GULF WAR ILLNESS

Verification of exercise-induced transient postural tachycardia phenotype in Gulf War Illness.

Garner RS[1], Rayhan RU[1], Baraniuk JN[1].

Am J Transl Res. **2018 Oct 15**;10(10):3254-3264. PMID: 30416666. eCollection 2018.

One third of Gulf War Illness (GWI) subjects in a recent study were found to develop transient postural tachycardia after submaximal exercise stress tests. Post-exercise postural tachycardia is a previously undescribed physiological finding. A new GWI cohort was studied to verify this novel finding and characterize this cardiovascular phenomenon. Subjects followed the same protocol as before. The change in heart rate between recumbent and standing postures (ΔHR) was measured before exercise, and after submaximal bicycle exercise. About one-fourth of the verification cohort (14/57) developed transient postural tachycardia after submaximal exercise. These subjects were the Stress Test Activated Reversible Tachycardia (START) phenotype. The largest change was observed between pre-exercise and time points 2 ± 1 (mean ± SD) hours post exercise (1st Peak Effect). Eleven subjects had Postural Tachycardia Syndrome (POTS) before and after exercise. The remaining subjects had normal ΔHR (12 ± 5 bpm) and no 1st Peak Effect, and were the Stress Test Originated Phantom Perception phenotype (STOPP). These findings indicate that about one-fourth of all Gulf War Illness study participants (24/90) developed transient postural tachycardia after the submaximal exercise stress test. The START phenotype was defined as being distinctly different from POTS. Additional studies are required to examine this phenomenon in other illnesses and to determine pathological mechanisms.

CHRONIC FATIGUE SYNDROME

CD24 Expression and B Cell Maturation Shows a Novel Link With Energy Metabolism: Potential Implications for Patients With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome.

Mensah FFK[1], Armstrong CW[2], Reddy V[1], Bansal AS[3], Berkovitz S[4], Leandro MJ[1], Cambridge G[1].

Front Immunol. **2018 Oct 22**;9:2421. doi: 10.3389/fimmu.2018.02421. PMCID: PMC6204382. PMID: 30405620. eCollection 2018.

CD24 expression on pro-B cells plays a role in B cell selection and development in the bone marrow. We previously detected higher CD24 expression and frequency within IgD+ naïve and memory B cells in patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) compared with age-matched healthy controls (HC). Here, we investigated the relationship between CD24 expression and B cell maturation. *In vitro* stimulation of isolated B cells in response to conventional agonists were used to follow the dynamics of CD24 positivity during proliferation and differentiation (or maturation). The relationship between CD24 expression to cycles of proliferation and metabolism in purified B cells from HC was also investigated using phospho-flow (phosphorylation of AMPK-pAMPK), 1proton nuclear magnetic resonance and Mitotracker Far-red (Mitochondrial mass-MM). *In vitro*, in the absence of stimulation, there was an increased percentage of CD24+ viable B cells in ME/CFS patients compared to HC ($p < 0.05$) following 5 days culture. Following stimulation with B cell agonists, percentage of CD24+B cells in both naïve and memory B cell populations decreased. $P < 0.01$). There was a negative relationship between percentage of CD24+B cells with MM ($R^2 = 0.76$; $p < 0.01$), which was subsequently lost over sequential cycles of proliferation. There was a significant correlation between CD24 expression on B cells and the usage of glucose and secretion of lactate *in vitro*. Short term ligation of the B cell receptor with anti-IgM antibody significantly reduced the viability of CD24+ memory B cells compared to those cross-linked by anti-IgD or anti-IgG antibody. A clear difference was found between naïve and memory B cells with respect to CD24 expression and pAMPK, most notably a strong positive association in IgD+IgM+ memory B cells. *In vitro* findings confirmed dysregulation of CD24-expressing B cells from ME/CFS patients previously suggested by immunophenotype studies of B cells from peripheral blood. CD24-negative B cells underwent productive proliferation whereas CD24+ B cells were either unresponsive or susceptible to cell death upon BCR-engagement alone. We suggest that CD24 expression may reflect variations in energy metabolism on different B cell subsets.

CHRONIC FATIGUE SYNDROME (Continued)

Dampness and mold hypersensitivity syndrome and vaccination as risk factors for chronic fatigue syndrome.

Tuuminen T[1], Jääskeläinen T[2], Vaali K[3], Polo O[4].

