GULF WAR ILLNESS

Characterising the gut microbiome in veterans with Gulf War Illness: a protocol for a longitudinal, prospective cohort study.

Keating JA[1], Shaughnessy C[2], Baubie K[1], Kates AE[1, 2], Putman-Buehler N[2], Watson L[2], Dominguez N[2], Watson K[1], Cook DB[1,3], Rabago D[4] , Suen G[5], Gangnon R[6], Safdar N[1,2].

BMJ Open. **2019 Aug 19**;9(8):e031114. doi: 10.1136/bmjopen-2019-031114. PMID: 31431446.

INTRODUCTION: Approximately 25%-35% of the 1991 Gulf War Veteran population report symptoms consistent with Gulf War Illness (GWI), a chronic, multi-symptom illness characterised by fatigue, pain, irritable bowel syndrome and problems with cognitive function. GWI is a disabling problem for Gulf War Veterans, and there remains a critical need to identify innovative, novel therapies. Gut microbiota perturbation plays a key role in the symptomatology of other chronic multi-symptom illnesses, including myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Given similarities between ME/CFS and GWI and the presence of gastrointestinal disorders in GWI patients, Veterans with GWI may also have gut abnormalities like those seen with ME/CFS. In this longitudinal cohort study, we are comparing the diversity (structure) and the metagenomes (function) of the gut microbiome between Gulf War Veterans with and without GWI. If we find differences in Veterans with GWI, the microbiome could be a target for therapeutic intervention to alleviate GWI symptoms.

METHODS AND ANALYSIS: Participants answer questions about diet, exercise and lifestyle factors. Participants also complete a questionnaire (based on the Kansas case definition of GWI) regarding their medical history and symptoms; we use this questionnaire to group participants into GWI versus healthy control cohorts. We plan to enrol 52 deployed Gulf War Veterans: 26 with GWI and 26 healthy controls. Participants provide stool and saliva samples weekly for an 8-week period for microbiome analyses. Participants also provide blood samples at the beginning and end of this period, which we will use to compare measures of inflammation markers between the groups.

ETHICS AND DISSEMINATION: The protocol was approved by the University of Wisconsin-Madison Health Sciences Institutional Review Board and the William S. Middleton Memorial Veterans Hospital Research and Development Committee. Results of this study will be submitted for publication in a peer-reviewed journal.

CHRONIC FATIGUE SYNDROME

The association of major life events with chronic fatigue.

Schmaling KB[1], Patterson TL[2].

J Psychosom Res. **2019 Aug 13**;125:109810. doi: 10.1016/j.jpsychores.2019.109810. PMID: 31445319. [Epub ahead of print]

OBJECTIVE: Major life events have been associated with the onset of unexplained chronic fatigue (CF) and with variability in illness course. The purpose of this study was to characterize the associations of major life events with illness status over time.

METHOD: Sentinel measures of clinical status were collected four times over 18 months in a cohort of 99 persons with CF; participants also were interviewed regarding major life events, which were independently rated by observers.

RESULTS: Over time, more major life events attributed to CF predicted a worse clinical course, suggesting that illness-related major life events rather than stressful life events in general are associated with worse clinical status for persons with CF.

CONCLUSION: This study adds to the literature regarding specific types of life events' relationship to illness course, which has implications for the management of CF.

CHRONIC FATIGUE SYNDROME (Continued)

Survey of activity pacing across healthcare professionals informs a new activity pacing framework for chronic pain/fatigue.

Antcliff D[1,2], Keenan AM[2], Keeley P[3], Woby S[4,5,6], McGowan L[2].

Musculoskeletal Care. **2019 Aug 20**. doi: 10.1002/msc.1421. PMID: 31430038. [Epub ahead of print]

INTRODUCTION: Activity pacing is considered a key component of rehabilitation programmes for chronic pain/fatigue. However, there are no widely used guidelines to standardize how pacing is delivered. This study aimed to undertake the first stage in developing a comprehensive evidence-based activity pacing framework.

METHODS: An online survey across pain/fatigue services in English National Health Service trusts explored healthcare professionals' opinions on the types/uses of pacing, aims, facets and perceived effects. Data were analysed using descriptive statistics for closed-ended questions and thematic analysis for open-ended questions. Purposeful recruitment with a snowball effect engaged 92 healthcare professionals (physiotherapists, occupational therapists, nurses, doctors and psychologists) to the study.

