## GULF WAR ILLNESS

### A permethrin metabolite is associated with adaptive immune responses in Gulf War Illness.

Joshi U[1], Pearson A[1], Evans JE[2], Langlois H[2], Saltiel N[2], Ojo J[1], Klimas N[3], Sullivan K[4], Keegan AP[5], Oberlin S[2], Darcey T[2], Cseresznye A[2], Raya B[2], Paris D[1], Hammock B[6], Vasylieva N[6], Hongsibsong S[7], Stern LJ[8], Mullan M[9], Crawford F[1], Abdullah L[10].

Brain Behav Immun. **2019 Jul 17**. pii: S0889-1591(19)30329-0. doi: 10.1016/j.bbi.2019.07.015. PMID: 31325531. [Epub ahead of print]

Gulf War Illness (GWI), affecting 30% of veterans from the 1991 Gulf War (GW), is a multi-symptom illness with features similar to those of patients with autoimmune diseases. The objective of the current work is to determine if exposure to GW-related pesticides, such as permethrin (PER), activates peripheral and central nervous system (CNS) adaptive immune responses. In the current study, we focused on a PER metabolite, 3-phenoxybenzoic acid (3-PBA), as this is a common metabolite previously shown to form adducts with endogenous proteins. We observed the presence of 3-PBA and 3-PBA modified lysine of protein peptides in the brain, blood and liver of PB+PER exposed mice at acute and chronic post-exposure timepoints. We tested whether 3-PBA-haptenated albumin (3-PBA-albumin) can activate immune cells since it is known that chemically haptenated proteins can stimulate immune responses. We detected autoantibodies against 3-PBA-albumin in plasma from PB+PER exposed mice and veterans with GWI at chronic post-exposure timepoints. We also observed that in vitro treatment of blood with 3-PBA-albumin resulted in the activation of B- and T-helper lymphocytes and that these immune cells were also increased in blood of PB+PER exposed mice and veterans with GWI. These immune changes corresponded with elevated levels of infiltrating monocytes in the brain and blood of PB+PER exposed mice which coincided with alterations in the markers of blood-brain barrier disruption, brain macrophages and neuroinflammation. These studies suggest that pesticide exposure associated with GWI may have resulted in the activation of the peripheral and CNS adaptive immune responses, possibly contributing to an autoimmune-type phenotype in veterans with GWI.

### Preliminary Evidence for a Hormetic Effect on DNA Nucleotide Excision Repair in Veterans with Gulf War Illness.

Latimer JJ[1,2], Alhamed A[1,2], Sveiven S[2], Almutairy A[1,2], Klimas NG[3,4], Abreu M[3], Sullivan K[5], Grant SG[2,6].

Mil Med. **2019 Jul 23**. pii: usz177. doi: 10.1093/milmed/usz177. PMID: 31334811. [Epub ahead of print]

INTRODUCTION: Veterans of the 1991 Gulf War were potentially exposed to a mixture of stress, chemicals and radiation that may have contributed to the persistent symptoms of Gulf War Illness (GWI). The genotoxic effects of some of these exposures are mediated by the DNA nucleotide excision repair (NER) pathway. We hypothesized that individuals with relatively low DNA repair capacity would suffer greater damage from cumulative genotoxic exposures, some of which would persist, causing ongoing problems.

MATERIALS AND METHODS: Blood samples were obtained from symptomatic Gulf War veterans and age-matched controls. The unscheduled DNA synthesis assay, a functional measurement of NER capacity, was performed on cultured lymphocytes, and lymphocyte mRNA was extracted and analyzed by sequencing.

RESULTS: Despite our hypothesis that GWI would be associated with DNA repair deficiency, NER capacity in lymphocytes from affected GWI veterans actually exhibited a significantly elevated level of DNA repair ($p = 0.016$). Both total gene expression and NER gene expression successfully differentiated individuals with GWI from unaffected controls. The observed functional increase in DNA repair capacity was accompanied by an overexpression of genes in the NER pathway, as determined by RNA sequencing analysis.

CONCLUSION: We suggest that the observed elevations in DNA repair capacity and NER gene expression are indicative of a "hormetic," i.e., induced or adaptive protective response to battlefield exposures. Normally such effects are short-term, but in these individuals this response has resulted in a long-term metabolic shift that may also be responsible for the persistent symptoms of GWI.

