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This e-newsletter - published the CPRA to keep the medical-scientific and patient communities abreast of research advances on Chronic Overlapping Pain Conditions (COPCs) - contains abstracts of studies on the epidemiology, pathophysiology and clinical management of COPCs published between June and December 2021.

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Pathophysiology Studies

Sources of Individual Differences in Pain.
Mogil JS.
Annu Rev Neurosci. 2021 Jul 8;44:1-25. doi: 10.1146/annurev-neuro-092820-105941. PMID: 34236890

Pain is an immense clinical and societal challenge, and the key to understanding and treating it is variability. Robust interindividual differences are consistently observed in pain sensitivity, susceptibility to developing painful disorders, and response to analgesic manipulations. This review examines the causes of this variability, including both organismic and environmental sources. Chronic pain development is a textbook example of a gene-environment interaction, requiring both chance initiating events (e.g., trauma, infection) and more immutable risk factors. The focus is on genetic factors, since twin studies have determined that a plurality of the variance likely derives from inherited genetic variants, but sex, age, ethnicity, personality variables, and environmental factors are also considered.

Cerebral Perfusion and Sensory Testing Results Differ in Interstitial Cystitis/Bladder Pain Syndrome Patients with and without Fibromyalgia: A Site-Specific MAPP Network Study.
Deutsch G, Deshpande H, Lai HH, Kutch JJ, Ness TJ.
J Pain Res. 2021 Dec 23;14:3887-3895. doi: 10.2147/JPR.S343695. eCollection 2021. PMCID: PMC8711634

PURPOSE: Fibromyalgia is a common co-morbidity in patients with interstitial cystitis/bladder pain syndrome. Quantitative sensory testing measures and regional cerebral blood flow

measures have been noted to differ from healthy controls in both subjects with fibromyalgia and those with interstitial cystitis when studied independently. The present study examined such measures in subjects with the diagnosis of interstitial cystitis both with and without the co-diagnosis of fibromyalgia to determine whether differences in these measures may be associated with co-morbidity. PATIENTS AND METHODS: Female subjects with the diagnosis of interstitial cystitis with (n = 15) and without (n = 19) the co-diagnosis of fibromyalgia as well as healthy control subjects (n = 41) underwent quantitative sensory testing. A subset of these patients (9 with and 9 without fibromyalgia) underwent brain perfusion studies using arterial spin labeled functional magnetic resonance imaging. An analysis was performed of absolute regional cerebral blood flow of regions-of-interest when experiencing a full bladder compared with an empty bladder. RESULTS: Subjects with both interstitial cystitis and fibromyalgia were more hypersensitive than those without fibromyalgia as well as healthy controls in most sensory measures except heat. Subjects with interstitial cystitis, but no fibromyalgia, differed from healthy controls only in toleration of the ischemic forearm task. Other co-morbidities were more common in those subjects with both interstitial cystitis and fibromyalgia. Bladder fullness was associated with significantly greater whole brain gray matter blood flow in subjects with interstitial cystitis and fibromyalgia when compared with that of subjects with interstitial cystitis without fibromyalgia. Examination of regional cerebral blood flow in individual regions-of-interest demonstrated statistically significant differences between the subjects with interstitial cystitis with and those without fibromyalgia bilaterally in the thalamus, amygdala and hippocampus, as well as the right prefrontal cortex and greater responsiveness to changes in bladder fullness in the insula. CONCLUSION: Quantitative sensory testing and brain perfusion data support that there are two phenotypes of interstitial cystitis patients, which can be differentiated by a co-diagnosis of fibromyalgia. This may affect responsiveness to treatment and suggest the utility of stratifying interstitial cystitis patients according to their co-morbidities.

Increased GABA+ in People with Migraine, Headache, and Pain Conditions – A Potential Marker of Pain.

Peek AL, Leaver AM, Foster S, Oeltzschner G, Puts NA, Galloway G, Sterling M, Ng K, Refshauge K, Aguila MR, Rebbeck T.

J Pain. 2021 Dec;22(12):1631-1645. doi: 10.1016/j.jpain.2021.06.005. PMID: 34182103; PMCID: PMC8935361.

Treatment outcomes for migraine and other chronic headache and pain conditions typically demonstrate modest results. A greater understanding of underlying pain mechanisms may better inform treatments and improve outcomes. Increased GABA+ has been identified in recent studies of migraine, however, it is unclear if this is present in other headache, and pain conditions. We primarily investigated GABA+ levels in the posterior cingulate gyrus (PCG) of people with migraine, whiplash-headache and low back pain compared to age- and sex-matched controls, GABA+ levels in the anterior cingulate cortex (ACC) and thalamus formed secondary aims. Using a cross-sectional design, we studied people with migraine, whiplash-headache or low back pain (n = 56) and compared them with a pool of age- and sex-matched controls (n = 22). We used spectral-edited magnetic resonance spectroscopy at 3T (MEGA-PRESS) to determine levels of GABA+ in the PCG, ACC and thalamus. PCG GABA+ levels were significantly higher in people with migraine and low back pain compared with controls (eg, migraine 4.89 IU ± 0.62 vs controls 4.62 IU ± 0.38; P = .02). Higher GABA+ levels in the PCG were not unique to migraine and could reflect a mechanism of chronic pain in general. A better understanding of pain at a neurochemical level informs the development of treatments that target aberrant brain neurochemistry to improve patient outcomes. PERSPECTIVE: This study provides insights into the underlying mechanisms of chronic pain. Higher levels of GABA+ in the PCG may reflect an underlying mechanism of chronic headache and pain conditions. This knowledge may help improve patient outcomes through developing treatments that specifically address this aberrant brain neurochemistry.

Fibromyalgia and Associated Disorders: From Pain to Chronic Suffering, From Subjective Hypersensitivity to Hypersensitivity Syndrome.

Maugars Y, Berthelot JM, Le Goff B, Darrieutort-Laffite C.

Front Med (Lausanne). 2021 Jul 14;8:666914. doi: 10.3389/fmed.2021.666914. PMID: 34336880; PMCID: PMC8316633.

The concept of fibromyalgia has progressed to achieve a certain consensus regarding the definition of the condition. We summarize what is known in 2020, be it in terms of diagnosis, with the criteria that have changed over the years, or at the level of the psychological profile,

via the notions of "catastrophizing" and "coping" and post-traumatic syndrome. The importance of fatigue and sleep disorders is underlined, with the chronological sequence of post-traumatic syndrome, chronic fatigue, and then amplification of the pain and the onset of multiple associated symptoms. The etiopathogenic debate has been enriched thanks to neuro-imaging data to discover the start of the central neurological signature. The many associated symptoms are reanalyzed in the context of so-called sister conditions which form sometimes more or less separate entities, such as chronic fatigue syndrome or restless legs syndrome for example. What these conditions have in common is hypersensitivity, not just to pain, but also to all exteroceptive stimuli, from deep sensitivity in the neuro-vegetative system, the sense organs and certain functions of the central nervous system, to the psychological aspects and sleep control. In summary, it is possible to define fibromyalgia as a cognitive disorder of cortical integration of chronic pain, with amplification of painful and sensory nociception, decrease in the threshold for the perception of pain, and persistence of a stimulus that maintains the process in chronicity. Fibromyalgia is part of a group of chronic hypersensitivity syndromes of central origin, with a very wide range of means of expression.

Genetic Aspects of Pain and its Variability in the Human Population.
Świtała WW, Szymańska-Adamcewicz O, Jurga S, Pilchowska-Ujma E, Krakowiak J.
Ann Agric Environ Med. 2021 Dec 29;28(4):569-574. doi: 10.26444/aaem/134151. Epub 2021 Mar 31. PMID: 34969212.