Autoimmun Rev. **2018 Nov 5**. pii: S1568-9972(18)30266-0. doi: 10.1016/j.autrev.2018.08.004. PMID: 30408578. [Epub ahead of print]

Dampness and Mold Hypersensitivity Syndrome (DMHS) associates with several other neglected medical conditions such as the Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) [1] and Multiple Chemical Sensitivity (MCS) [3]. In DMHS 5 criteria have been proposed: *1)* exposure to dampness microbiota (DM); *2)* recurrent and/or unusual infections; *3)* Sick Building Syndrome (SBS); *4)* development of MCS and *5)* sensitized olfactory scenting [5]. We hypothesized that previous exposure to DM could be a risk factor for vaccination to trigger disability with/or without neurological sequelae. Therefore we investigated the potential combined risks of DMHS and Pandemrix®, Gardasil® or Cervarix® (PGC) to cause severe disability. Conditions such as Ehlers-Danlos Syndrome (EDS) [7], ME/CFS [9], Postural Orthostatic Tachycardia Syndrome (POTS) (), Complex Regional Pain Syndrome (CRPS), Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) and Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) were considered.

Families of 100 children, who developed disabilities, responded within a closed Facebook group to our questionnaire. The parents used self-assessment that was blinded to the principle investigator [TT] and were interviewed by another investigator [TJ]. Groups 1–4 were study groups, and Groups 5–8 served as controls. Three cases were excluded as not fulfilling the criteria. The parents of 16 cases were too exhausted to participate. Finally, 81 cases were included. The cases were asked to allocate themselves into one of the following groups:

Group1: Exposure to DM at home and school and vaccination with PGC.

Group2: Exposure to DM only at home and vaccination with PGC.

Group3: Exposure to DM only at school and vaccination with PGC.

Group4: Questionable exposure to DM at home or school and vaccination with PGC.

Group5: Definitely no exposure to DM and vaccination with PGC.

Group6: Definite exposure to DM at home or at school but no PGC vaccination.

Group7: Questionable exposure to DM but no PCG vaccination.

Group8: Questionable exposure to DM, no PGC vaccination but vaccination with other vaccines within the 5 years before the onset of the disease.

The study did not require ethical clearance, because it was based on a questionnaire initiated by parents of sick children.

The diagnoses reported by participants are collected in the Table. The reported symptoms were: Migraine; fatigue; headache; dizziness; balance, visual, hearing or speech disturbance; cognitive problems; problems in the perception of the environment; hyperactivity when tired; difficulty falling asleep; sensory hypersensitivity; *petit mal* epilepsy; insomnia, nightmares, abnormal sleep (waking up, not deep sleep); tachycardia when sitting; irritability; adaptation difficulties in the change of situations; impulsiveness; concentration problems, hyperactivity, occasional dizziness during infection.

- No abstract: For above summary excerpt, see Table, Full Text, and References in PubMed Elsevier link to Article Accepted Manuscript in Press for *Autoimmunity Reviews*.

Associations between clinical symptoms, plasma norepinephrine and deregulated immune gene networks in subgroups of adolescent with Chronic Fatigue Syndrome.

Nguyen CB[1], Kumar S[2], Zucknick M[3], Kristensen VN[4], Gjerstad J[5], Nilsen H[6], Wyller VB[7].

Brain Behav Immun. **2018 Nov 9**. pii: S0889-1591(18)30796-7. doi: 10.1016/j.bbi.2018.11.008. PMID: 30419269. [Epub ahead of print]

BACKGROUND: Chronic fatigue syndrome (CFS) is one of the most important causes of disability among adolescents while limited knowledge exists on genetic determinants underlying disease pathophysiology.

METHODS: We analyzed deregulated immune-gene modules using Pathifier software on whole blood gene expression data (29 CFS patients, 18 controls). Deconvolution of immune cell subtypes based on gene expression profile was performed using CIBERSORT. Supervised consensus clustering on pathway deregulation score (PDS) was used to define CFS subgroups. Associations between PDS and immune, neuroendocrine/autonomic and clinical markers were examined. The impact of plasma norepinephrine level on clinical markers over time was assessed in a larger cohort (91 patients).

RESULTS: A group of 29 immune-gene sets was shown to differ patients from controls and detect subgroups within CFS. Group 1P (high PDS, low norepinephrine, low naïve CD4+ composition) had strong association with levels of serum C-reactive protein and Transforming Growth Factor-beta. Group 2P (low PDS, high norepinephrine, high naïve CD4+ composition) had strong associations with neuroendocrine/autonomic markers. The corresponding plasma norepinephrine level delineated 91 patients into two subgroups with significant differences in fatigue score.