## CHRONIC FATIGUE SYNDROME

### The development of a short form of the DePaul Symptom Questionnaire.

Sunnquist M[1], Lazarus S[1], Jason LA[1].

Rehabil Psychol. **2019 Jul 18**. doi: 10.1037/rep0000285. PMID: 31318234. [Epub ahead of print]

PURPOSE/OBJECTIVE: The DePaul Symptom Questionnaire (DSQ) is a widely used instrument that assesses common symptoms of myalgic encephalomyelitis (ME) and chronic fatigue syndrome (CFS). The DSQ has strong psychometric properties; however, it consists of 99 items, and the energy limitations and cognitive difficulties experienced by individuals with ME and CFS may hinder their ability to easily complete the questionnaire.

METHOD: The current study examined symptom prevalence and discriminative ability to develop a short form of the DSQ (DSQ-SF).

RESULTS: The resulting short form questionnaire consists of 14 items that were highly prevalent among individuals with ME and CFS. Additionally, the items demonstrated the ability to differentiate individuals with ME and CFS from adult controls and, to a lesser extent, individuals with multiple sclerosis.

CONCLUSIONS/IMPLICATIONS: The DSQ-SF may serve as an effective, brief screening tool for symptoms of ME and CFS. (PsycINFO Database Record (c) 2019 APA, all rights reserved).

### Establishment and evaluation of prediction model for multiple disease classification based on gut microbial data.

Bang S[1,2], Yoo D[1], Kim SJ[3], Jhang S[1,2], Cho S[2], Kim H[4,5,6].

Sci Rep. **2019 Jul 15**;9(1):10189. doi: 10.1038/s41598-019-46249-x. PMID: 31308384.

Diseases prediction has been performed by machine learning approaches with various biological data. One of the representative data is the gut microbial community, which interacts with the host's immune system. The abundance of a few microorganisms has been used as markers to predict diverse diseases. In this study, we hypothesized that multi-classification using machine learning approach could distinguish the gut microbiome from following six diseases: multiple sclerosis, juvenile idiopathic arthritis, myalgic encephalomyelitis/chronic fatigue syndrome, acquired immune deficiency syndrome, stroke and colorectal cancer. We used the abundance of microorganisms at five taxonomy levels as features in 696 samples collected from different studies to establish the best prediction model. We built classification models based on four multi-class classifiers and two feature selection methods including a forward selection and a backward elimination. As a result, we found that the performance of classification is improved as we use the lower taxonomy levels of features; the highest performance was observed at the genus level. Among four classifiers, LogitBoost-based prediction model outperformed other classifiers. Also, we suggested the optimal feature subsets at the genus-level obtained by backward elimination. We believe the selected feature subsets could be used as markers to distinguish various diseases simultaneously. The finding in this study suggests the potential use of selected features for the diagnosis of several diseases.

## HEADACHE and MIGRAINE

### Cochrane systematic review and meta-analysis of botulinum toxin for the prevention of migraine.

Herd CP[1], Tomlinson CL[2], Rick C[3], Scotton WJ[4], Edwards J[5], Ives NJ[2], Clarke CE[6], Sinclair AJ[4].

BMJ Open. **2019 Jul 16**;9(7):e027953. doi: 10.1136/bmjopen-2018-027953. PMID: 31315864

OBJECTIVES: To assess the effects of botulinum toxin for prevention of migraine in adults.

DESIGN: Systematic review and meta-analysis.

DATA SOURCES: CENTRAL, MEDLINE, Embase and trial registries.

ELIGIBILITY CRITERIA: We included randomised controlled trials (RCTs) of botulinum toxin compared with placebo, active treatment or clinically relevant different dose for adults with chronic or episodic migraine, with or without the additional diagnosis of medication overuse headache.

DATA EXTRACTION AND SYNTHESIS: Cochrane methods were used to review double-blind RCTs. Twelve week post-treatment time-point data was analysed.