RESULTS: Pacing was highly utilized, with perceived long-term benefits for patients (n = 83, 90.2% healthcare professionals instructed pacing). The most endorsed aim of pacing was "achievement of meaningful activities" (24.5% of ranked votes). The least endorsed aim was "to conserve energy" (0.1% of ranked votes). The most frequently supported facet of pacing was "breaking down tasks" (n = 91, 98.9%). The least supported facet was "stopping activities when symptoms increase" (n = 6, 6.5%). Thematic analysis showed recurring themes that pacing involved flexibility and sense of choice.

CONCLUSIONS: Pacing is a multidimensional coping strategy and complex behaviour. The message is clear that pacing should enable increases in meaningful activities, as opposed to attempting to avoid symptoms. The survey findings have informed the development of an activity pacing framework to guide healthcare professionals on the multiple components of pacing. This will help to standardize and optimize treatments for chronic pain/fatigue and enable future investigations.

HEADACHE and MIGRAINE

Predicting initiation of preventive migraine medications: exploratory study in a large U.S. medical claims database.

Ford JH[1], Schroeder K[1], Buse DC[2], Joshi S[3], Gelwicks S[1,4], Foster SA[1], Aurora SK[1].

Curr Med Res Opin. **2019 Aug 17**:1. doi: 10.1080/03007995.2019.1657716. PMID: 31422701. [Epub ahead of print]

Objective: Despite guidelines that identify potential patients eligible for preventive migraine medications, their underutilization leaves patients at risk of acute medication overuse, disease progression, and higher healthcare resource utilization and disability. This exploratory, retrospective, observational study aimed to identify which factors predict preventive migraine medication initiation. Demographics and initiation of acute medication use were hypothesized to be predictive of initiation of preventive migraine medication.

Methods: The Truven Health Analytics MarketScan® U.S. Commercial and Medicare Supplemental claims database (2011-2013) was used to identify adults newly diagnosed with migraine. Patients were divided into 2 subgroups: initiated a preventive migraine medication (antidepressants, anti-epileptics, beta-blockers, or neurotoxins) within 1 year of migraine diagnosis and did not initiate a preventive migraine medication. Logistic regression models were constructed to identify factors associated with preventive migraine medication initiation.

Results: Study population included 147,923 patients: 43,660 preventive migraine medication initiators and 104,263 non-preventive migraine medication patients. Best-fit model for predicting preventive migraine medication initiation included: female gender (odds ratio =1.181 [95%CI =1.144,1.218]; measured at date of first migraine diagnosis); headache diagnosis prior to migraine diagnosis (odds ratio =1.538 [95%CI =1.498,1.579]; measured 1-year before first migraine diagnosis); and sleep disorder (odds ratio =1.206 [95%CI =1.161,1.252]), headache/migraine-specific Emergency Department (ED) visit (odds ratio =1.224 [95%CI =1.168,1.283]), neurologist visit (odds ratio =1.502 [95%CI =1.459,1.547]), and acute medication refills with <90-day gap (odds ratio =1.509 [95%CI =1.470,1.549]) each measured at 1-year before first preventive migraine medication.

Conclusions: In addition to consistent acute medication refills, specific comorbidity diagnoses, headache/migraine-specific ED utilization, and neurologist care are predictive of preventive migraine medication initiation in the 1-year post-incident migraine diagnosis.

HEADACHE and MIGRAINE (Continued)

Unmet Acute Treatment Needs From the 2017 Migraine in America Symptoms and Treatment Study.

Lipton RB[1], Munjal S[2], Buse DC[1], Alam A[2], Fanning KM[3], Reed ML[3], Schwedt TJ[4], Dodick DW[4].

Headache. **2019 Aug 13**. doi: 10.1111/head.13588. PMID: 31410844. [Epub ahead of print]

OBJECTIVES: To characterize unmet treatment needs in a sample of Migraine in America Symptoms and Treatment (MAST) Study participants using oral, acute prescription migraine medications.