CONCLUSION: We identified 29 immune-gene sets linked to plasma norepinephrine level that could delineate CFS subgroups. Plasma norepinephrine stratification revealed that lower levels of norepinephrine were associated with higher fatigue. Our data suggests potential involvement of neuro-immune dysregulation and genetic stratification in CFS.

HEADACHE and MIGRAINE

A phase 3, long-term, open-label safety study of Galcanezumab in patients with migraine.

Camporeale A[1], Kudrow D[2,3], Sides R[4], Wang S[4], Van Dycke A[5], Selzler KJ[4], Stauffer VL[6].

BMC Neurol. **2018 Nov 9**;18(1):188. doi: 10.1186/s12883-018-1193-2. PMID: 30413151.

BACKGROUND: Galcanezumab, a humanized monoclonal antibody that selectively binds to the calcitonin gene-related peptide, has demonstrated in previous Phase 2 and Phase 3 clinical studies (≤6-month of treatment) a reduction in the number of migraine headache days and improved patients' functioning. This study evaluated the safety and tolerability, as well as the effectiveness of galcanezumab for up to 12 months of treatment in patients with migraine.

METHODS: Patients diagnosed with episodic or chronic migraine, 18 to 65 years old, that were not exposed previously to galcanezumab, were randomized to receive galcanezumab 120 mg or 240 mg, administered subcutaneously once monthly for a year. Safety and tolerability were evaluated by frequency of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse events (AEs) leading to study discontinuation. Laboratory values, vital signs, electrocardiograms, and suicidality were also analyzed. Additionally, overall change from baseline in the number of monthly migraine headache days, functioning, and disability were assessed.

RESULTS: One hundred thirty five patients were randomized to each galcanezumab dose group. The majority of patients were female (> 80%) and on average were 42 years old with 10.6 migraine headache days per month at baseline. 77.8% of the patients completed the open-label treatment phase, 3.7% of patients experienced an SAE, and 4.8% discontinued due to AEs. TEAEs with a frequency ≥ 10% of patients in either dose group were injection site pain, nasopharyngitis, upper respiratory tract infection, injection site reaction, back pain, and sinusitis. Laboratory values, vital signs, or electrocardiograms did not show anyclinically meaningful differences between galcanezumab doses. Overall mean reduction in monthly migraine headache days over 12 months for the galcanezumab dose groups were 5.6 (120 mg) and 6.5 (240 mg). Level of functioning was improved and headache-related disability was reduced in both dose groups.

CONCLUSION: Twelve months of treatment with self-administered injections of galcanezumab was safe and associated with a reduction in the number of monthly migraine headache days. Safety and tolerability of the 2 galcanezumab dosing regimens were comparable.

TRIAL REGISTRATION: ClinicalTrials.gov as NCT02614287 , posted November 15, 2015. These data were previously presented as a poster at the International Headache Congress 2017: PO-01-184, Late-Breaking Abstracts of the 2017 International Headache Congress. (2017). Cephalalgia, 37(1_suppl), 319-374.

Post traumatic headache (PTH) in a cohort of UK compensation claimants.

Lane R[1], Davies P[2].

Cephalalgia. **2018 Nov 8**:333102418812091. doi: 10.1177/0333102418812091. PMID: 30409039. [Epub ahead of print]

AIM: To explore post traumatic headache characteristics and risk factors in compensation claimants by observational retrospective cohort analysis.

CASE RESULTS: Medicolegal reports on 116 consecutive compensation claimants aged 41.9 ± 15.0 years were reviewed 21 ± 14 months after injury. Eighty eight had suffered head and neck injuries, 21 reported only neck injury and seven had "other injuries". Ninety four percent of the head injuries were "mild". The incidence of post traumatic headache following neck injury did not differ from that following head and neck injury, and none of the "other injuries" cases developed post traumatic headache. We anticipated that all head and neck injury claimants would seek compensation for post traumatic headache, but 25% denied developing headache. Post traumatic headache was very strongly correlated with a past history of primary headache ($p < 0.0001$) but no other risk factors were identified. Post traumatic headache semiology was consistent with "migraine" or "probable migraine" in 90% of cases. Headache resolved in 30% of claimants between 3 and 24 months after injury but 70% continued to suffer headaches at the time of assessment. Forty one percent of claimants had received no treatment for post traumatic headache in primary care.