RESULTS: Twenty-eight trials (n=4190) were included. Trial quality was mixed. Botulinum toxin treatment resulted in reduced frequency of -2.0 migraine days/month (95% CI -2.8 to -1.1, n=1384) in chronic migraineurs compared with placebo. An improvement was seen in migraine severity, measured on a numerical rating scale 0 to 10 with 10 being maximal pain, of -2.70 cm (95% CI -3.31 to -2.09, n=75) and -4.9 cm (95% CI -6.56 to -3.24, n=32) for chronic and episodic migraine respectively. Botulinum toxin had a relative risk of treatment related adverse events twice that of placebo, but a reduced risk compared with active comparators (relative risk 0.76, 95% CI 0.59 to 0.98) and a low withdrawal rate (3%). Although individual trials reported non-inferiority to oral treatments, insufficient data were available for meta-analysis of effectiveness outcomes.

CONCLUSIONS: In chronic migraine, botulinum toxin reduces migraine frequency by 2 days/month and has a favourable safety profile. Inclusion of medication overuse headache does not preclude its effectiveness. Evidence to support or refute efficacy in episodic migraine was not identified.

### Real-world effectiveness of onabotulinumtoxinA treatment for the prevention of headaches in adults with chronic migraine in Australia: a retrospective study.

Stark C[1], Stark R[2], Limberg N[3], Rodrigues J[4], Cordato D[5], Schwartz R[5], Jukic R[6].

J Headache Pain. **2019 Jul 15**;20(1):81. doi: 10.1186/s10194-019-1030-z. PMID: 31307383.

BACKGROUND: OnabotulinumtoxinA (BOTOX®, Allergan plc, Dublin, Ireland) is approved for the preventive treatment of headaches in adult patients with chronic migraine (CM) in Australia by the country's reimbursement mechanism for medicines, the Pharmaceutical Benefits Scheme (PBS). To our knowledge, this study represents the first focused report evaluating real-world evidence of onabotulinumtoxinA treatment via the PBS in Australian clinics.

METHODS: This study reviewed the medical records of adults with inadequately controlled CM from 7 private neurology practices in Australia who, beginning in March 2014, received PBS-subsidized onabotulinumtoxinA per product labelling for the first time. The primary effectiveness measure was the percentage of patients achieving a response defined by 50% or greater reduction in headache days from baseline after 2 treatment cycles. Additional data were recorded in the case report form when available and included demographics, clinical characteristics, headache severity and frequency, Headache Impact Test (HIT-6) score, medication use, and days missed of work or study at baseline, after 2 treatment cycles, and at last follow-up. Differences in mean changes from baseline were evaluated with a 1-tailed t-test or Pearson's chi-squared test ($p < 0.05$).

RESULTS: The study population included 211 patients with a mean (SD) of 25.2 (5.3) monthly headache days at baseline. In the primary outcome analysis, 74% of patients achieved a response, with a mean (SD) of 10.6 (7.9) headache days after 2 treatment cycles ($p < 0.001$). Secondary effectiveness outcomes included mean (SD) reductions in HIT-6 score of - 11.7 (9.8) and - 11.8 (12.2) after 2 treatment cycles ($p < 0.001$) and final follow-up ($p < 0.001$), respectively, and mean (SD) decreases in days per month of acute pain medication use of - 11.5 (7.6) after 2 treatment cycles ($p < 0.001$) and - 12.7 (8.1) at final follow-up ($p < 0.001$).

CONCLUSION: This study provides additional clinical evidence for the consistent effectiveness of onabotulinumtoxinA for the treatment of CM in Australia. This effectiveness was made evident by reductions in migraine days, severe headache days, and HIT-6 scores from baseline.

## HEADACHE and MIGRAINE (Continued)

### OnabotulinumtoxinA wear-off in chronic migraine, observational cohort study.

Zidan A[1], Roe C[2], Burke D[3], Mejico L[3].

J Clin Neurosci. **2019 Jul 18**. pii: S0967-5868(19)30877-X. doi: 10.1016/j.jocn.2019.07.043. PMID: 31327585. [Epub ahead of print]

INTRODUCTION: The current standard-of-care protocol for OnabotulinumtoxinA (BoNTA) injections consists of fixed-site injections every 12 weeks. This pattern is based on clinical practice and extrapolated from BoNTA injections for other, non-migraine-related indications. It is unclear if this protocol is optimal for chronic migraine. In clinical practice, migraine patients frequently describe a period of increased headache frequency and intensity in the few weeks preceding their next injections. In order to evaluate the duration of the clinical effect of BoNTA injections in chronic migraine, we studied the variation in headache frequency on a weekly basis during the 12-week period following treatment in a cohort of migraine patients.