BACKGROUND: The MAST Study is a 2017 study of US adults with migraine that profiles current treatment patterns and identifies and quantifies unmet treatment needs.

METHODS: Cross-sectional data from an online survey of US adults meeting ICHD-3 beta criteria for migraine. For inclusion in this paper, respondents self-reported a history of 3 or more monthly headache days (MHDs) in the past 3 months and at least 1 MHD in the past 30 days, and current use of orally administered acute prescription medication for headache. Three domains of unmet need were identified: inadequate treatment response (ie, inadequate 2-hour pain freedom, recurrence within 24 hours of initial relief), demanding attack characteristics (rapid onset of attack, headache associated with sleep), and unique patient characteristics (opioid or barbiturate overuse, cardiovascular comorbidity). Sociodemographics, oral medication use, and coexisting conditions and symptoms (ie, level of treatment optimization, psychological symptoms, attack-related cutaneous allodynia, and migraine symptom severity) were assessed for each domain and by the number of unmet need domains.

RESULTS: Overall, 15,133 respondents met inclusion criteria, 26.0% (3930/15,133) reported current use of oral acute prescription medication to treat headache. Eligible participants had a mean age of 45.0 years, 73.6% [2892/3930] were women and 81.1% [3186/3930]) were White. A total of 95.8% (3765/3930) of respondents had at least 1 unmet acute treatment need; 89.5% (3516/3930) reported demanding attack characteristics, 74.1% (2912/3930) reported inadequate treatment response, and 16.1% (634/3930) presented with unique patient characteristics. Common areas of unmet need were rapid headache onset (65.3% [2567/3930]), moderate to severe disability (55.6% [2187/3930]), inadequate 2-hours pain freedom (49.0% [1892/3930]), and headache recurrence within 24 hours (38.0% [1493/3930]). An increasing number of unmet treatment need domains was associated with worsening psychological symptoms, attack-related cutaneous allodynia and migraine symptom severity.

CONCLUSION: Nearly all MAST Study respondents using acute oral prescription medications for migraine reported at least 1 unmet treatment need. As unmet needs increased, so did coexisting conditions and symptom severity.

Association Between Migraine Headaches and Dementia in More than 7,400 Patients Followed in General Practices in the United Kingdom.

Kostev K[1], Bohlken J[2], Jacob L[3].

J Alzheimers Dis. **2019 Aug 6**. doi: 10.3233/JAD-190581. [Epub ahead of print]

BACKGROUND: Most previous studies focusing on the migraine headache-dementia relationship have failed to simultaneously adjust for several common comorbidities.

OBJECTIVE: The goal of this retrospective cohort study was to investigate the association between migraine headaches and dementia in general practices in the UK.

METHODS: The current study sample included patients who received a migraine diagnosis in one of 67 general practices in the UK between January 1997 and December 2016 (index date). Patients without migraine diagnoses were matched 1:1 to patients with migraine diagnoses based on propensity scores using a greedy algorithm and derived from the logistic regression using age, sex, index year, and co-diagnoses. The main outcome of the study was the association between migraine headaches and the incidence of dementia within 10 years of the index date.

RESULTS: This study included 7,454 individuals with or without migraine diagnoses. Mean age was 67.7 years (SD=5.8 years), and 72.9% of patients were women. Within 10 years of the index date, 5.2% of participants with and 3.7% of those without migraine headaches were diagnosed with dementia (log-rank $p<0.001$). The respective figures were 5.8% and 3.6% in women (log-rank $p<0.001$) and 4.5% and 3.4% in men (log-rank $p=0.722$). We observed a positive association between migraine diagnoses and all-cause dementia (hazard-ratio [HR]=1.43) as well as Alzheimer's disease (HR=1.87). Sensitivity analyses further revealed that these associations were only significant in women (all-cause dementia: HR=1.65; Alzheimer's disease: HR=2.27).

CONCLUSION: Migraine diagnoses were positively associated with all-cause dementia and Alzheimer's disease in women.

HEADACHE and MIGRAINE (Continued)

Life With Migraine: Effects on Relationships, Career, and Finances From the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study.

Buse DC[1], Fanning KM[2], Reed ML[2], Murray S[3], Dumas PK[4], Adams AM[5], Lipton RB[1,6].