CONCLUSIONS: Our data suggest that post traumatic headache is essentially "migraine" provoked by head or neck concussion. It is not clear why so many post traumatic headache sufferers receive poor or inadequate treatment for this condition.

HEADACHE and MIGRAINE (Continued)

Positional Patterns Among the Auriculotemporal Nerve, Superficial Temporal Artery, and Superficial Temporal Vein for use in Decompression Treatments for Migraine.

Lee HJ[1], Choi YJ[2], Lee KW[1], Kim HJ[3, 4].

Sci Rep. **2018 Nov 8**;8(1):16539. doi: 10.1038/s41598-018-34765-1. PMID: 30409986.

This study aimed to clarify intersection patterns and points among the superficial temporal artery (STA), superficial temporal vein (STV), and auriculotemporal nerve (ATN) based on surface anatomical landmarks to provide useful anatomical information for surgical decompression treatments of migraine headaches in Asians. Thirty-eight hemifaces were dissected. The positional patterns among the ATN, STA, and STV were divided into three morphological types. In type I, the ATN ran toward the temporal region and superficially intersected the STA and STV (n = 32, 84.2%). In type II, the ATN ran toward the temporal region and deeply intersected the STA and STV (n = 4, 10.5%). In type III, the ATN ran toward the temporal region and deeply intersected the STV alone (n = 2, 5.3%). The intersection points of types II and III were 10.3 ± 5.6 mm (mean ± SD) and 10.4 ± 6.1 mm anterior and 42.1 ± 21.6 mm and 41.4 ± 18.7 mm superior to the tragus, respectively. The ATN superficially intersected the STA and STV in all the Korean cadaver, while the ATN deeply intersected the STA and STV in 15% of the Thai cadavers. The pattern of the ATN deeply intersecting the STA and STV was less common in present Asian populations than in previously-reported Caucasian populations, implying that migraine headaches (resulting from the STA and STV compressing the ATN) are less common in Asians.

Migraine induction with calcitonin gene-related peptide in patients from erenumab trials.

Christensen CE[1], Younis S[1], Deen M[1], Khan S[1], Ghanizada H[1], Ashina M[2].

J Headache Pain. **2018 Nov 8**;19(1):105. doi: 10.1186/s10194-018-0927-2. PMID: 30409109.

BACKGROUND: Migraine prevention with erenumab and migraine induction by calcitonin gene-related peptide (CGRP) both carry notable individual variance. We wanted to explore a possible association between individual efficacy of anti-CGRP treatment and susceptibility to migraine induction by CGRP.

METHODS: Thirteen migraine patients, previously enrolled in erenumab anti-CGRP receptor monoclonal antibody trials, received CGRP in a double-blind, placebo-controlled, randomized cross-over design to investigate their susceptibility to migraine induction. A standardized questionnaire was used to assess the efficacy of previous antibody treatment. The patients were stratified into groups of high responders and poor responders. Primary outcomes were incidence of migraine-like attacks and area under the curve of headache intensity after infusion of CGRP and placebo. All interviews and experiments were performed in laboratories at the Danish Headache Center, Copenhagen, Denmark.

RESULTS: Ten high responders and three poor responders were included. CGRP induced migraine-like attacks in ten (77%) patients, whereof two were poor responders, compared to none after placebo (p = 0.002). The area under the curve for headache intensity was greater after CGRP, compared to placebo, at 0-90 min (p = 0.009), and 2-12 h (p = 0.014). The median peak headache intensity score was 5 (5-9) after CGRP, compared to 2 (0-4) after placebo (p = 0.004).

CONCLUSIONS: Patients with an excellent effect of erenumab are highly susceptible to CGRP provocation. If an association is evident, CGRP provocation could prove a biomarker for predicting antibody treatment efficacy.

TRIAL REGISTRATION: Retrospectively registered at clinicaltrials.gov with identifier: NCT03481400 .

CHRONIC PAIN

Is excess weight a burden for older adults who suffer chronic pain?

Dong HJ[1], Larsson B[2], Levin LÅ[3], Bernfort L[3], Gerdle B[2].

BMC Geriatr. **2018 Nov 8**;18(1):270. doi: 10.1186/s12877-018-0963-4. PMID: 30409125.

BACKGROUND: Obesity and chronic pain are common comorbidities and adversely influence each other. Advanced age is associated with more comorbidities and multi-morbidities. In this study, we investigated the burden of overweight/obesity and its comorbidities and their associations with chronic pain in a random population sample of Swedish older adults.