METHOD: 38 consecutive subjects were enrolled from an outpatient headache clinic, and asked to keep daily headache journals. 24 completed headache journals were analyzed. Headache frequency, duration and severity, as well as intake of symptomatic headache medications were recorded and compared among the different weeks.

RESULTS: The time-response plot following BoNTA injection was roughly U-shaped, with 3 distinct phases: an induction phase, a maximum efficacy phase, and a wear-off phase. The time-response plot revealed that the wear-off commenced around the eighth week post injection. The mean difference in the number of headache days per week between the first and the eighth week was 1.8 (95% CI [0.670-2.830], p = 0.003).

CONCLUSION: The effect of BoNTA injections on chronic migraines was not uniform throughout a 12-week period. A window of vulnerability to migraine attacks exist in the beginning and end of each cycle.

### Efficacy, safety, and tolerability of rimegepant orally disintegrating tablet for the acute treatment of migraine: a randomised, phase 3, double-blind, placebo-controlled trial.

Croop R[1], Goadsby PJ[2], Stock DA[3], Conway CM[3], Forshaw M[3], Stock EG[3], Coric V[3], Lipton RB[4].

Lancet. **2019 Jul 12**. pii: S0140-6736(19)31606-X. doi: 10.1016/S0140-6736(19)31606-X. PMID: 31311674. [Epub ahead of print]

BACKGROUND: Rimegepant, a small molecule calcitonin gene-related peptide receptor antagonist, has shown efficacy in the acute treatment of migraine using a standard tablet formulation. The objective of this trial was to compare the efficacy, safety, and tolerability of a novel orally disintegrating tablet formulation of rimegepant at 75 mg with placebo in the acute treatment of migraine.

METHODS: In this double-blind, randomised, placebo-controlled, multicentre phase 3 trial, adults aged 18 years or older with history of migraine of at least 1 year were recruited to 69 study centres in the USA. Participants were randomly assigned to receive rimegepant (75 mg orally disintegrating tablet) or placebo and instructed to treat a single migraine attack of moderate or severe pain intensity. The randomisation was stratified by the use of prophylactic medication (yes or no), and was carried out using an interactive web response system that was accessed by each clinical site. All participants, investigators, and the sponsor were masked to treatment group assignment. The coprimary endpoints were freedom from pain and freedom from the most bothersome symptom at 2 h postdose. The efficacy analyses used the modified intention-to-treat population, which included all patients who were randomly assigned, had a migraine attack with pain of moderate or severe intensity, took a dose of rimegepant or placebo, and had at least one efficacy assessment after administration of the dose. The safety analyses included all randomly assigned participants who received at least one dose of study medication. This study is registered with ClinicalTrials.gov, number NCT03461757, and is closed to accrual.

FINDINGS: Between Feb 27 and Aug 28, 2018, 1811 participants were recruited and assessed for eligibility. 1466 participants were randomly assigned to the rimegepant (n=732) or placebo (n=734) groups, of whom 1375 received treatment with rimegepant (n=682) or placebo (n=693), and 1351 were evaluated for efficacy (rimegepant n=669, placebo n=682). At 2 h postdose, rimegepant orally disintegrating tablet was superior to placebo for freedom from pain (21% vs 11%, p<0·0001; risk difference 10, 95% CI 6-14) and freedom from the most bothersome symptom (35% vs 27%, p=0·0009; risk difference 8, 95% CI 3-13). The most common adverse events were nausea (rimegepant n=11 [2%]; placebo n=3 [<1%]) and urinary tract infection (rimegepant n=10 [1%]; placebo n=4 [1%]). One participant in each treatment group had a transaminase concentration of more than 3 × the upper limit of normal; neither was related to study medication, and no elevations in bilirubin greater than 2 × the upper limit of normal were reported. Treated participants reported no serious adverse events.

INTERPRETATION: In the acute treatment of migraine, a single 75 mg dose of rimegepant in an orally disintegrating tablet formulation was more effective than placebo. Tolerability was similar to placebo, with no safety concerns.