Headache. **2019 Aug 12**. doi: 10.1111/head.13613. PMID: 31407321. [Epub ahead of print]

OBJECTIVE: To assess the effects of migraine on important life domains and compare differences between respondents with episodic and chronic migraine and between sexes.

BACKGROUND: Migraine is associated with a substantial personal and societal burden and can also affect the interpersonal dynamics, psychological health and well-being, and financial stability of the entire family of the person with migraine.

METHODS: The Chronic Migraine Epidemiology and Outcomes (CaMEO) Study is a prospective, longitudinal, Web-based survey study undertaken between September 2012 and November 2013 in a systematic U.S. sample of people meeting modified International Classification of Headache Disorders, 3rd edition migraine criteria: 19,891 respondents were invited to complete the Family Burden Module, which assessed the perceived impact of migraine on family relationships and life, career and finances, and overall health. Respondents were stratified by episodic migraine (<15 headache days/month) and chronic migraine (≥15 headache days/month) and sex for comparisons.

RESULTS: A total of 13,064 respondents (episodic migraine: 11,944 [91.4%]; chronic migraine: 1120 [8.6%]) provided valid data. Approximately 16.8% of respondents not currently in a romantic relationship (n = 536 of 3189) and 17.8% of those in a relationship but not living together (n = 236 of 1323) indicated that headaches had contributed to relationship problems. Of those in a relationship and living together (n = 8154), 3.2% reported that they chose not to have children, delayed having children or had fewer children because of migraine (n = 260; episodic migraine: n = 193 of 7446 [2.6%]; chronic migraine: n = 67 of 708 [9.5%]; P < .001). Of individuals responding to career/finance items (n = 13,061/13,036), 32.7% indicated that headaches negatively affected ≥1 career area (n = 4271; episodic migraine: n = 3617 of 11,942 [30.3%]; chronic migraine: n = 654 of 1119 [58.4%]), and 32.1% endorsed worry about long-term financial security due to migraine (n = 4180; episodic migraine: n = 3539 of 11,920 [29.7%]; chronic migraine: n = 641 of 1116 [57.4%]).

CONCLUSIONS: Migraine can negatively affect many important aspects of life including marital, parenting, romantic and family relationships, career/financial achievement and stability, and overall health. Reported burden was consistently greater among those with chronic migraine than among people with episodic migraine; however, few differences were seen between the sexes.

Prospective Cohort Study of Caffeinated Beverage Intake as a Potential Trigger of Headaches among Migraineurs.

Mostofsky E[1], Mittleman MA[2], Buettner C[3], Li W [4], Bertisch SM[5].

Am J Med. **2019 Aug 2**. pii: S0002-9343(19)30210-4. doi: 10.1016/j.amjmed.2019.02.015. PMID: 31402050. [Epub ahead of print]

OBJECTIVE: We aimed to evaluate the role of caffeinated beverage intake as a potential trigger of migraine headaches on that day or on the following day.

METHODS: In this prospective cohort study, 101 adults with episodic migraine completed electronic diaries every morning and evening. Ninety-eight participants completed at least 6 weeks of diaries in March 2016-October 2017. Every day, participants reported caffeinated beverage intake, other lifestyle factors, and the timing and characteristics of each migraine headache. We compared a participant's incidence of migraines on days with caffeinated beverage intake to the incidence of migraines among the same individual on days with no intake, accounting for day of week. We used conditional logistic regression to estimate odds ratios (OR) and 95% confidence intervals.

RESULTS: Among 98 participants (86 women, 12 men) with mean age 35.1 years, 83% white, and 10% Hispanic or Latino, the average age when headaches started was 16.3 years. In total, the participants reported 825 migraines during 4467 days of observation. There was a statistically significant nonlinear association between the number of caffeinated beverages and the odds of migraine headache occurrence on that day (P-quadratic trend = .024), though estimates for each level of intake were not statistically significant. The associations varied according to habitual intake and oral contraceptive use.

CONCLUSIONS: There was a nonlinear association between caffeinated beverage intake and the odds of migraine headache occurrence on that day. This suggests that high levels of caffeinated beverage intake may be a trigger of migraine headaches on that day.