The sensation of pain is common to both animals and human beings. Its threshold, intensity, tolerability, and characteristics are variable and depend on ethnicity, gender, stress exposure, co-existing mental disorders, such as depression or anxiety, social and economical background, as well as on genetic factors. It is estimated that about 5 and 20 percent of population suffer from acute and chronic pain, respectively, which results in the search for medical advice in healthcare facilities, and causes great expenses in health care budgets worldwide. Research aimed at identifying the causative agents of pain syndromes include single nucleotidepolymorphism (SNP), family history studies, twin siblings' genetic diversity studies, and recently, also a genome-wide association study (GWAS). Clinical syndromes of erangement of pain sensation are generally caused by single gene mutations (e.g. erythromelalgia and paroxysmal extreme pain disorder caused by mutations of SCN9A), but can also be associated with multiple gene mutations, as happens in migraine, fibromyalgia or hereditary sensory and autonomic neuropathies. Structural changes of proteins caused by gene mutations involve various cellular element, such as ion channels, receptors, scaffolding proteins, enzymes, transporting proteins, eventually leading to numerous clinical entities in which pain or its lack remain the leading symptoms. The sensation of pain is initiated by a stimulus, which activates the free nerve endings via chemical mediators, and the mechanical stimuli is then transmitted to the brain along the neurons and spinal tracts. Synaptic neurotransmitters and cell structures take part in this process and eventually affect the intensity of pain sensation.

Small Fiber Polyneuropathy Is Associated with Non-Bladder-Centric Interstitial Cystitis/Bladder Pain Syndrome Patients.
Overholt TL, Matthews CA, Evans RJ, Badlani G, Ahn C, Simon T, Walker SJ.
Female Pelvic Med Reconstr Surg. 2021 Sep 1;27(9):581-585. doi: 10.1097/SPV.0000000000000972. PMID: 33109931; PMCID: PMC8071833.

OBJECTIVES: Interstitial cystitis/bladder pain syndrome (IC/BPS) comprises at least 2 phenotypes. Bladder centric patients typically demonstrate low bladder capacity (BC), often with Hunner lesion (HL), whereas non-bladder-centric patients typically have normal cystoscopic findings and more co-occurring nonurologic symptoms/syndromes (NUS), contributing to widespread pain beyond the bladder. Small fiber polyneuropathy (SFPN) is significantly associated with fibromyalgia, a frequent IC/BPS codiagnosis and may play an etiologic role in IC/BPS. We assessed SFPN status in bladder-centric versus non-bladder-centric IC/BPS patients. METHODS: Distal leg biopsies were obtained from 11 IC/BPS patients after therapeutic hydrodistention. Specimens were embedded/sectioned per standard protocol and stained for protein gene product 9.5, an intraepidermal nerve fiber marker. To determine SFPN status, intraepidermal nerve fiber density was calculated and compared with normative reference values stratified by age/sex. The SFPN prevalence and reported comorbidities were compared between low BC and/or HL-positive (bladder-centric) versus non-low BC, HL (non-bladder-centric) patients. RESULTS: Seven patients (63.6%) were SFPN positive. Non-bladder-centric patients demonstrated significantly more SFPN (6/7, 85.7%) compared with bladder-centric patients (1/4, 25.0%; P = 0.027). Non-bladder-centric

patients also reported more comorbid NUS overall (1.25 ± 0.83 vs 5.86 ± 2.47; P = 0.003), including fibromyalgia (P = 0.010), migraines (P = 0.035), anxiety/panic disorder (P = 0.035), allergies (P = 0.027), and asthma (P = 0.035). CONCLUSIONS: In this pilot study, SFPN was significantly more common in non-bladder-centric IC/BPS, that is, those patients who also reported greater prevalence of NUS, including fibromyalgia, migraines, anxiety/panic disorders, allergies, and asthma. These findings suggest that SFPN may have an etiologic role in a larger, systemic pain syndrome and should be explored further.

Blunted Pain Modulation Response to Induced Stress in Women with Fibromyalgia with and without Posttraumatic Stress Disorder Comorbidity: New Evidence of Hypo-Reactivity to Stress in Fibromyalgia?
López-López A, Matías-Pompa B, Fernández-Carnero J, Gil-Martínez A, Alonso-Fernández M, Alonso Pérez JL, González Gutierrez JL.
Behav Med. 2021 Jul-Sep;47(4):311-323. doi: 10.1080/08964289.2020.1758611. Epub 2020 May 1. PMID: 32356678.

There is evidence regarding the presence of alterations in both the stress response and the endogenous pain modulation systems of people with fibromyalgia (FM). However, research on pain modulation under induced stress on FM patients is scarce and contradictory. The present study analyzes stress-induced changes in pain and intolerance thresholds among FM patients, examining the possible existence of differences linked to PTSD comorbidity and gaining insights into the role of cardiovascular reactivity. Eighteen women diagnosed with FM and comorbid PTSD (FM + PTSD), 18 women diagnosed with FM and no PTSD (FM-PTSD), and 38 healthy women (HC) were exposed to the Social Stress Test task. Pressure pain thresholds and intolerance thresholds were measured before and during stress induction, and after a recovery period, while systolic blood pressure and heart rate were simultaneously recorded. Overall, while pain thresholds decreased during stress and recovery for HC, no significant changes were observed for women with FM. The intolerance threshold decreased for HC during stress, but was maintained at basal level during recovery. FM-PTSD women exhibited a delayed response, with a drop at recovery. For FM + PTSD, tolerance levels remained unchanged. In addition, cardiovascular reactivity did not seem to explain these results. This performance of the pain modulation system seems to follow the same pattern of hypoactive responsiveness under stressors that has previously been observed in FM patients on the autonomic and neuroendocrine axes. Such a hypoactive pattern may involve a non-adaptive response that may contribute to the development and maintenance of chronic pain.

Irritable Bowel Syndrome, Depression, and Neurodegeneration: A Bidirectional Communication from Gut to Brain.
Aziz MNM, Kumar J, Muhammad Nawawi KN, Raja Ali RA, Mokhtar NM.
Nutrients. 2021 Aug 31;13(9):3061. doi: 10.3390/nu13093061. PMID: 34578939; PMCID: PMC8468817.

Patients with irritable bowel syndrome (IBS) are increasingly presenting with a wide range of neuropsychiatric symptoms, such as deterioration in gastroenteric physiology, including visceral hypersensitivity, altered intestinal membrane permeability, and gastrointestinal motor dysfunction. Functional imaging of IBS patients has revealed several abnormalities in various brain regions, such as significant activation of amygdala, thinning of insular and anterior cingulate cortex, and increase in hypothalamic gray matter, which results in poor psychiatric and cognitive outcomes. Interrelations between the enteric and central events in IBS-related gastrointestinal, neurological, and psychiatric pathologies have compelled researchers to study the gut-brain axis-a bidirectional communication that maintains the homeostasis of the gastrointestinal and central nervous system with gut microbiota as the protagonist. Thus, it can be disrupted by any alteration owing to the gut dysbiosis or loss of diversity in microbial composition. Available evidence indicates that the use of probiotics as a part of a balanced diet is effective in the management of IBS and IBS-associated neurodegenerative and psychiatric comorbidities. In this review, we delineate the pathogenesis and complications of IBS from gastrointestinal and neuropsychiatric standpoints while also discussing the neurodegenerative events in enteric and central nervous systems of IBS patients and the therapeutic potential of gut microbiota-based therapy established on clinical and preclinical data.

Sex Differences in Neuroimmune and Glial Mechanisms of Pain.
Gregus AM, Levine IS, Eddinger KA, Yaksh TL, Buczynski MW.
Pain. 2021 Aug 1;162(8):2186-2200. doi: 10.1097/j.pain.0000000000002215. PMID: 34256379; PMCID: PMC8277970.

Pain is the primary motivation for seeking medical care. Although pain may subside as inflammation resolves or an injury heals, it is increasingly evident that persistency of the pain state can occur with significant regularity. Chronic pain requires aggressive management to minimize its physiological consequences and diminish its impact on quality of life. Although opioids commonly are prescribed for intractable pain, concerns regarding reduced efficacy, as well as risks of tolerance and dependence, misuse, diversion, and overdose mortality rates limit their utility. Advances in development of nonopioid interventions hinge on our appreciation of underlying mechanisms of pain hypersensitivity. For instance, the contributory role of immunity and the associated presence of autoimmune syndromes has become of particular interest. Males and females exhibit fundamental differences in innate and adaptive immune responses, some of which are present throughout life, whereas others manifest with reproductive maturation. In general, the incidence of chronic pain conditions, particularly those with likely autoimmune covariates, is significantly higher in women. Accordingly, evidence is now accruing in support of neuroimmune interactions driving sex differences in the development and maintenance of pain hypersensitivity and chronicity. This review highlights known sexual dimorphisms of neuroimmune signaling in pain states modeled in rodents, which may yield potential high-value sex-specific targets to inform future analgesic drug discovery efforts.