FUNDING: Biohaven Pharmaceuticals.

## CHRONIC PAIN

### Examination of pain threshold and neuropeptides in patients with acute suicide risk.

Kim DJ[1], Blossom SJ[2], Delgado PL[3], Carbajal JM[1], Cáceda R[4].

Prog Neuropsychopharmacol Biol Psychiatry. **2019 Jul 18**:109705. doi: 10.1016/j.pnpbp.2019.109705. PMID: 31326514. [Epub ahead of print]

INTRODUCTION: One of the main challenges in suicide prevention is the limited understanding of the biological mechanisms underlying suicide. Recent findings suggest impairments in pain processing in acutely suicidal patients. However, little is known about the biological factors that may drive these discrete physiological abnormalities. In this study, we examined plasma peptides involved in analgesic and inflammatory responses and physical pain threshold in acutely suicidal patients.

METHODS: Thirty-seven depressed patients of both sexes hospitalized for severe suicidal ideation or a recent suicide attempt were characterized clinically including history of suicidal ideation and behavior. Psychological and physical pain, and pressure pain threshold was also measured. Plasma levels of β-endorphin, neurotensin, agouti-related protein (AgRP), C-reactive protein (CRP), adrenocorticotropic hormone (ACTH), and brain-derived neurotrophic factor (BDNF) were run in Milliplex multiplex assays.

RESULTS: The number of lifetime suicide attempts was positively correlated with β-endorphin ($r = 0.702$; $p = 0.007$), and neurotensin ($r = 0.728$, $p = 0.007$) plasma levels. Higher pain threshold was measured in the suicide attempt group as compared to the suicidal ideation group. Pain threshold was strongly and negatively associated with CRP plasma levels ($r = -0.548$; $p < 0.001$). In patients reporting chronic pain, lower AgRP levels and lower pain threshold were observed ($t = 4.472$; $p = 0.001$).

CONCLUSION: Our results suggest that abnormalities in the opioid and neurotensin systems may underlie the increase in pain threshold found in suicide attempters, and possibly risk for suicidal behavior. Targeting pain circuits and systems may provide therapeutic mechanisms for suicide prevention.

### A Brief Mindfulness Intervention for Medically Hospitalized Patients with Acute Pain: A Pilot Randomized Clinical Trial.

Miller-Matero LR[1,2], Coleman JP[1,2], Smith-Mason CE[1], Moore DA[1,3], Marszalek D[1], Ahmedani BK[1,2].

Pain Med. **2019 Apr 24**. pii: pnz082. doi: 10.1093/pm/pnz082. PMID: 31329961. [Epub ahead of print].

[Note: Delayed posting in PubMed—Not previously listed in RAC Research Alerts.]

OBJECTIVE: Mindfulness interventions may be beneficial for patients with chronic pain; however, the effects for acute pain are not understood. The purpose of this study was to pilot test a brief mindfulness intervention for acute pain and stress for patients in an inpatient medical setting.

DESIGN: Pilot randomized clinical trial.

SETTING: An inpatient Acute Care Surgery service at an urban hospital.

SUBJECTS: Sixty patients with acute pain were randomly selected and agreed to participate.

METHODS: Interested patients consented to the study and were randomized to the 10-minute intervention (i.e., mindfulness strategy) or comparison group (i.e., education on the Gate Control Theory of Pain). Participants completed pre- and post-assessment measures on pain severity and stress.

RESULTS: Preliminary results showed that within the intervention and comparison groups, participants experienced decreases in pain from pre- to post-intervention ($P = 0.002$ and 0.005, respectively). Within the intervention group, there was a significant decrease in stress from pre- to post-intervention ($P = 0.001$). There were no significant changes for stress within the comparison group ($P = 0.32$). There were no significant differences between the intervention and comparison groups for pain ($P = 0.44$) or stress ($P = 0.07$) at post-intervention, although Cohen's d effect sizes were small to medium for pain and stress, respectively.

CONCLUSIONS: A brief mindfulness intervention for medically hospitalized patients with acute pain may decrease pain and stress. Future research should examine this intervention with a fully powered, larger sample to examine efficacy.