HEADACHE and MIGRAINE (Continued)

Dynamic functional connectivity of migraine brain: a resting-state fMRI study.

Lee MJ[1,2], Park BY[3,4], Cho S[1], Park H[4,5], Kim ST[6], Chung CS[1,2].

Pain. **2019 Aug 10**. doi: 10.1097/j.pain.0000000000001676. PMID: 31408050. [Epub ahead of print]

Migraine headache is an episodic phenomenon, and patients with episodic migraine have ictal (headache), peri-ictal (premonitory, aura, and postdrome), and interictal (asymptomatic) phases. We aimed to find the functional characteristics of migraine brain regardless of headache phase using dynamic functional connectivity analysis. We prospectively recruited 50 patients with migraine and 50 age- and sex-matched controls. All subjects underwent a resting-state functional MRI. Significant networks were defined in a data-driven fashion from the interictal (>48 hours apart from headache phases) patients and matched controls (interictal dataset) and tested to ictal or peri-ictal patients and controls (ictal/peri-ictal dataset). Both static and dynamic analyses were used for the between-group comparison. A false discovery rate correction was performed. As a result, the static analysis did not reveal a network which was significant in both interictal and ictal/peri-ictal datasets. Dynamic analysis revealed significant between-group differences in seven brain networks in the interictal dataset, among which a frontoparietal network (controls > patients, p=0.0467), two brainstem networks (patients > controls, p=0.0467 and <0.001), and a cerebellar network (controls > patients, p=0.0408 and <0.001 in two states) remained significant in the ictal/peri-ictal dataset. Using these networks, migraine was classified with a sensitivity of 0.70 and specificity of 0.76 in the ictal/peri-ictal dataset. In conclusion, the dynamic connectivity analysis revealed more functional networks related to migraine than the conventional static analysis, suggesting a substantial temporal fluctuation in functional characteristics. Our data also revealed migraine-related networks which show significant difference regardless of headache phases between patients and controls.

CHRONIC PAIN

Daily and bidirectional linkages between pain catastrophizing and spouse responses.

Martire LM[1], Zhaoyang R[2], Marini CM[2], Nah S[1], Darnall BD[3].

Pain. **2019 Aug 10**. doi: 10.1097/j.pain.0000000000001673. PMID: 31408052. [Epub ahead of print]

Pain catastrophizing has been shown to predict greater pain and less physical function in daily life for chronic pain sufferers, but its effects on close social partners have received much less attention. The overall purpose of the present study was to examine the extent to which pain catastrophizing is an interpersonal coping strategy that is maladaptive for patients and their spouses. A total of 144 older knee osteoarthritis patients and their spouses completed baseline interviews and a 22-day diary assessment. Multilevel lagged models indicated that, on days when patients reported greater catastrophizing in the morning, their spouses experienced more negative affect throughout the day. In addition, a higher level of punishing responses from the spouse predicted greater pain catastrophizing the next morning, independent of patient pain and negative affect. Multilevel mediation models showed that patients' morning pain catastrophizing was indirectly associated with spouses' negative affect and punishing responses via patients' own greater negative affect throughout the day. There was no evidence that spouses' empathic or solicitous responses either followed or preceded patients' catastrophizing. These findings suggest that cognitive-behavioral interventions that reduce pain catastrophizing should be modified for partnered patients to address dyadic interactions and the spouse's role in pain catastrophizing.

CHRONIC PAIN (Continued)

Sensory Function and Pain Experience in Arthritis, Complex Regional Pain Syndrome, Fibromyalgia Syndrome and Healthy Volunteers: A Cross-sectional Study.

Palmer S[1], Bailey J[1,2], Brown C[3], Jones A[4], McCabe CS[1,5,6].

Clin J Pain. **2019 Aug 12**. doi: 10.1097/AJP.0000000000000751. PMID: 31408010. [Epub ahead of print]

OBJECTIVES: This study aimed to identify relationships between sensory function and pain in common pain conditions (Arthritis, Complex Regional Pain Syndrome (CRPS) and Fibromyalgia Syndrome (FMS)) and healthy participants. Sensory abnormalities are known to be concomitant with some types of chronic pain but comparison across pain conditions using existing research is difficult due to methodological differences. Pragmatic Quantitative Sensory Testing (QST) methods were used.