METHODS: The cross-sectional analysis involved a random sample of a population ≥ 65 years in south-eastern Sweden (N = 6243). Data were collected from a postal questionnaire that addressed pain aspects, body mass index (BMI), and health experiences. Chronic pain was defined as pain during the previous three months. According to the 0-10 Numeric Rating Scale, pain scored ≥7 corresponds to severe pain. Binary logistic regression was used to determine the variables associated to pain aspects.

RESULTS: A total of 2633 (42%) reported chronic pain. More obese older adults (BMI ≥30 kg/m^2) experienced chronic pain (58%) than those who were low-normal weight (BMI < 25 kg/m^2, 39%) or overweight (25 ≤ BMI < 30 kg/m^2, 41%). Obese elderly more frequently had pain in extremities and lower back than their peers. In the multivariate model, obesity (Odds Ratio (OR) 1.59, 95% Confidence Interval (CI) 1.33-1.91) but not overweight (OR 1.08, 95% CI 0.95-1.22) was associated with chronic pain. Obesity (OR 1.53, 95% CI 1.16-2.01) was also significantly related to severe pain. We also found other comorbidities - i.e., traumatic history (OR 2.52, 95% CI 1.99-3.19), rheumatic diseases (OR 5.21, 95% CI 4.54-5.97), age ≥ 85 years (OR 1.66, 95% CI 1.22-2.25), and depression or anxiety diagnosis (OR 1.83, 95% CI 1.32-2.53) - showed stronger associations with pain aspects than weight status.

CONCLUSION: In older adults, excess weight (BMI 30 or above) is a potentially modifiable factor but not the only risk factor that is associated with chronic pain and severe pain. Future studies should investigate the effectiveness of interventions that treat comorbid pain and obesity in older adults.

Longitudinal pattern of pain medication utilization in peripheral neuropathy patients.

Callaghan B[1,2], Reynolds E[3], Banerjee M[3], Kerber K[1], Skolarus L[1], Burke J[1,2].

Pain. **2018 Nov 5**. doi: 10.1097/j.pain.0000000000001439. PMID: 30418352. [Epub ahead of print]

We aimed to investigate the pattern and utilization of neuropathic pain medications in peripheral neuropathy patients. Using a privately-insured, healthcare claims database from 2001-2014, we identified a retrospective cohort of incident peripheral neuropathy patients (validated ICD-9 definition) after excluding other chronic pain conditions. Outcome measures included opioid prescriptions, chronic opioid therapy (greater than or equal to 90 days of continuous supply), guideline-recommended medications for painful peripheral neuropathy (serotonin reuptake inhibitors, tricyclic antidepressants, and gabapentinoids), and pain specialists (neurologists, physiatrists, and anesthesiologists). Multivariable logistic regression was used to evaluate associations of patient-level factors with these outcomes. The peripheral neuropathy population included 14,426 individuals with a mean (SD) age of 43.1 years (2.8) and 52.4% men followed for 3.1 (1.7) years before and 4.5 (1.4) years after the diagnosis. In this population, 65.9% received ≥ 1 opioid prescription, and 8.8% received chronic opioid therapy. Of those receiving chronic opioid therapy, only 26.4% received a guideline-recommended medication prior to chronic opioid status. For guideline-recommended medications, 35.7% received ≥1, 12.4% ≥2, and 3.8% ≥3 different medications. No patient level factors were associated with both high opioid utilization (initiation and chronic use) and low guideline-recommended medication utilization. Pain specialists were associated with high opioid utilization and high guideline-recommended medication utilization. In conclusion, opioid initiation and transition to chronic opioid therapy is frequent in a peripheral neuropathy population despite few patients receiving more than one guideline-recommended medication. Efforts to decrease opioid utilization and increase guideline-recommended medication use are needed to improve current neuropathic pain treatment.

CHRONIC PAIN (Continued)

Gender Differences in the Prevalence of Fibromyalgia and in Concomitant Medical and Psychiatric Disorders: A National Veterans Health Administration Study.

Arout CA[1,2], Sofuoglu M[1,3], Bastian LA[4,5], Rosenheck RA[1,3].

J Womens Health (Larchmt). **2018 Aug**;27(8):1035-1044. doi: 10.1089/jwh.2017.6622. PMID: 29608126. Epub 2018 Apr 2.