Assessment of Pain Modulatory and Somatosensory Profiles in Chronic Tension-Type Headache Patients.
Exposto FG, Bendixen KH, Ernberg M, Bach FW, Svensson P.
Pain Med. 2021 Oct 8;22(10):2356-2365. doi: 10.1093/pm/pnab084. PMID: 33690821.

OBJECTIVE: The aim of this study was to thoroughly phenotype a group of chronic tension-type headache (CTTH) patients. METHODS: Fifteen CTTH patients diagnosed according to the International Classification of Headache Disorders-3 and 15 healthy controls were included in this study. Furthermore, 70 healthy controls were included to establish normative values. Quantitative sensory testing (QST), including temporal summation of pain (TSP), conditioned pain modulation (CPM), and psychological and sleep variables, was assessed in a single session. TSP and CPM were then combined to build pain modulation profiles (PMP) for each individual. RESULTS: No difference was found between groups for PMP, TSP, and CPM. However, 10 CTTH patients showed a pronociceptive PMP, with 8 related to a deficient CPM and 2 to both a deficient CPM and increased TSP. Increased cold detection thresholds were the most common sensory disturbance found in CTTH patients. Significant differences were seen between groups for pain catastrophizing, depression, and sleep quality although not all patient's scores were above the clinically meaningful cutoffs. CONCLUSIONS: In summary, CTTH patients presented with different PMP. These PMP may be related to increased TSP, deficient CPM, alterations in thermal detection that may be related to autonomic dysregulation, or a combination of all three. Overall, this suggests that due to their heterogeneous pathophysiology, CTTH patients should be managed according to their underlying pathophysiology and not with a one-size-fits-all approach.

Long-Term Evaluation of Temporomandibular Disorders in Association with Cytokine and Autoantibody Status in Young Women.
Son C, Park YK, Park JW.
Cytokine. 2021 Aug;144:155551. doi: 10.1016/j.cyto.2021.155551. PMID: 33941445.

Temporomandibular disorders (TMD) is a chronic pain disease affecting 4-60% of general population. Its suggested etiology includes mechanical overloading to related structures, psychosocial factors, and genetic vulnerability. However, its pathogenesis is yet to be fully understood, especially in cases with a higher level of pain and more associated comorbidities. Recently chronic systemic inflammation and possible autoimmunity has been indicated in several pain conditions as the underlying mechanism of chronicity but this aspect has not been rigorously investigated in TMD. This article focuses on analyzing the levels of cytokines, chemokines, autoantibodies and nonspecific inflammatory markers and comparing their levels according to pain severity and duration in 66 female TMD patients in their 20 s and investigating their association with clinical indices of TMD and comorbidities. The high pain disability group showed decreased range of jaw function and more pain on palpation of capsule areas compared to the low pain disability group. Comorbidities such as anxiety and sleep disturbance were also significantly more prevalent. The level of IL-8 and IgG were significantly higher in the high pain disability group. IL-2, -8, -13, IFN- γ, RANTES, PGE2, and thrombopoietin levels showed a significant effect on indices reflecting jaw function, generalized pain intensity, and health related quality of life. Such results imply that longer

pain duration and higher pain intensity is associated with higher levels of systemic inflammation suggesting the possible role of immunologic disturbance as an underlying factor of chronic TMD pain and warranting further investigation for its consideration in diagnosis and treatment.

Polymorphisms in COMT, ADRB2 and HTR1A Genes are Associated with Temporomandibular Disorders in Individuals with Other Arthralgias.
Bonato LL, Quinelato V, de Felipe Cordeiro PC, Vieira AR, Granjeiro JM, Tesch R, Casado PL.
Cranio. 2021 Jul;39(4):351-361. doi: 10.1080/08869634.2019.1632406. PMID: 31264537.

Objective: To evaluate the association between polymorphisms in genes and comorbid presence of arthralgias and TMD. Methods: This is a case-control study. The groups formed were individuals with chronic arthralgia and 1) myofascial pain (n = 42); 2) articular (n = 16); 3) multiple diagnoses (n = 69); 4) with TMD and without some other arthralgia (n = 16); 5) without TMD but with pain in other joints (n = 82); and 6) a control group (n = 72). SNPs in COMT, ADRB2, and HTR1A genes were investigated. Results: The CT genotype for the COMT (rs9332377) gene was associated with the absence of myofascial pain (p = .05). In the ADRB2 (rs1042713) gene, the AA genotype was associated with the absence of myofascial pain (p = .03). Discussion: This study supports the hypothesis that alterations in the COMT, ADRB2, and HTR1A genes influence the presence of chronic pain and TMD.

Brain to Belly: Abdominal Variants of Migraine and Functional Abdominal Pain Disorders Associated with Migraine.
Lenglar TL, Caula C, Moulding T, Lyles A, Wohrer D, Titomanlio L.
J Neurogastroenterol Motil. 2021 Oct 30;27(4):482-494. doi: 10.5056/jnm20290. PMID: 34642268; PMCID: PMC8521460.

Migraine is one of the most frequent causes of primary headache and 9% of children suffer from migraines. Most children will continue to experience migraine attacks as adults, therefore it is imperative that we have a thorough understanding of this major health issue. This article considers the so-called abdominal variants of migraine, which are more commonly seen in children rather than adults: abdominal migraine, cyclic vomiting syndrome, and infantile colic. Other functional abdominal pain disorders such as irritable bowel syndrome and functional dyspepsia have also been linked to migraine in clinical studies. The common pathophysiological root of these diseases seems to be the gut-brain axis mechanism. Abdominal variants of migraine are considered pediatric precursors of migraine whereas the functional abdominal pain disorders related to migraine seem to share a pathophysiological root with no temporarily link as for today. In this review we aim to describe the epidemiological background, the current pathophysiological theories and the relationship of each disease to migraine. This review is the first to compile abdominal variants of migraine and functional abdominal pain disorders associated with migraine and we endeavor to elucidate the broad spectrum of migraine-related episodes in children.

Preclinical Models of Endometriosis and Interstitial Cystitis/Bladder Pain Syndrome: An Innovative Medicines Initiative-Pain Care initiative to Improve their Value for Translational Research in Pelvic Pain.
Nunez-Badinez P, De Leo B, Laux-Biehlmann A, Hoffmann A, Zollner TM, Saunders PTK, Simitsidellis I, Charrua A, Cruz F, Gomez R, Tejada MA, McMahon SB, Lo Re L, Barthas F, Vincent K, Birch J, Meijlink J, Hummelshoj L, Sweeney PJ, Armstrong JD, Treede RD, Nagel J.
Pain. 2021 Sep 1;162(9):2349-2365. doi: 10.1097/j.pain.0000000000002248. PMID: 34448751; PMCID: PMC8374713.

Endometriosis (ENDO) and interstitial cystitis/bladder pain syndrome (IC/BPS) are chronic pain conditions for which better treatments are urgently needed. Development of new therapies with proven clinical benefit has been slow. We have conducted a review of existing preclinical in vivo models for ENDO and IC/BPS in rodents, discussed to what extent they replicate the phenotype and pain experience of patients, as well as their relevance for translational research. In 1009 publications detailing ENDO models, 41% used autologous, 26% syngeneic, 18% xenograft, and 11% allogeneic tissue in transplantation models. Intraperitoneal injection of endometrial tissue was the subcategory with the highest construct validity score for translational research. From 1055 IC/BPS publications, most interventions were bladder centric (85%), followed by complex mechanisms (8%) and stress-induced models (7%). Within these categories, the most frequently used models were instillation of

irritants (92%), autoimmune (43%), and water avoidance stress (39%), respectively. Notably, although pelvic pain is a hallmark of both conditions and a key endpoint for development of novel therapies, only a small proportion of the studies (models of ENDO: 0.5%-12% and models of IC/BPS: 20%-44%) examined endpoints associated with pain. Moreover, only 2% and 3% of publications using models of ENDO and IC/BPS investigated nonevoked pain endpoints. This analysis highlights the wide variety of models used, limiting reproducibility and translation of results. We recommend refining models so that they better reflect clinical reality, sharing protocols, and using standardized endpoints to improve reproducibility. We are addressing this in our project Innovative Medicines Initiative-PainCare/Translational Research in Pelvic Pain.

