improvement in treatment is slow, a primary reason being the lack of objective and systematic methods for measuring the delivery of psychotherapy.

Objective: To use a deep learning model applied to a large-scale clinical data set of cognitive behavioral therapy (CBT) session transcripts to generate a quantifiable measure of treatment delivered and to determine the association between the quantity of each aspect of therapy delivered and clinical outcomes.

Design, Setting, and Participants: All data were obtained from patients receiving internet-enabled CBT for the treatment of a mental health disorder between June 2012 and March 2018 in England. Cognitive behavioral therapy was delivered in a secure online therapy room via instant synchronous messaging. The initial sample comprised a total of 17 572 patients (90 934 therapy session transcripts). Patients self-referred or were referred by a primary health care worker directly to the service.

Exposures: All patients received National Institute for Heath and Care Excellence-approved disorder-specific CBT treatment protocols delivered by a qualified CBT therapist.

Main Outcomes and Measures: Clinical outcomes were measured in terms of reliable improvement in patient symptoms and treatment engagement. Reliable improvement was calculated based on 2 severity measures: Patient Health Questionnaire (PHQ-9) and Generalized Anxiety Disorder 7-item scale (GAD-7), corresponding to depressive and anxiety symptoms respectively, completed by the patient at initial assessment and before every therapy session (see eMethods in the Supplement for details).

Results: Treatment sessions from a total of 14 899 patients (10 882 women) aged between 18 and 94 years (median age, 34.8 years) were included in the final analysis. We trained a deep learning model to automatically categorize therapist utterances into 1 or more of 24 feature categories. The trained model was applied to our data set to obtain quantifiable measures of each feature of treatment delivered. A logistic regression revealed that increased quantities of a number of session features, including change methods (cognitive and behavioral techniques used in CBT), were associated with greater odds of reliable improvement in patient symptoms (odds ratio, 1.11; 95% CI, 1.06-1.17) and patient engagement (odds ratio, 1.20, 95% CI = 1.12-1.27). The quantity of nontherapy-related content was associated with reduced odds of symptom improvement (odds ratio, 0.89; 95% CI, 0.85-0.92) and patient engagement (odds ratio, 0.88, 95% CI, 0.84-0.92).

Conclusions and Relevance: This work demonstrates an association between clinical outcomes in psychotherapy and the content of therapist utterances. These findings support the principle that CBT change methods help produce improvements in patients' presenting symptoms. The application of deep learning to large clinical data sets can provide valuable insights into psychotherapy, informing the development of new treatments and helping standardize clinical practice.

OTHER RESEARCH OF INTEREST (Continued)

Contextual Factors Associated With County-Level Suicide Rates in the United States, 1999 to 2016.

Steelesmith DL[1], Fontanella CA[1], Campo JV[2], Bridge JA[3,4], Warren KL[5], Root ED[6].

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Importance: Understanding geographic and community-level factors associated with suicide can inform targeted suicide prevention efforts.

Objectives: To estimate suicide rates and trajectories, assess associated county-level contextual factors, and explore variation across the rural-urban continuum.

Design, Setting, and Participants: This cross-sectional study included all individuals aged 25 to 64 years who died by suicide from January 1, 1999, to December 31, 2016, in the United States. Spatial analysis was used to map excess risk of suicide, and longitudinal random-effects models using negative binomial regression tested associations of contextual variables with suicide rates as well as interactions among county-level contextual variables. Data analyses were conducted between January 2019 and July 2019.

Exposure: County of residence.

Main Outcomes and Measures: Three-year county suicide rates during an 18-year period stratified by rural-urban location.

Results: Between 1999 and 2016, 453 577 individuals aged 25 to 64 years died by suicide in the United States. Decedents were primarily male (349 082 [77.0%]) with 101 312 (22.3%) aged 25 to 34 years, 120 157 (26.5%) aged 35 to 44 years, 136 377 (30.1%) aged 45 to 54 years, and 95 771 (21.1%) aged 55 to 64 years. Suicide rates were higher and increased more rapidly in rural than in large metropolitan counties. The highest deprivation quartile was associated with higher suicide rates compared with the lowest deprivation quartile, especially in rural areas, although this association declined during the period studied (rural, 1999-2001: incidence rate ratio [IRR], 1.438; 95% CI, 1.319-1.568; P < .001; large metropolitan, 1999-2001: 1.208; 95% CI, 1.149-1.270; P < .001; rural, 2014-2016: IRR, 1.121; 95% CI, 1.032-1.219; P = .01; large metropolitan, 2014-2016: IRR, 0.942; 95% CI, 0.887-1.001; P = .06). The presence of more gun shops was associated with an increase in county-level suicide rates in all county types except the most rural (rural: IRR, 1.001; 95% CI, 0.999-1.004; P = .40; micropolitan: IRR, 1.005; 95% CI, 1.002-1.007; P < .001; small metropolitan: IRR, 1.010; 95% CI, 1.006-1.014; P < .001; large metropolitan: IRR, 1.012; 95% CI, 1.006-1.018; P < .001). High social capital was associated with lower suicide rates than low social capital (IRR, 0.917; 95% CI, 0.891-0.943; P < .001). High social fragmentation, an increasing percentage of the population without health insurance, and an increasing percentage of veterans in a county were associated with higher suicide rates (high social fragmentation: IRR, 1.077; 95% CI, 1.050-1.103; P < .001; percentage of population without health insurance: IRR, 1.005; 95% CI, 1.004-1.006; P < .001; percentage of veterans: IRR, 1.025; 95% CI, 1.021-1.028; P < .001).

Conclusions and Relevance: This study found that suicide rates have increased across the nation and most rapidly in rural counties, which may be more sensitive to the impact of social deprivation than more metropolitan counties. Improving social connectedness, civic opportunities, and health insurance coverage as well as limiting access to lethal means have the potential to reduce suicide rates across the rural-urban continuum.

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