BACKGROUND: Fibromyalgia is a poorly understood, chronically disabling pain syndrome. While research has focused on its clinical presentation and treatment, less is known about fibromyalgia's clinical epidemiology in real-world healthcare systems. Gender differences have been difficult to study because relatively few males are diagnosed with fibromyalgia.

METHODS: Veterans Health Administration (VHA) patients diagnosed with fibromyalgia nationwide in FY 2012 were compared to Veterans with other pain diagnoses on sociodemographic characteristics, medical and psychiatric diagnoses, health service use, and opioid and psychotropic prescription fills. Additional analyses compared characteristics of men and women diagnosed with fibromyalgia. Risk ratios and Cohen's d were used for bivariate comparisons, followed by logistic regression analyses to identify independent factors associated with a diagnosis of fibromyalgia in the VHA.

RESULTS: Altogether, 77,087 of 2,216,621 Veterans with pain diagnoses (3.48%) were diagnosed with fibromyalgia. They were more likely to be female, younger than patients with other pain conditions, more likely to have multiple psychiatric comorbidities and other types of pain, and used more medical outpatient services. Women diagnosed with fibromyalgia were younger and more likely to have headaches, connective tissue diseases (CTD), and psychiatric comorbidities, while men had more comorbid medical conditions.

CONCLUSIONS: In this large, predominantly older male sample of Veterans with pain diagnoses, those with fibromyalgia were far more likely to be women. Gender comparisons showed women with fibromyalgia were more likely to be diagnosed with psychiatric disorders and CTD, while males were more likely to be diagnosed with medical conditions. Fibromyalgia shows a striking, gender-dependent picture of multimorbidity, which should be considered in treatment.

Effect of Intensive Patient Education vs Placebo Patient Education on Outcomes in Patients With Acute Low Back Pain: A Randomized Clinical Trial.

Traeger AC[1,2], Lee H[1,3], Hübscher M[1], Skinner IW[1,4], Moseley GL[1,5], Nicholas MK[6], Henschke N[2], Refshauge KM[7], Blyth FM[8], Main CJ[9], Hush JM[10], Lo S[11,12], McAuley JH[1,13].

JAMA Neurol. **2018 Nov 5**. doi: 10.1001/jamaneurol.2018.3376. PMID: 30398542. [Epub ahead of print]

Importance: Many patients with acute low back pain do not recover with basic first-line care (advice, reassurance, and simple analgesia, if necessary). It is unclear whether intensive patient education improves clinical outcomes for those patients already receiving first-line care.

Objective: To determine the effectiveness of intensive patient education for patients with acute low back pain.

Design, Setting, and Participants: This randomized, placebo-controlled clinical trial recruited patients from general practices, physiotherapy clinics, and a research center in Sydney, Australia, between September 10, 2013, and December 2, 2015. Trial follow-up was completed in December 17, 2016. Primary care practitioners invited 618 patients presenting with acute low back pain to participate. Researchers excluded 416 potential participants. All of the 202 eligible participants had low back pain of fewer than 6 weeks' duration and a high risk of developing chronic low back pain according to Predicting the Inception of Chronic Pain (PICKUP) Tool, a validated prognostic model. Participants were randomized in a 1:1 ratio to either patient education or placebo patient education.

Interventions: All participants received recommended first-line care for acute low back pain from their usual practitioner. Participants received additional 2 × 1-hour sessions of patient education (information on pain and biopsychosocial contributors plus self-management techniques, such as remaining active and pacing) or placebo patient education (active listening, without information or advice).

Main Outcomes and Measures: The primary outcome was pain intensity (11-point numeric rating scale) at 3 months. Secondary outcomes included disability (24-point Roland Morris Disability Questionnaire) at 1 week, and at 3, 6, and 12 months.

Results: Of 202 participants randomized for the trial, the mean (SD) age of participants was 45 (14.5) years and 103 (51.0%) were female. Retention rates were greater than 90% at all time points. Intensive patient education was not more effective than placebo patient education at reducing pain intensity (3-month mean [SD] pain intensity: 2.1 [2.4] vs 2.4 [2.2]; mean difference at 3 months, -0.3 [95% CI, -1.0 to 0.3]). There was a small effect of intensive patient education on the secondary outcome of disability at 1 week (mean difference, -1.6 points on a 24-point scale [95% CI, -3.1 to -0.1]) and 3 months (mean difference, -1.7 points, [95% CI, -3.2 to -0.2]) but not at 6 or 12 months.