Kynurenine Pathway of Tryptophan Metabolism in Migraine and Functional Gastrointestinal Disorders.
Fila M, Chojnacki J, Pawlowska E, Szczepanska J, Chojnacki C, Blasiak J.
Int J Mol Sci. 2021 Sep 20;22(18):10134. doi: 10.3390/ijms221810134. PMID: 34576297; PMCID: PMC8469852.

Migraine, the leading cause of disability in the population aged below 50, is associated with functional gastrointestinal (GI) disorders (FGIDs) such as functional nausea, cyclic vomiting syndrome, and irritable bowel syndrome (IBS). Conversely, changes in intestinal GI transit may cause diarrhea or constipation and are a component of the autonomic symptoms associated with pre- and post-dorsal phases of migraine attack. These mutual relationships provoke a question on a common trigger in migraine and FGIDs. The kynurenine (l-kyn) pathway (KP) is the major route for l-tryptophan (l-Trp) metabolism and transforms l-Trp into several neuroactive compounds. Changes in KP were reported in both migraine and FGIDs. Migraine was largely untreatable, but several drugs approved lately by the FDA, including monoclonal antibodies for calcitonin gene-related peptide (CGRP) and its receptor, create a hope for a breakthrough in migraine treatment. Derivatives of l-kyn were efficient in pain relief with a mechanism including CGRP inhibition. KP products are important ligands to the aryl hydrocarbon receptor (AhR), whose activation is implicated in the pathogenesis of GI and migraine. Toll-like receptors (TLRs) may play a role in migraine and IBS pathogeneses, and KP metabolites detected downstream of TLR activation may be an IBS marker. The TLR4 signaling was observed in initiating and maintaining migraine-like behavior through myeloid differentiation primary response gene 88 (MyD88) in the mouse. The aim of this review is to justify the view that KP modulation may provide common triggers for migraine and FGIDs with the involvement of TLR, AhR, and MyD88 activation.

IL-23/IL-17A/TRPV1 Axis Produces Mechanical Pain via Macrophage-Sensory Neuron Crosstalk in Female Mice.
Luo X, Chen O, Wang Z, Bang S, Ji J, Lee SH, Huh Y, Furutani K, He Q, Tao X, Ko MC, Bortsov A, Donnelly CR, Chen Y, Nackley A, Berta T, Ji RR.
Neuron. 2021 Sep 1;109(17):2691-2706.e5. doi: 10.1016/j.neuron.2021.06.015. Epub 2021 Jul 19. PMID: 34473953; PMCID: PMC8425601.

Although sex dimorphism is increasingly recognized as an important factor in pain, female-specific pain signaling is not well studied. Here we report that administration of IL-23 produces mechanical pain (mechanical allodynia) in female but not male mice, and chemotherapy-induced mechanical pain is selectively impaired in female mice lacking Il23 or Il23r. IL-23-induced pain is promoted by estrogen but suppressed by androgen, suggesting an involvement of sex hormones. IL-23 requires C-fiber nociceptors and TRPV1 to produce pain but does not directly activate nociceptor neurons. Notably, IL-23 requires IL-17A release from macrophages to evoke mechanical pain in females. Low-dose IL-17A directly activates nociceptors and induces mechanical pain only in females. Finally, deletion of estrogen receptor subunit α (ERα) in $TRPV1^{+}$ nociceptors abolishes IL-23- and IL-17-induced pain in females. These findings demonstrate that the IL-23/IL-17A/TRPV1 axis regulates female-specific mechanical pain via neuro-immune interactions. Our study also reveals sex dimorphism at both immune and neuronal levels.

Sex Differences in the Expression of the Endocannabinoid System Within V1M Cortex and PAG of Sprague Dawley Rats.
Levine A, Liktor-Busa E, Lipinski AA, Couture S, Balasubramanian S, Aicher SA, Langlais PR, Vanderah TW, Largent-Milnes TM.
Biol Sex Differ. 2021 Nov 8;12(1):60. doi: 10.1186/s13293-021-00402-2. PMID: 34749819; PMCID: PMC8577021.

BACKGROUND: Several chronic pain disorders, such as migraine and fibromyalgia, have an increased prevalence in the female population. The underlying mechanisms of this sex-biased prevalence have yet to be thoroughly documented, but could be related to endogenous differences in neuromodulators in pain networks, including the endocannabinoid system. The cellular endocannabinoid system comprises the endogenous lipid signals 2-AG (2-arachidonoylglycerol) and AEA (anandamide); the enzymes that synthesize and degrade them; and the cannabinoid receptors. The relative prevalence of different components of the endocannabinoid system in specific brain regions may alter responses to endogenous and exogenous ligands. METHODS: Brain tissue from naïve male and estrous staged female Sprague Dawley rats was harvested from V1M cortex, periaqueductal gray, trigeminal nerve, and trigeminal nucleus caudalis. Tissue was analyzed for relative levels of endocannabinoid enzymes, ligands, and receptors via mass spectrometry, unlabeled quantitative proteomic analysis, and immunohistochemistry. RESULTS: Mass spectrometry revealed significant differences in 2-AG and AEA concentrations between males and females, as well as between female estrous cycle stages. Specifically, 2-AG concentration was lower within female PAG as compared to male PAG (*p = 0.0077); female 2-AG concentration within the PAG did not demonstrate estrous stage dependence. Immunohistochemistry followed by proteomics confirmed the prevalence of 2-AG-endocannabinoid system enzymes in the female PAG. CONCLUSIONS: Our results suggest that sex differences exist in the endocannabinoid system in two CNS regions relevant to cortical spreading depression (V1M cortex) and descending modulatory networks in pain/anxiety (PAG). These basal differences in endogenous endocannabinoid mechanisms may facilitate the development of chronic pain conditions and may also underlie sex differences in response to therapeutic intervention.

Sex Differences in Protein Kinase A Signaling of the Latent Postoperative Pain Sensitization that is Masked by Kappa Opioid Receptors in the Spinal Cord.
Basu P, Custodio-Patsey L, Prasoon P, Smith BN, Taylor BK.
J Neurosci. 2021 Nov 24;41(47):9827-9843. doi: 10.1523/JNEUROSCI.2622-20.2021. PMID: 34531285; PMCID: PMC8612640.

Latent sensitization (LS) of pain engages pronociceptive signaling pathways in the dorsal horn that include NMDA receptor (NMDAR)→adenylyl cyclase-1 (AC1)→protein kinase A (PKA), and exchange proteins directly activated by cyclic AMP (Epacs). To determine whether these pathways operate similarly between males and females or are under the inhibitory control of spinal κ opioid receptors (KOR), we allowed hyperalgesia to resolve after plantar incision and then blocked KOR with intrathecal administration of LY2456302, which reinstated hyperalgesia and facilitated touch-evoked immunoreactivity of phosphorylated extracellular signal-regulated kinase (pERK) in neurons (NeuN) but not astrocytes (GFAPs) nor microglia (Iba1). LY2456302 reinstated hyperalgesia even when administered 13 months later, indicating that chronic postoperative pain vulnerability persists for over a year in a latent state of remission. In both sexes, intrathecal MK-801 (an NMDAR competitive antagonist) prevented LY2456302-evoked reinstatement of hyperalgesia as did AC1 gene deletion or the AC1 inhibitor NB001. NB001 also prevented stimulus-evoked pERK. In both sexes, the Epac inhibitor ESI-09 prevented reinstatement, whereas the Epac activator 8-CPT reinstated hyperalgesia. By contrast, the PKA inhibitor H89 prevented reinstatement only in male mice, whereas the PKA activator 6-bnz-cAMP itself evoked reinstatement at all doses tested (3-30 nmol, i.t.). In neither sex did incision change gene expression of KOR, GluN1, PKA, or Epac1 in dorsal horn. We conclude that sustained KOR signaling inhibits spinal PKA-dependent mechanisms that drive postoperative LS in a sex-dependent manner. Our findings support the development of AC1, PKA, and Epac inhibitors toward a new pharmacotherapy for chronic postoperative pain. SIGNIFICANCE STATEMENT Because of neural mechanisms that are not well understood, men and women respond differently to treatments for chronic pain. We report that surgical incision recruits a pronociceptive latent pain sensitization that persisted for over a year and was kept in check by the sustained analgesic activity of κ opioid receptors. NMDAR→AC1→cAMP→Epac signaling pathways in the dorsal horn of the spinal cord maintain latent sensitization in both males and females; however, only males recruit a PKA-dependent mechanism. This work presents a novel male-specific mechanism for the promotion of chronic postoperative pain.