METHODS: Hot and cold sensitivity, light touch threshold (LTT), two-point discrimination (TPD) and pressure pain threshold (PPT) were assessed in 143 participants (n=37 Healthy, n=34 Arthritis, n=36 CRPS, n=36 FMS). Outcomes were assessed in the index ("affected" or right) and contralateral arm. Participants also completed the Brief Pain Inventory and McGill Pain Questionnaire.

RESULTS: There were statistically significant differences between groups for all QST outcomes except TPD. Relative to healthy participants, FMS displayed heat hyperesthesia in both arms and cold hyperesthesia in the contralateral arm. CRPS demonstrated no changes in thermal sensitivity. Both CRPS and FMS exhibited bilateral pressure hyperalgesia. LTT hypoesthesia was observed bilaterally for CRPS but only in the contralateral arm for FMS. CRPS and FMS had pressure hyperalgesia in the index arm relative to Arthritis patients. There were no differences between Arthritis and Healthy participants for any QST outcome. In CRPS there were significant correlations between LTT and pain outcomes bilaterally.

DISCUSSION: People with FMS and CRPS demonstrate extensive sensory dysfunction. Arthritis patients had sensory profiles closer to healthy participants. LTT may provide a clinically relevant and accessible assessment for CRPS.

IRRITABLE BOWEL SYNDROME

Delivery of Care for Functional Gastrointestinal Disorders: A Systematic Review.

Basnayake C[1,2], Kamm MA[1,2], Salzberg MR[1,2], Wilson-O'Brien A[1,2], Stanley A[1], Thompson AJ[1,2].

J Gastroenterol Hepatol. **2019 Aug 14**. doi: 10.1111/jgh.14830. PMID: 31411755. [Epub ahead of print]

BACKGROUND: A diverse range of treatments are available for the treatment of functional gastro-intestinal disorders (FGIDs). Individual treatments, including drug therapies, behavioural therapy ("biofeedback"), psychological therapies, and dietary therapies have been well validated in controlled, randomised trials and real-life case series. However, few studies have evaluated models of delivery of care for the whole population of referred patients with a FGID. This review evaluates models of specialist outpatient care for the management of FGIDs.

METHODS: A systematic review was performed of full-text articles published until October 2018 in PUBMED/Medline and EMBASE. Studies were included if they evaluated a model of outpatient care in a specialist setting for the treatment of adult patients with a FGID, and included patient-reported outcomes comprising symptoms, quality of life or psychological well-being.

RESULTS: Few studies have evaluated the delivery of care for the whole population of referred patients with a FGID, and there was one randomised comparison of different models of care. Two studies that evaluated the outcome of gastroenterologist-only clinics suggested poor long-term results. Two non-comparative case series reported the outcome of multi-disciplinary care, including gastroenterologists and psychological therapists, suggesting improved patient quality of life and psychological well-being.

CONCLUSIONS: Despite the high prevalence and cost of treating FGIDs, and the availability of effective treatments, there are few data, and limited randomised comparisons, reporting the outcome of different types of specialist care. The few data available suggest that multi-disciplinary care is superior to gastroenterologist-only care, but this needs to be validated in prospective comparative studies.

IRRITABLE BOWEL SYNDROME

A 5Ad Dietary Protocol for Functional Bowel Disorders.

Ibrahim F[1], Stribling P[2].

Nutrients. **2019 Aug 17**;11(8). pii: E1938. doi: 10.3390/nu11081938. PMCID: PMC6722668. PMID: 31426496.

Functional bowel disorders (FBDs) affect around 20% of the population worldwide and are associated with reduced quality of life and high healthcare costs. Dietary therapies are frequently implemented to assist with symptom relief in these individuals, however, there are concerns regarding their complexity, restrictiveness, nutritional adequacy, and effectiveness. Thus, to overcome these limitations, a novel approach, the 5Ad Dietary Protocol, was designed and tested for its efficacy in reducing the severity of a range of gastrointestinal symptoms in 22 subjects with FBDs. The protocol was evaluated in a repeated measures MANOVA design (baseline week and intervention week). Measures of stool consistency and frequency were subtyped based on the subject baseline status. Significant improvements were seen in all abdominal symptom measures ($p < 0.01$). The effect was independent of body mass index (BMI), age, gender, physical activity level, and whether or not the subjects were formally diagnosed with irritable bowel syndrome (IBS) prior to participation. Stool consistency and frequency also improved in the respective contrasting subtypes. The 5Ad Dietary Protocol proved to be a promising universal approach for varying forms and severities of FBDs. The present study paves the way for future research encompassing a longer study duration and the exploration of underlying physiological mechanisms.