## CHRONIC PAIN (Continued)

### Insights on nutrients as analgesics in chronic pain.

Bjørklund G[1], Chirumbolo S[2], Dadar M[3], Pen JJ[4], Doşa MD[5], Pivina L[6], Semenova Y[7], Aaseth J[8].

Curr Med Chem. **2019 Jul 12**. doi: 10.2174/0929867326666190712172015. [Epub ahead of print]

Many serious inflammatory disorders and nutrient deficiencies induce chronic pain, and anti-inflammatory diets have been applied successfully to modify the inflammatory symptoms causing chronic pain. Numerous scientific data and clinical investigations have demonstrated that long-term inflammation could lead to an inappropriate or exaggerated sensibility to pain. Also, some non-steroidal anti-inflammatory drugs (NSAID), which directly act on the many enzymes involved in pain and inflammation, including cyclooxygenases, are used to dampen the algesic signal to the central nervous system, reducing the responses of soft C-fibers to pain stimuli. On the other hand, there are a few reports from both health authorities and physicians, reporting that decreased transmission of pain signals can be achieved and improved, depending on the patient's dietary habit. Many nutrients, as well as a suitable level of exercise (resistance training), is the best method for improving the total mitochondrial capacity in muscle cells, which can lead to a reduction in sensitivity to pain, particularly by lowering the inflammatory signaling to C-fibers. According to the current literature, it could be proposed that chronic pain results from the changed ratio of neuropeptides, hormones, and poor nutritional status, often related to an underlying inflammatory disorder. The current review also evaluates the effective role of nutrition-related interventions on the severity of chronic pain. This review pointed out that nutritional interventions can have a positive effect on pain experience through the indirect inhibitory effect on prostaglandin E2 and attenuation of mitochondrial dysfunction caused by ischemia/reperfusion in skeletal muscle, improving the intracellular antioxidant defense system. These data highlight the need for more nutrition studies where chronic pain is the primary outcome, using accurate interventions. To date, no nutritional recommendation for chronic pain has been officially proposed. Therefore, the goal of this article is to explore pain management and pain modulation, searching for a mode of nutrition efficient in reducing pain.

## IRRITABLE BOWEL SYNDROME

### Effects of a Cod Protein Hydrolysate Supplement on Symptoms, Gut Integrity Markers and Fecal Fermentation in Patients with Irritable Bowel Syndrome.

Dale HF[1,2,3], Jensen C[4], Hausken T[4,5,6], Valeur J[7,8], Hoff DAL[9,10], Lied GA[4,5,6].

Nutrients. **2019 Jul 17**;11(7). pii: E1635. doi: 10.3390/nu11071635. PMCID: PMC6682970. PMID: 31319590.

Peptides from fish may beneficially affect several metabolic outcomes, including gut health and inflammation. The effect of fish peptides in subjects with irritable bowel syndrome (IBS) has not previously been investigated, hence this study aimed to evaluate the effect of a cod protein hydrolysate (CPH) supplement on symptom severity, gut integrity markers and fecal fermentation in IBS-patients. A double-blind, randomized parallel-intervention with six weeks of supplementation with 2.5 g CPH ($n$ = 13) or placebo ($n$ = 15) was conducted. The outcomes were evaluated at baseline and the end of the study. The primary outcomes were symptom severity evaluated by the IBS severity scoring system (IBS-SSS) and quality of life. The secondary outcomes included gut integrity markers and pro-inflammatory cytokines in serum, fecal fermentation measured by concentration of short-chain fatty acids (SCFAs) and fecal calprotectin. The groups were comparable at baseline. The total IBS-SSS-scores were reduced in both the CPH-group (298 ± 69 to 236 ± 106, $p$ = 0.081) and the placebo-group (295 ± 107 to 202 ± 103, $p$ = 0.005), but the end of study-scores did not differ ($p$ = 0.395). The concentrations of serum markers and SCFAs did not change for any of the groups. The baseline measures for the whole group showed that the total SCFA concentrations were inversely correlated with the total IBS-SSS-score ($r$ = -0.527, $p$ = 0.004). Our study showed that a low dose of CPH taken daily by IBS-patients for six weeks did not affect symptom severity, gut integrity markers or fecal fermentation when compared to the placebo group.