IL-23 Enhances C-Fiber-Mediated and Blue Light-Induced Spontaneous Pain in Female Mice.
Ji J, He Q, Luo X, Bang S, Matsuoka Y, McGinnis A, Nackley AG, Ji RR.
Front Immunol. 2021 Dec 7;12:787565. doi: 10.3389/fimmu.2021.787565. PMID: 34950149;

PMCID: PMC8688771.

The incidence of chronic pain is especially high in women, but the underlying mechanisms remain poorly understood. Interleukin-23 (IL-23) is a pro-inflammatory cytokine and contributes to inflammatory diseases (e.g., arthritis and psoriasis) through dendritic/T cell signaling. Here we examined the IL-23 involvement in sexual dimorphism of pain, using an optogenetic approach in transgenic mice expressing channelrhodopsin-2 (ChR2) in TRPV1-positive nociceptive neurons. In situ hybridization revealed that compared to males, females had a significantly larger portion of small-sized (100-200 μm2) Trpv1 + neurons in dorsal root ganglion (DRG). Blue light stimulation of a hindpaw of transgenic mice induced intensity-dependent spontaneous pain. At the highest intensity, females showed more intense spontaneous pain than males. Intraplantar injection of IL-23 (100 ng) induced mechanical allodynia in females only but had no effects on paw edema. Furthermore, intraplantar IL-23 only potentiated blue light-induced pain in females, and intrathecal injection of IL-23 also potentiated low-dose capsaicin (500 ng) induced spontaneous pain in females but not males. IL-23 expresses in DRG macrophages of both sexes. Intrathecal injection of IL-23 induced significantly greater p38 phosphorylation (p-p38), a marker of nociceptor activation, in DRGs of female mice than male mice. In THP-1 human macrophages estrogen and chemotherapy co-application increased IL-23 secretion, and furthermore, estrogen and IL-23 co-application, but not estrogen and IL-23 alone, significantly increased IL-17A release. These findings suggest a novel role of IL-23 in macrophage signaling and female-dominant pain, including C-fiber-mediated spontaneous pain. Our study has also provided new insight into cytokine-mediated macrophage-nociceptor interactions, in a sex-dependent manner.

Interleukin-6 Induces Spatially Dependent Whole-Body Hypersensitivity in Rats: Implications for Extracephalic Hypersensitivity in Migraine.
Avona A, Price TJ, Dussor G.
J Headache Pain. 2021 Jul 13;22(1):70. doi: 10.1186/s10194-021-01286-8. PMID: 34256692; PMCID: PMC8278737.

BACKGROUND: Migraine is a complex neurological disorder that is characterized by throbbing head pain, increased sensitivity to light, sound, and touch, as well as nausea and fatigue. It is one of the most common and most disabling disorders globally but mechanisms causing migraine are poorly understood. While head pain is a typical feature of attacks, they also often present with cutaneous hypersensitivity in the rest of the body. In contrast, primary pain conditions in the lower parts of the body are less commonly associated with cephalic hypersensitivity. Previous studies indicate that application of stimuli to the meninges of rodents causes cutaneous facial as well as hindpaw hypersensitivity. In the present study, we asked whether widespread hypersensitivity is a unique feature of dural stimulation or whether body-wide responses occur similarly when the same stimulus is given in other locations. METHODS: Rats were given the same dose of IL-6 either via dural, intraplantar, subcutaneous, intramuscular, intracisternal, or intrathecal injection. Cutaneous facial and hindpaw allodynia was assessed using Von Frey following injection into each location. RESULTS: Hindpaw allodynia was observed following dural and intraplantar injection of IL-6 in both males and females. Hindpaw allodynia was only observed in females following intracisternal and intrathecal IL-6 injections. In contrast, facial allodynia was only observed in either sex following dural and intracisternal injections, which would activate meningeal afferents and the trigeminal nucleus caudalis (TNC), respectively. CONCLUSIONS: Here we show that while stimulation of upper body regions with IL-6 including the meninges and brainstem can cause widespread hypersensitivity spreading to the paws, similar stimulation of the lower body does not cause the spread of hypersensitivity into the head. These data are consistent with the observations that whole body hypersensitivity is specific to conditions such as migraine where pain is present in the head and they may provide insight into co-morbid pain states associated with migraine.

Spinal CCK Contributes to Somatic Hyperalgesia Induced by Orofacial Inflammation Combined with Stress in Adult Female Rats.
Duan LL, Qiu XY, Wei SQ, Su HY, Bai FR, Traub RJ, Zhou Q, Cao DY.
Eur J Pharmacol. 2021 Dec 15;913:174619. doi: 10.1016/j.ejphar.2021.174619. Epub 2021 Nov 5. PMID: 34748768; PMCID: PMC9016487.

In some chronic primary pain conditions such as temporomandibular disorder (TMD) and fibromyalgia syndrome (FMS), mild or chronic stress enhances pain. TMD and FMS often occur together, but the underlying mechanisms are unclear. The purpose of this study was to

investigate the role of cholecystokinin (CCK) in the spinal cord in somatic hyperalgesia induced by orofacial inflammation combined with stress. Somatic hyperalgesia was detected by the thermal withdrawal latency and mechanical withdrawal threshold. The expression of CCK1 receptors, CCK2 receptors, ERK1/2 and p-ERK1/2 in the spinal cord was examined by Western blot. After the stimulation of orofacial inflammation combined with 3 day forced swim, the expression of CCK2 receptors and p-ERK1/2 protein in the L4-L5 spinal dorsal horn increased significantly, while the expression of CCK1 receptors and ERK1/2 protein remained unchanged. Intrathecal injection of the CCK2 receptor antagonist YM-022 or mitogen-activated protein kinase (MAPK) kinase (MEK) inhibitor PD98059 blocked somatic hyperalgesia induced by orofacial inflammation combined with stress. Intrathecal administration of the MEK inhibitor blocked somatic sensitization caused by the CCK receptor agonist CCK8. The CCK2 receptor antagonist YM-022 significantly reduced the expression of p-ERK1/2. These data indicate that upregulation of CCK2 receptors through the MAPK pathway contributes to somatic hyperalgesia in this comorbid pain model. Thus, CCK2 receptors and MAPK pathway may be potential targets for the treatment of TMD comorbid with FMS.

Differential Activation of Colonic Afferents and Dorsal Horn Neurons Underlie Stress-Induced and Comorbid Visceral Hypersensitivity in Female Rats.
Cao DY, Hu B, Xue Y, Hanson S, Dessem D, Dorsey SG, Traub RJ.
J Pain. 2021 Oct;22(10):1283-1293. doi: 10.1016/j.jpain.2021.04.004. Epub 2021 Apr 20. PMID: 33887444; PMCID: PMC8500917.

Chronic Overlapping Pain Conditions, including irritable bowel syndrome (IBS) and temporomandibular disorder (TMD), represent a group of idiopathic pain conditions that likely have peripheral and central mechanisms contributing to their pathology, but are poorly understood. These conditions are exacerbated by stress and have a female predominance. The presence of one condition predicts the presence or development of additional conditions, making this a significant pain management problem. The current study was designed to determine if the duration and magnitude of peripheral sensitization and spinal central sensitization differs between restraint stress-induced visceral hypersensitivity (SIH) and chronic comorbid pain hypersensitivity (CPH; stress during pre-existing orofacial pain). SIH in female rats, as determined by the visceromotor response, persisted at least four but resolved by seven weeks. In contrast, CPH persisted at least seven weeks. Surprisingly, colonic afferents in both SIH and CPH rats were sensitized at seven weeks. CPH rats also had referred pain through seven weeks, but locally anesthetizing the colon only attenuated the referred pain through four weeks, suggesting a transition to colonic afferent independent central sensitization. Different phenotypes of dorsal horn neurons were sensitized in the CPH rats seven weeks post stress compared to four weeks or SIH rats. The current study suggests differential processing of colonic afferent input to the lumbosacral spinal cord contributes to visceral hypersensitivity during comorbid chronic pain conditions. PERSPECTIVE: Chronic Overlapping Pain Conditions represent a unique challenge in pain management. The diverse nature of peripheral organs hinders a clear understanding of underlying mechanisms accounting for the comorbidity. This study highlights a mismatch between the condition-dependent behavior and peripheral and spinal mechanisms that contribute to visceral pain hypersensitivity.