Diet in Irritable Bowel Syndrome (IBS): Interaction with Gut Microbiota and Gut Hormones.

El-Salhy M[1,2,3], Hatlebakk JG[4,5], Hausken T[4,5].

Nutrients. **2019 Aug 7**;11(8). pii: E1824. doi: 10.3390/nu11081824. PMCID: PMC6723613. PMID: 31394793.

Diet plays an important role not only in the pathophysiology of irritable bowel syndrome (IBS), but also as a tool that improves symptoms and quality of life. The effects of diet seem to be a result of an interaction with the gut bacteria and the gut endocrine cells. The density of gut endocrine cells is low in IBS patients, and it is believed that this abnormality is the direct cause of the symptoms seen in IBS patients. The low density of gut endocrine cells is probably caused by a low number of stem cells and low differentiation progeny toward endocrine cells. A low fermentable oligo-, di-, monosaccharide, and polyol (FODMAP) diet and fecal microbiota transplantation (FMT) restore the gut endocrine cells to the level of healthy subjects. It has been suggested that our diet acts as a prebiotic that favors the growth of a certain types of bacteria. Diet also acts as a substrate for gut bacteria fermentation, which results in several by-products. These by-products might act on the stem cells in such a way that the gut stem cells decrease, and consequently, endocrine cell numbers decrease. Changing to a low-FODMAP diet or changing the gut bacteria through FMT improves IBS symptoms and restores the density of endocrine cells.

OTHER RESEARCH OF INTEREST

Evaluation of the Central Vein Sign as a Diagnostic Imaging Biomarker in Multiple Sclerosis.

Sinnecker T[1,2,3,4], Clarke MA[5,6], Meier D[2,4], Enzinger C[7], Calabrese M[8], De Stefano N[9], Pitiot A[10], Giorgio A[9], Schoonheim MM[11], Paul F[3,12], Pawlak MA[13], Schmidt R[14], Kappos L[1], Montalban X[15,16], Rovira À[15], Evangelou N[17], Wuerfel J[2,3,4,12]; MAGNIMS Study Group.

JAMA Neurol. **2019 Aug 19**. doi: 10.1001/jamaneurol.2019.2478. PMID: 31424490. [Epub ahead of print]

Importance: The central vein sign has been proposed as a specific imaging biomarker for distinguishing between multiple sclerosis (MS) and not MS, mainly based on findings from ultrahigh-field magnetic resonance imaging (MRI) studies. The diagnostic value of the central vein sign in a multicenter setting with a variety of clinical 3 tesla (T) MRI protocols, however, remains unknown.

Objective: To evaluate the sensitivity and specificity of various central vein sign lesion criteria for differentiating MS from non-MS conditions using 3T brain MRI with various commonly used pulse sequences.

Design, Setting, and Participants: This large multicenter, cross-sectional study enrolled participants (n = 648) of ongoing observational studies and patients included in neuroimaging research databases of 8 neuroimaging centers in Europe. Patient enrollment and MRI data collection were performed between January 1, 2010, and November 30, 2016. Data analysis was conducted between January 1, 2016, and April 30, 2018. Investigators were blinded to participant diagnosis by a novel blinding procedure.

Main Outcomes and Measures: Occurrence of central vein sign was detected on 3T T2*-weighted or susceptibility-weighted imaging. Sensitivity and specificity were assessed for these MRI sequences and for different central vein sign lesion criteria, which were defined by the proportion of lesions with central vein sign or by absolute numbers of lesions with central vein sign.