## IRRITABLE BOWEL SYNDROME (Continued)

### The Structure and Function of the Human Small Intestinal Microbiota: Current Understanding and Future Directions.

Kastl AJ Jr[1], Terry NA[2], Albenberg LG[2], Wu GD[3].

Cell Mol Gastroenterol Hepatol. **2019 Jul 22**. pii: S2352-345X(19)30094-3. doi: 10.1016/j.jcmgh.2019.07.006. PMID: 31344510.

Despite growing literature characterizing the fecal microbiome and its association with health and disease, few studies have analyzed the microbiome of the small intestine. Here, we examine what is known about the human small intestinal microbiota in terms of community structure and functional properties. We examine temporal dynamics of select bacterial populations in the small intestine, and the effects of dietary carbohydrates and fats on shaping these populations. We then evaluate dysbiosis in the small intestine in several human disease models, including small bacterial overgrowth, short-bowel syndrome, pouchitis, environmental enteric dysfunction, and irritable bowel syndrome. What is clear is that the bacterial biology, and mechanisms of bacteria-induced pathophysiology, are enormously broad and elegant in the small intestine. Studying the small intestinal microbiota is challenged by rapidly fluctuating environmental conditions in these intestinal segments, as well as the complexity of sample collection and bioinformatic analysis. Because the functionality of the digestive tract is determined primarily by the small intestine, efforts must be made to better characterize this unique and important microbial ecosystem.

### Fecal and Mucosal Microbiota Profiling in Irritable Bowel Syndrome and Inflammatory Bowel Disease.

Lo Presti A[1], Zorzi F[2], Del Chierico F[3], Altomare A[4], Cocca S[4], Avola A[4], De Biasio F[4], Russo A[3], Cella E[5], Reddel S[3], Calabrese E[2], Biancone L[2], Monteleone G[2], Cicala M[4], Angeletti S[6], Ciccozzi M[5], Putignani L[7], Guarino MPL[4].

Front Microbiol. **2019 Jul 17**;10:1655. doi: 10.3389/fmicb.2019.01655. PMCID: PMC6650632. PMID: 31379797. eCollection 2019.

An imbalance in the bacterial species resulting in the loss of intestinal homeostasis has been described in inflammatory bowel diseases (IBD) and irritable bowel syndrome (IBS). In this prospective study, we investigated whether IBD and IBS patients exhibit specific changes in richness and distribution of fecal and mucosal-associated microbiota. Additionally, we assessed potential 16S rRNA gene amplicons biomarkers for IBD, IBS, and controls (CTRLs) by comparison of taxonomic composition. The relative abundance of bacteria, at phylum and genus/species levels, and the bacterial diversity were determined through 16S rRNA sequence-based fecal and mucosal microbiota analysis. Linear discriminant analysis effect size (LEfSe) was used for biomarker discovery associated to IBD and IBS as compared to CTRLs. In fecal and mucosal samples, the microbiota richness was characterized by a microbial diversity reduction, going from CTRLs to IBS to IBD. β-diversity analysis showed a clear separation between IBD and CTRLs and between IBD and IBS with no significant separation between IBS and CTRLs. β-diversity showed a clear separation between mucosa and stool samples in all the groups. In IBD, there was no difference between inflamed and not inflamed mucosa. Based upon the LEfSe data, the *Anaerostipes* and Ruminococcaceae were identified as the most differentially abundant bacterial taxa in CTRLs. Erysipelotrichi was identified as potential biomarker for IBS, while Gammaproteobacteria, *Enterococcus*, and Enterococcaceae for IBD. This study provides an overview of the alterations of microbiota and may aid in identifying potential 16S rRNA gene amplicons mucosal biomarkers for IBD and IBS.

### Inflammation in gastrointestinal disorders: prevalent socioeconomic factors.

Ribaldone DG[1], Pellicano R[2], Actis GC[3].

Clin Exp Gastroenterol. **2019 Jul 19**;12:321-329. doi: 10.2147/CEG.S210844. PMCID: PMC6650093. PMID: 31410046. eCollection 2019.