Clinical Studies

Presence of Widespread Pain Predicts Comorbidities and Treatment Response in Temporomandibular Disorders Patients.
Jo JH, Son C, Chung JW, Park JW. Oral Dis. 2022 Sep;28(6):1682-1696. doi: 10.1111/odi.13987. Epub 2021 Aug 13. PMID: 34342093.

Objectives: Investigate the presence of widespread pain in a well-defined TMD group and analyze its interrelationship with various comorbidities. Also, longitudinally seek the difference in treatment response according to the presence of widespread pain. Subjects and methods: The observational study involved 45 female TMD patients in their 20s. Patients were grouped into localized and widespread pain groups based on the widespread pain index (WPI ≥ 4). Clinical characteristics and levels of comorbidities were analyzed through physical examination and validated questionnaires. Differences between the groups and the power of pre-treatment WPI in predicting pre-treatment comorbidities and post-treatment pain level improvement were statistically analyzed. Results: Patients with widespread pain showed

higher somatization and anxiety levels. SF-36 scores were significantly lower and more patients complained of gastrointestinal symptoms. Conventional treatment significantly reduced pain intensity in both groups but less in the widespread pain group. WPI showed significant chances to predict patients showing improvement in pain levels with treatment with a cutoff value of 4. WPI was also effective in differentiating patients that showed a higher level of somatization. Conclusion: Widespread pain index could be effectively applied in differentiating those with a higher level of psychological distress and predicting TMD treatment response with further investigations into its reliability.

Central Sensitivity and Fibromyalgia.
Mezhov V, Guymer E, Littlejohn G.
Intern Med J. 2021 Dec;51(12):1990-1998. doi: 10.1111/imj.15430. PMID: 34139045.

Fibromyalgia presents with symptoms of widespread pain, fatigue, sleeping and cognitive disturbances as well as other somatic symptoms. It often overlaps with other conditions termed 'central sensitivity syndromes', such as irritable bowel syndrome, chronic fatigue syndrome and temporomandibular disorder. Central sensitisation, mediated by amplified processing in the central nervous system, has been identified as the key pathogenic mechanism in these disorders. The term 'central sensitivity' can be used to describe collectively the clinical presentation of these disorders. Fibromyalgia is highly prevalent in most rheumatic diseases as well as non-rheumatic chronic diseases and if unrecognised results in high morbidity. It is diagnosed clinically after excluding important differential diagnoses. Diagnostic criteria have been developed as tools to help identify and diagnose fibromyalgia. Such tools can fulfil an important need when managing patients with rheumatic disease and other chronic diseases as a way to identify fibromyalgia and improve patient outcomes. Treatment involves an integrated approach including education, exercise, stress reduction and pharmacological therapies targeting the central nervous system. This approach is suitable for all presentations of central sensitivity and some central sensitivity syndromes have additional treatment options specific to the clinical presentation.

Impact of Fibromyalgia Phenotype in Temporomandibular Disorders.
Harper DE, Sayre K, Schrepf A, Clauw DJ, Aronovich S.
Pain Med. 2021 Sep 8;22(9):2050-2056. doi: 10.1093/pm/pnab077. PMID: 33674851; PMCID: PMC8427347.

BACKGROUND: Mounting evidence suggests that central nervous system amplification, similar to that seen in fibromyalgia (FM), contributes to the pain experience in a subset of patients with temporomandibular disorders (TMD). METHODS: In this prospective observational study, patients with TMD completed the 2011 FM survey questionnaire, a surrogate measure of "centralized" pain. The influence of centralized pain on TMD pain, dysfunction, and disability was assessed dichotomously by determining the incidence of FM-positive cases in the sample and by using FM survey scores as a continuous measure of "fibromyalgia-ness" ("FM-ness"). RESULTS: The patients meeting criteria for FM diagnosis (17 of 89) had significantly more disease burden on numerous measures. FM-ness was positively associated with pain at rest, negative mood, tenderness to palpation, perceived jaw functional limitation, and pain-related disability, and it was negatively associated with comfortable pain-free jaw opening. The impact of FM-ness on perceived jaw functional limitation and disability was mediated by levels of spontaneous, ongoing pain in the orofacial region. Importantly, this pattern of findings was still present even in those not meeting the criteria for FM diagnosis. CONCLUSION: Together, these results imply that higher FM-ness increases TMD patient burden by amplifying spontaneous pain and further hampering painless jaw function, even in patients who do not meet criteria for FM diagnosis. These results are highly relevant for the clinical management of TMD, as they imply that targeting the central nervous system in the treatment of patients with TMD with evidence of pain centralization may help ameliorate both pain and jaw dysfunction.

Multidisciplinary Care: Myalgic Encephalomyelitis (or Encephalopathy) / Chronic Fatigue Syndrome: Diagnosis and Management: Evidence Review I.
National Guideline Centre (UK).
London: National Institute for Health and Care Excellence (NICE); 2021 Oct. PMID: 35438861.

People with ME/CFS can require care from a variety of different health and social care professionals because of the problems associated with ME/CFS and its association with a number of co-morbidities. Care may be required from professionals from primary, community,

secondary and tertiary care at different stages and severities of the illness. This can include delivery of particular interventions and programmes over shorter timeframes, as well as ongoing monitoring and review. NICE has developed general guidance on principles of organisation of care. The NICE guideline on Patient experience makes recommendations on continuity of care and co-ordination of services based on patient needs and priorities. The NICE guideline on Multimorbidity recognises the potential burden of interactions with multiple services.

Measuring Resilience in Women with Endometriosis.
Lubián-López DM, Moya-Bejarano D, Butrón-Hinojo CA, Marín-Sánchez P, Blasco-Alonso M, Jiménez-López JS, Villegas-Muñoz E, González-Mesa E.
J Clin Med. 2021 Dec 17;10(24):5942. doi: 10.3390/jcm10245942. PMID: 34945238; PMCID: PMC8708759.

Endometriosis is a multifactorial disease with pathophysiological factors not yet well known; it also presents a wide symptomatic range that makes us think about the need for multidisciplinary management. It is a chronic disease in which there is no definitive treatment, and is associated in a large majority of cases with psychological pathology. Connecting comorbidities and multimorbidities on a neurobiological, neuropsychological, and pathophysiological level could significantly contribute to their more successful prevention and treatment. In our study, resilience is analyzed as an adjunctive measure in the management of endometriosis. Methods: A multi-centre, cross-sectional study was performed to analyse resilience levels in a sample of Spanish women suffering from endometriosis. CDRIS-25, CDRIS-10, BDI, the STAI, and the SF-36 Health Questionnaire were used for assessments. A representative group of 202 women with endometriosis was recruited by consecutive sampling. Exploratory and confirmatory factor analyses were performed for both resilience scales. Results: Mean CDRIS-25 and CDRIS-10 scores were 69.58 (SD 15.1) and 29.37 (SD 7.2), respectively. Women with adenomyosis and without signs of deep endometriosis showed the lowest scores. The best predictive model included women's age, years of endometriosis evolution, number of pregnancies, and history of fertility problems as the best predictive factors. Conclusions: Women build resilience as the number of years of evolution of the disease increases. Symptoms such as dyspareunia and continued abdominal pain were more prevalent among less resilient women.

Phenotypes of Women with and Without Endometriosis and Relationship with Functional Pain Disability.
Evans S, Mikocka-Walus A, Olive L, Seidman LC, Druitt M, Payne LA.
Pain Med. 2021 Jul 25;22(7):1511-1521. doi: 10.1093/pm/pnaa362. PMID: 33260211.