Results: A total of 606 participants were included in the study after exclusion of 42 participants. Among the 606 participants, 413 (68.2%) were women. Patients with clinically isolated syndrome and relapsing-remitting MS (RRMS) included 235 women (66.6%) and had a median (range) age of 37 (14.7-61.4) years, a median (range) disease duration of 2 (0-33) years, and a median (range) Expanded Disability Status Scale score of 1.5 (0-6.5). Patients without MS included 178 women (70.4%) and had a median (range) age of 54 (18-83) years. A total of 4447 lesions were analyzed in a total of 487 patients: 690 lesions in 98 participants with clinically isolated syndrome, 2815 lesions in 225 participants with RRMS, 54 lesions in 13 participants with neuromyelitis optica spectrum disorder, 54 lesions in 14 participants with systemic lupus erythematosus, 121 lesions in 29 participants with migraine or cluster headache, 240 lesions in 20 participants with diabetes, and 473 lesions in 88 participants with other types of small-vessel disease. The sensitivity was 68.1% and specificity was 82.9% for distinguishing MS from not MS using a 35% central vein sign proportion threshold. The 3 central vein sign lesion criteria had a sensitivity of 61.9% and specificity of 89.0%. Sensitivity was higher when an optimized T2*-weighted sequence was used.

Conclusions and Relevance: In this study, use of the central vein sign at 3T MRI yielded a high specificity and a moderate sensitivity in differentiating MS from not MS; international, multicenter studies may be needed to ascertain whether the central vein sign-based criteria can accurately detect MS.

OTHER RESEARCH OF INTEREST (Continued)

Efficacy and Safety of Cholinesterase Inhibitors for Mild Cognitive Impairment: A Systematic Review and Meta-Analysis.

Matsunaga S[1], Fujishiro H[2], Takechi H[1].

J Alzheimers Dis. **2019 Aug 12**;-1(1):1. doi: 10.3233/JAD-190546. PMID: 31424411. ,

BACKGROUND: The clinical benefit of cholinesterase inhibitors (ChEIs) for mild cognitive impairment (MCI) remains inconclusive.

OBJECTIVE: We performed a systematic review and meta-analysis of the efficacy/safety of ChEIs on subjects with MCI.

METHODS: We included randomized controlled trials (RCTs) of ChEIs in subjects with MCI, using cognitive function scores as a primary outcome measure.

RESULTS: Fourteen RCTs (six using donepezil, four using galantamine, and four using rivastigmine) with 5,278 subjects were included. We found no significant difference in cognitive function scores between the ChEIs and placebo groups [standardized mean difference (SMD)=-0.06, p=0.38, I2=76%]. However, in the secondary outcomes, ChEIs were associated with a lower incidence of progression to dementia compared with placebo (risk ratio=0.76, the number needed to treat=20). For safety outcomes, ChEIs were associated with a lower prevalence of fall than placebo. On the other hand, compared with placebo, ChEIs were associated with a higher incidence of discontinuation due to all causes, discontinuation due to adverse events, at least one adverse event, abnormal dreams, diarrhea, dizziness, headache, insomnia, loose stools, muscle cramps, nausea, vomiting, and weight loss.

CONCLUSIONS: Although ChEIs have a slight efficacy in the treatment of MCI, there are many safety issues. Therefore, ChEIs are difficult to recommend for MCI. However, the efficacy and safety of ChEIs on MCI with a biomarker-based diagnosis is unclear. Further RCTs are needed to confirm the efficacy and safety of ChEIs when used for individual neuropathological classifications of MCI.

High Glucose Intake Exacerbates Autoimmunity through Reactive-Oxygen-Species-Mediated TGF-β Cytokine Activation.

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Diet has been suggested to be a potential environmental risk factor for the increasing incidence of autoimmune diseases, yet the underlying mechanisms remain elusive. Here, we show that high glucose intake exacerbated autoimmunity in mouse models of colitis and experimental autoimmune encephalomyelitis (EAE). We elucidated that high amounts of glucose specifically promoted T helper-17 (Th17) cell differentiation by activating transforming growth factor-β (TGF-β) from its latent form through upregulation of reactive oxygen species (ROS) in T cells. We further determined that mitochondrial ROS (mtROS) are key for high glucose-induced TGF-β activation and Th17 cell generation. We have thus revealed a previously unrecognized mechanism underlying the adverse effects of high glucose intake in the pathogenesis of autoimmunity and inflammation.

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