Conclusions and Relevance: Adding 2 hours of patient education to recommended first-line care for patients with acute low back pain did not improve pain outcomes. Clinical guideline recommendations to provide complex and intensive support to high-risk patients with acute low back pain may have been premature.

Trial Registration: Australian Clinical Trial Registration Number: 12612001180808.

OTHER RESEARCH OF INTEREST

Serial circulating omega 3 polyunsaturated fatty acids and healthy ageing among older adults in the Cardiovascular Health Study: prospective cohort study.

Lai HT[1], de Oliveira Otto MC[2], Lemaitre RN[3], McKnight B[4], Song X[5], King IB[6], Chaves PH[7], Odden MC[8], Newman AB[9], Siscovick DS[10], Mozaffarian D[11].

Erratum in: **Serial circulating omega 3 polyunsaturated fatty acids and healthy ageing among older adults in the Cardiovascular Health Study: prospective cohort study.** [BMJ. 2018]

BMJ. **2018 Oct 17**;363:k4067. doi: 10.1136/bmj.k4067. PMCID: PMC6191654. PMID: 30333104.

OBJECTIVE: To determine the longitudinal association between serial biomarker measures of circulating omega 3 polyunsaturated fatty acid (n3-PUFA) levels and healthy ageing.

DESIGN: Prospective cohort study.

SETTING: Four communities in the United States (Cardiovascular Health Study) from 1992 to 2015.

PARTICIPANTS: 2622 adults with a mean (SD) age of 74.4 (4.8) and with successful healthy ageing at baseline in 1992-93.

EXPOSURE: Cumulative levels of plasma phospholipid n3-PUFAs were measured using gas chromatography in 1992-93, 1998-99, and 2005-06, expressed as percentage of total fatty acids, including α-linolenic acid from plants and eicosapentaenoic acid, docosapentaenoic acid, and docosahexaenoic acid from seafoood.

MAIN OUTCOME MEASURE: Healthy ageing defined as survival without chronic diseases (ie, cardiovascular disease, cancer, lung disease, and severe chronic kidney disease), the absence of cognitive and physical dysfunction, or death from other causes not part of the healthy ageing outcome after age 65. Events were centrally adjudicated or determined from medical records and diagnostic tests.

RESULTS: Higher levels of long chain n3-PUFAs were associated with an 18% lower risk (95% confidence interval 7% to 28%) of unhealthy ageing per interquintile range after multivariable adjustments with time-varying exposure and covariates. Individually, higher eicosapentaenoic acid and docosapentaenoic acid (but not docosahexaenoic acid) levels were associated with a lower risk: 15% (6% to 23%) and 16% (6% to 25%), respectively. α-linolenic acid from plants was not noticeably associated with unhealthy ageing (hazard ratio 0.92, 95% confidence interval 0.83 to 1.02).

CONCLUSIONS: In older adults, a higher cumulative level of serially measured circulating n3-PUFAs from seafood (eicosapentaenoic acid, docosapentaenoic acid, and docosahexaenoic acid), eicosapentaenoic acid, and docosapentaenoic acid (but not docosahexaenoic acid from seafood or α-linolenic acid from plants) was associated with a higher likelihood of healthy ageing. These findings support guidelines for increased dietary consumption of n3-PUFAs in older adults.

Repetitive transcranial magnetic stimulation (rTMS) as a treatment for chronic dizziness following mild traumatic brain injury.

Paxman E[1], Stilling J[1], Mercier L[1], Debert CT [1,2].

BMJ Case Rep. **2018 Nov 5**;2018. pii: bcr-2018-226698. doi: 10.1136/bcr-2018-226698. PMID: 30396889.

A 61-year-old man sustained a mild traumatic brain injury (mTBI) following a pedestrian versus vehicle traffic accident. Post injury, he began to experience symptoms including light-headedness, spatial disorientation, nausea, fatigue and prominent dizziness brought on by postural change, physical activity or eye movements. Symptoms of dizziness persisted for over 5 years, despite numerous extensive and rigorous vestibular and vision therapy regimens. All investigations suggested normal peripheral and central vestibular functioning. The patient underwent 10 sessions of repetitive transcranial magnetic stimulation (rTMS) treatment, with stimulation of the left dorsolateral prefrontal cortex at 70% of resting motor threshold and a frequency of 10 Hz. Dizziness symptom severity and frequency were reduced by greater than 50% at 3 months post treatment, with a clinically significant reduction of dizziness disability from 40 to 21 points on the Dizziness Handicap Inventory. We propose rTMS as a safe, effective and cost-effective treatment option for patients who experience persistent post-traumatic dizziness secondary to mTBI.