OBJECTIVE: Primary dysmenorrhea and secondary dysmenorrhea due to endometriosis share overlapping symptoms and likely demonstrate aspects of central sensitization. The present study aimed to identify distinct phenotypes of women who have dysmenorrhea with and without endometriosis to shed light on the unique mechanisms contributing to the pathogenesis of each condition. METHODS: An online survey was used to investigate the relationship between ratings of menstrual pain severity, menstrual symptoms (abdominal cramps, abdominal discomfort, low back pain, headache, body aches, bloating, nausea, diarrhea, increased bowel movements), widespread pain, and functional pain disability in a community sample of 1,354 women (aged 18-50) with menstrual pain in Australia. RESULTS: Compared with women without endometriosis, those with endometriosis had statistically significant higher menstrual pain severity ($P<0.01$), symptom severity and fatigue (all symptoms $P<0.001$, although only cramps and bloating were clinically significant), widespread pain sites ($P<0.001$), and functional pain disability ($P<0.001$, although this difference was not clinically significant). When examining symptoms by pain severity, women with severe menstrual pain were more likely to experience symptoms than women with less severe pain, regardless of the presence of endometriosis. Similar predictors of functional pain disability emerged for women with and without endometriosis, such as body aches, nausea, fatigue, and widespread pain, respectively, suggesting the presence of central sensitization in both groups. Logistic regression revealed that after accounting for menstrual pain severity (odds ratio [OR], 1.61) and duration (OR, 1.04), symptoms of bloating (OR, 1.12), nausea (OR, 1.07), and widespread pain sites (OR, 1.06) significantly predicted the presence of endometriosis. CONCLUSIONS: The findings suggest that phenotypes specific to endometriosis can be identified.

Clinical Heterogeneity in ME/CFS. A Way to Understand Long-COVID19 Fatigue.
Murga I, Aranburu L, Gargiulo PA, Gómez Esteban JC, Lafuente JV.

Front Psychiatry. 2021 Oct 11;12:735784. doi: 10.3389/fpsyt.2021.735784. PMID: 34707521; PMCID: PMC8542754.

The aim of present paper is to identify clinical phenotypes in a cohort of patients affected of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Ninety-one patients and 22 healthy controls were studied with the following questionnaires, in addition to medical history: visual analogical scale for fatigue and pain, DePaul questionnaire (post-exertional malaise, immune, neuroendocrine), Pittsburgh sleep quality index, COMPASS-31 (dysautonomia), Montreal cognitive assessment, Toulouse-Piéron test (attention), Hospital Anxiety and Depression test and Karnofsky scale. Co-morbidities and drugs-intake were also recorded. A hierarchical clustering with clinical results was performed. Final study group was made up of 84 patients, mean age 44.41 ± 9.37 years (66 female/18 male) and 22 controls, mean age 45 ± 13.15 years (14 female/8 male). Patients meet diagnostic criteria of Fukuda-1994 and Carruthers-2011. Clustering analysis identify five phenotypes. Two groups without fibromyalgia were differentiated by various levels of anxiety and depression (13 and 20 patients). The other three groups present fibromyalgia plus a patient without it, but with high scores in pain scale, they were segregated by prevalence of dysautonomia (17), neuroendocrine (15), and immunological affectation (19). Regarding gender, women showed higher scores than men in cognition, pain level and depressive syndrome. Mathematical tools are a suitable approach to objectify some elusive features in order to understand the syndrome. Clustering unveils phenotypes combining fibromyalgia with varying degrees of dysautonomia, neuroendocrine or immune features and absence of fibromyalgia with high or low levels of anxiety-depression. There is not a specific phenotype for women or men.

Morphological Changes in the Temporomandibular Joints in Women with Fibromyalgia and Myofascial Pain: A Case Series.
Santos CEM, Rodrigues VP, De Oliveira ICV, De Assis DSFR, De Oliveira MM, Conti CF. Cranio. 2021 Sep;39(5):440-444. doi: 10.1080/08869634.2019.1650215. Epub 2019 Aug 3. PMID: 31379267.

Objective: This study investigated the temporomandibular joint (TMJ) morphological changes in women with fibromyalgia (FM) through clinical and tomographic evaluation. Methods: Ten women diagnosed with myofascial pain who were being treated for FM in a university hospital were included in this study. The data were collected through clinical examination and cone beam computed tomography evaluation of the TMJ in closed and open mouth positions. Results: All patients had crackling in the joint, a habit of grinding teeth during sleep, muscle stiffness, and tinnitus. The tomographic findings revealed a higher frequency of condylar bone wear, reduction of joint space, and posterior positioning of the mandibular condyle. The temporomandibular disorders with the highest prevalence were osteoarthritis and disc displacement with reduction. Conclusion: The findings suggest that women with FM have a high frequency of TMD related to the displacement of the articular disc, condyle position, and occurrence of osteoarthritis.

The Impact of COVID-19 Stress on Pain and Fatigue in People with and without a Central Sensitivity Syndrome.
Koppert TY, Jacobs JWG, Lumley MA, Geenen R.
J Psychosom Res. 2021 Dec;151:110655. doi: 10.1016/j.jpsychores.2021.110655. Epub 2021 Oct 29. PMID: 34739944; PMCID: PMC8553422.

OBJECTIVES: Stress may augment somatic symptoms in central sensitivity syndromes (CSS) such as fibromyalgia, chronic fatigue syndrome, and irritable bowel syndrome. To test this hypothesis, we examined whether the association between COVID-19 stress and somatic symptom severity would be stronger in people with than without CSS and whether psychological flexibility would buffer the impact of this stress on symptom severity. METHODS: In a 2-sample, repeated cross-sectional design, we analysed questionnaire data from Dutch people with and without CSS, collected in two independent surveys: before the COVID-19 pandemic (2018; CSS: n = 194, non-CSS: n = 337) and at the peak of the pandemic (2020; CSS: n = 428, non-CSS: n = 1101). Somatic symptom severity, worry and stress due to the pandemic, and psychological flexibility were examined in regression analyses. Two stress operationalisations were analysed: stress levels during the peak of the pandemic, and a comparison of measurements in 2020 and 2018 (assuming higher stress levels in 2020). RESULTS: Higher worry and stress during the pandemic (standardized $\beta = 0.14$), the presence of a CSS ($\beta = 0.40$), and lower psychological flexibility ($\beta = -0.33$) were all ($p < .0001$) associated with more severe somatic symptoms, but the associations of each stress operationalisation with somatic symptoms was not particularly strong in people

with CSS (β = -0.026, p = .27; β = -0.037, p = .22), and psychological flexibility (β = -0.025, p = .18; β = 0.076, p = .35) did not buffer this association. CONCLUSIONS: Findings do not support the hypotheses that COVID-19 stress augments somatic symptoms, particularly in CSS, or that psychological flexibility buffers this impact. Rather, COVID-19-related stress appears to have an uncertain impact on somatic symptoms.

Association of Endometriosis with Interstitial Cystitis in Chronic Pelvic Pain Syndrome: Short Narrative on Prevalence, Diagnostic Limitations, and Clinical Implications.
Al-Shaiji TF, Alshammaa DH, Al-Mansouri MM, Al-Terki AE.
Qatar Med J. 2021 Oct 7;2021(3):50. doi: 10.5339/qmj.2021.50. PMID: 34660218; PMCID: PMC8497779.

INTRODUCTION: Chronic pelvic pain (CPP) is a diagnostic and therapeutic challenge affecting women of all ages globally. The syndrome is not well understood, but the association of interstitial cystitis (IC) with endometriosis in causing CPP should not be overlooked in managing this cohort. Herein, we present a mini review of this association to evaluate the literature in determining the prevalence of endometriosis and IC concomitantly in patients with CPP, diagnostic limitations, and clinical implications. METHODS: A Medline search of the key words "evil twins' syndrome," "interstitial cystitis," "bladder pain syndrome," and "endometriosis" was conducted for full-text articles published in English over the past 20 years. The search yielded 40 articles, of which 21 were selected. Cross-referencing bibliographies of each publication yielded an additional 25 references. RESULTS: Both endometriosis and IC share a similar array of symptoms that are often exacerbated during the perimenstrual period. Multiple authors have reported the frequent coexistence of these two conditions. Over 80% of patients with CPP were found to have both conditions. The prevalence of endometriosis and IC coexistence was greater than that of each condition separately. CONCLUSIONS: It is crucial to look beyond the traditionally diagnosed endometriosis as the cause of CPP. This is true especially in patients whose previous treatment was ineffective. Simultaneous assessment for both conditions is essential to avoid the frequently delayed diagnosis and prevent unsuccessful medical and surgical therapies.