Western populations harbor a chronic inflammation pattern that lacks organ cardinal signs (edema, increased temperature, pain, and impaired function), releases increased levels of C-reactive protein, and often runs a creeping clinical course with generalized debilitating disease superimposed on system-specific involvement, mostly including nervous tissue (multiple sclerosis, Parkinson's syndromes), joints (arthritis), and skin (psoriasis). A finalistic interpretation may apply to the consideration of the gut as the source of inflammation. In fact, these kind of local events as well as the remote manifestations named above, could be conditioned by the microbiome, the huge cell population indwelling the gut which is under growing scrutiny. The role of the gut as a barrier organ justifies lingering submucosal inflammation as a patrolling activity to maintain bodily integrity; the microbiome, launching inflammogenic signals in response to abrupt diet changes, confers to gut inflammation a socioeconomic vector calling for hitherto unrecognized multi-disciplinary interventions.

## OTHER RESEARCH OF INTEREST

### Chronic medical conditions and metabolic syndrome as risk factors for incidence of major depressive disorder: A longitudinal study based on 4.7 million adults in South Korea.

Han KM[1], Kim MS[2], Kim A[3], Paik JW[4], Lee J[2], Ham BJ[5].

J Affect Disord. **2019 Jul 2**;257:486-494. doi: 10.1016/j.jad.2019.07.003. PMID: 31319340. [Epub ahead of print]

BACKGROUND: The assessment of comorbid physical illness and metabolic or cardiovascular risk factors as potential risk factors for onset of major depressive disorder (MDD) is crucial. We aimed to investigate potential risk factors for the development of MDD among individuals with chronic medical conditions and metabolic and behavioral risk factors using a large population-based retrospective cohort from the data of the National Health Insurance Service (NHIS) in South Korea.

METHODS: The population-based retrospective cohort included data from 2,370,815 adults (age ≥20 years) diagnosed with MDD between January 1, 2010, and December 31, 2016 and age- and gender-matched 2,370,815 healthy controls obtained from the claims data of the NHIS. The data of the regular health checkup provided by the NHIS were also included (age ≥40 years). Logistic regression analyses were performed to investigate the potential risk factors for the incidence of MDD.

RESULTS: Chronic medical conditions such as Parkinson's disease (odds ratio [OR] = 7.808, 95% confidence interval [CI] = 7.517-8.11), epilepsy (OR = 6.119, 95% CI = 6.019-6.22), multiple sclerosis (OR = 5.532, 95% CI = 4.976-6.151), Huntington's disease (OR = 5.387, 95% CI = 3.258-8.909), migraine (OR = 4.374, 95% CI = 4.341-4.408), stroke (OR = 4.074, 95% CI = 4.032-4.117), and cancer; metabolic syndrome (OR = 1.049, 95% CI = 1.041-1.057) and several of its components including central obesity, elevated fasting blood glucose and triglyceride levels, and reduced high-density lipoprotein level; and cigarette smoking, frequent alcohol consumption, and low physical activity are potential risk factors for the development of MDD.

CONCLUSION: Our results may support previous evidence on the association between physical conditions and the incidence of MDD as reported by individual population-based studies with modest sample sizes.

### Impact of water therapy on pain management in patients with fibromyalgia: current perspectives.

Zamunér AR[1], Andrade CP[2], Arca EA[3], Avila MA[4].

J Pain Res. **2019 Jul 3**;12:1971-2007. doi: 10.2147/JPR.S161494. PMCID: PMC6613198. PMID: 31308729. eCollection 2019.

Exercise-related interventions have been recommended as one of the main components in the management of fibromyalgia syndrome (FMS). Water therapy, which combines water's physical properties and exercise benefits, has proven effective in improving the clinical symptoms of FMS, especially pain, considered the hallmark of this syndrome. However, to our knowledge, the mechanisms underlying water therapy effects on pain are still scarcely explored in the literature. Therefore, this narrative review aimed to present the current perspectives on water therapy and the physiological basis for the mechanisms supporting its use for pain management in patients with FMS. Furthermore, the effects of water therapy on the musculoskeletal, neuromuscular, cardiovascular, respiratory, and neuroendocrine systems and inflammation are also addressed. Taking into account the aspects reviewed herein, water therapy is recommended as a nonpharmacologic therapeutic approach in the management of FMS patients, improving pain, fatigue, and quality of life. Future studies should focus on clarifying whether mechanisms and long-lasting effects are superior to other types of nonpharmacological interventions, as well as the economic and societal impacts that this intervention may present.

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