OTHER RESEARCH OF INTEREST (Continued)

Association of Psoriasis With Inflammatory Bowel Disease: A Systematic Review and Meta-analysis.

Fu Y[1], Lee CH[2], Chi CC[1,3].

JAMA Dermatol. **2018 Oct 24**. doi: 10.1001/jamadermatol.2018.3631. PMID: 30422277. [Epub ahead of print]

Importance: Patients with psoriasis may experience comorbidities involving cardiovascular diseases, chronic kidney disease, uveitis, psychiatric disturbances, and metabolic syndrome. However, the association between psoriasis and inflammatory bowel disease (IBD) has been largely unclear.

Objective: To investigate the association of psoriasis with IBD.

Data Sources: For this systematic review and meta-analysis, MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials were searched for relevant studies from inception to January 17, 2018.

Study Selection: Case-control, cross-sectional, or cohort studies that examined either the odds or risk of IBD in patients with psoriasis were included. No geographic or language limitations were used in the search.

Data Extraction and Synthesis: The PRISMA and MOOSE guidelines were followed for data extraction. The Newcastle-Ottawa Scale was used to evaluate the risk of bias of included studies. Crohn disease and ulcerative colitis were analyzed separately and random-effects model meta-analysis was conducted. A subgroup analysis was performed on psoriatic arthritis.

Main Outcomes and Measures: The risk and odds of IBD, Crohn disease, and ulcerative colitis in patients with psoriasis.

Results: A total of 5 case-control or cross-sectional studies and 4 cohort studies with 7 794 087 study participants were included. Significant associations were found between psoriasis and Crohn disease (odds ratio, 1.70; 95% CI, 1.20-2.40) and between psoriasis and ulcerative colitis (odds ratio, 1.75; 95% CI, 1.49-2.05). Patients with psoriasis had an increased risk of Crohn disease (risk ratio, 2.53; 95% CI, 1.65-3.89) and ulcerative colitis (risk ratio, 1.71; 95% CI, 1.55-1.89).

Conclusions and Relevance: These findings suggest that psoriasis is significantly associated with IBD. Gastroenterology consultation may be indicated when patients with psoriasis present with bowel symptoms.

Coenzyme Q10 supplementation in acute ischemic stroke: Is it beneficial in short-term administration?

Ramezani M[1], Sahraei Z[2], Simani L[1,3], Heydari K[1], Shahidi F[1].

Nutr Neurosci. **2018 Nov 7**:1-6. doi: 10.1080/1028415X.2018.1541269. PMID: 30404563. [Epub ahead of print]

BACKGROUNDS AND AIMS: Clinical studies demonstrated that the efficacy of Coenzyme Q10 (CoQ10) as an adjuvant therapeutic agent in several neurological diseases such as Parkinson disease (PD), Huntington disease (HD), and migraine. The purpose of this study is to investigate oxidative stress effects, antioxidant enzymes activity, neuroinflammatory markers levels, and neurological outcome in acute ischemic stroke (AIS) patients following administration of CoQ10 (300 mg/day).

METHODS: Patients with AIS (n = 60) were randomly assigned to a placebo group (wheat starch, n = 30) or CoQ10-supplemented group (300 mg/day, n = 30). The intervention was administered for 4 weeks. Serum CoQ10 concentration, malondialdehyde (MDA), superoxide dismutase (SOD) activity, glial fibrillary acidic protein (GFAP) levels as primary outcomes and National Institute of Health Stroke Scale (NIHSS), Modified Ranking Scale (MRS), and Mini-Mental State Examination (MMSE) as secondary outcome were measured at the both beginning and end of the study.

RESULTS: Forty-four subjects with AIS completed the intervention study. A significant increase in CoQ10 level was observed in the supplement-treated group compared with placebo group (mean difference = 26.05 ± 26.63 ng/ml, 14.12 ± 14.69 ng/ml, respectively; P = 0.01), moreover CoQ10 supplementation improved NIHSS and MMSE scores significantly (P = 0.05, P = 0.03 respectively). but there were no statistically significant differences in MRS score, MDA, SOD, and GFAP levels between the two groups.

CONCLUSIONS: CoQ10 probably due to low dose and short duration of supplementation, no favorable effects on MDA level, SOD activity and GFAP level.

###