Is Irritable Bowel Syndrome Considered as Comorbidity in Clinical Trials of Physical Therapy Interventions in Fibromyalgia? A Scoping Review.
Rodríguez-Castillejo PM, Fernández-de-Las-Peñas C, Alburquerque-Sendín F, Rodrigues-de-Souza DP.
J Clin Med. 2021 Oct 18;10(20):4776. doi: 10.3390/jcm10204776. PMID: 34682899; PMCID: PMC8541581.

Evidence supports the presence of comorbid conditions, e.g., irritable bowel syndrome (IBS), in individuals with fibromyalgia (FM). Physical therapy plays an essential role in the treatment of FM; however, it is not currently known whether the IBS comorbidity is considered in the selection criteria for clinical trials evaluating physiotherapy in FM. Thus, the aim of the review was to identify whether the presence of IBS was considered in the selection criteria for study subjects for those clinical trials that have been highly cited or published in the high-impact journals investigating the effects of physical therapy in FM. A literature search in the Web of Science database for clinical trials that were highly cited or published in high-impact journals, i.e., first second quartile (Q1) of any category of the Journal Citation Report (JCR), investigating the effects of physical therapy in FM was conducted. The methodological quality of the selected trials was assessed with the Physiotherapy Evidence Database (PEDro) scale. Authors, affiliations, number of citations, objectives, sex/gender, age, and eligibility criteria of each article were extracted and analyzed independently by two authors. From a total of the 412 identified articles, 20 and 61 clinical trials were included according to the citation criterion or JCR criterion, respectively. The PEDro score ranged from 2 to 8 (mean: 5.9, SD: 0.1). The comorbidity between FM and IBS was not considered within the eligibility criteria of the participants in any of the clinical trials. The improvement of the eligibility criteria is required in clinical trials on physical therapy that include FM patients to avoid selection bias.

Effectiveness of Pregabalin Treatment for Trigger Points in Patients with Comorbid Myofascial Pain Syndrome and Fibromyalgia Syndrome: A Randomized Controlled Trial.
Karamanlioglu DS, Geler Kulcu D, Ozturk G, Akpinar P, Unlu Ozkan F, Aktas I.
Somatosens Mot Res. 2021 Dec;38(4):327-332. doi: 10.1080/08990220.2021.1977265. Epub 2021 Sep 20. Erratum in: Somatosens Mot Res. 2021 Oct 4;:1. PMID: 34544324.

AIM OF THE STUDY: Myofascial pain syndrome (MPS) is a common problem in the general population. MPS should not be a local/peripheral painful syndrome and considered to be a

syndrome of central sensitivity. We aimed to investigate the effect of pregabalin in patients with MPS in this study. MATERIALS AND METHODS: We randomized 40 patients into two groups, and 17 patients per group completed the study. Female patients in group I received pregabalin and exercise therapy, whereas those in group II received exercise therapy alone. All patients were evaluated as follows: for pain by visual analog scale (VAS); trigger-point pressure pain threshold-(PPT) by algometry; neuropathic pain using the Douleur Neuropathique en 4 Questions (DN4) and quality of life with the Short Form-36 (SF36). Evaluations were performed pre-treatment and at the end of the first and third months of treatment. Clinical trial ID: NCT04600037, retrospectively registered 20/10/2020.RESULTS: In group I, significant improvements were observed in VAS, trigger-point-PPT, physical component summary-SF-36, at the first and third months. In group II, statistically significant improvements were observed in VAS, trigger-point-PPT after the first and third months. Group I showed statistically better improvements in VAS, trigger points-PPT, physical component summary-SF36 compared with group II by the third month. CONCLUSION: Pregabalin treatment is effective for controlling trigger points. Pregabalin treatment is also more effective than exercise treatment at improving quality of life in patients with MPS.

Hierarchical Clustering by Patient-Reported Pain Distribution Alone Identifies Distinct Chronic Pain Subgroups Differing by Pain Intensity, Quality, and Clinical Outcomes.
Alter BJ, Anderson NP, Gillman AG, Yin Q, Jeong JH, Wasan AD.
PLoS One. 2021 Aug 4;16(8):e0254862. doi: 10.1371/journal.pone.0254862. PMID: 34347793; PMCID: PMC8336800.

BACKGROUND: In clinical practice, the bodily distribution of chronic pain is often used in conjunction with other signs and symptoms to support a diagnosis or treatment plan. For example, the diagnosis of fibromyalgia involves tallying the areas of pain that a patient reports using a drawn body map. It remains unclear whether patterns of pain distribution independently inform aspects of the pain experience and influence patient outcomes. The objective of the current study was to evaluate the clinical relevance of patterns of pain distribution using an algorithmic approach agnostic to diagnosis or patient-reported facets of the pain experience. METHODS AND FINDINGS: A large cohort of patients (N = 21,658) completed pain body maps and a multi-dimensional pain assessment. Using hierarchical clustering of patients by body map selection alone, nine distinct subgroups emerged with different patterns of body region selection. Clinician review of cluster body maps recapitulated some clinically-relevant patterns of pain distribution, such as low back pain with radiation below the knee and widespread pain, as well as some unique patterns. Demographic and medical characteristics, pain intensity, pain impact, and neuropathic pain quality all varied significantly across cluster subgroups. Multivariate modeling demonstrated that cluster membership independently predicted pain intensity and neuropathic pain quality. In a subset of patients who completed 3-month follow-up questionnaires (N = 7,138), cluster membership independently predicted the likelihood of improvement in pain, physical function, and a positive overall impression of change related to multidisciplinary pain care. CONCLUSIONS: This study reports a novel method of grouping patients by pain distribution using an algorithmic approach. Pain distribution subgroup was significantly associated with differences in pain intensity, impact, and clinically relevant outcomes. In the future, algorithmic clustering by pain distribution may be an important facet in chronic pain biosignatures developed for the personalization of pain management.

Review Article: Physical and Psychological Comorbidities Associated with Irritable Bowel Syndrome.
Shiha MG, Aziz I.
Aliment Pharmacol Ther. 2021 Dec;54 Suppl 1:S12-S23. doi: 10.1111/apt.16589. PMID: 34927759.

Irritable bowel syndrome (IBS) is one of the most common gastrointestinal disorders encountered by physicians in primary and secondary care. Patients with IBS commonly present with various extraintestinal complaints, which account for a substantial clinical and economic burden. The common extraintestinal comorbidities associated with IBS include anxiety, depression, somatisation, fibromyalgia, chronic fatigue syndrome, chronic pelvic pain, interstitial cystitis, sexual dysfunction and sleep disturbance. The presence of comorbidity in IBS poses a diagnostic and therapeutic challenge with patients frequently undergoing unnecessary investigations and interventions, including surgery. This review discusses the different physical and psychological comorbidities associated with IBS, the shared pathophysiological mechanisms and potential management strategies.

The Emerging Role of Gut Microbiota in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): Current Evidence and Potential Therapeutic Applications.

Varesi A, Deumer US, Ananth S, Ricevuti G.

J Clin Med. 2021 Oct 29;10(21):5077. doi: 10.3390/jcm10215077. PMID: 34768601; PMCID: PMC8584653.

The well-known symptoms of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) are chronic pain, cognitive dysfunction, post-exertional malaise and severe fatigue. Another class of symptoms commonly reported in the context of ME/CFS are gastrointestinal (GI) problems. These may occur due to comorbidities such as Crohn's disease or irritable bowel syndrome (IBS), or as a symptom of ME/CFS itself due to an interruption of the complex interplay between the gut microbiota (GM) and the host GI tract. An altered composition and overall decrease in diversity of GM has been observed in ME/CFS cases compared to controls. In this review, we reflect on genetics, infections, and other influences that may factor into the alterations seen in the GM of ME/CFS individuals, we discuss consequences arising from these changes, and we contemplate the therapeutic potential of treating the gut to alleviate ME/CFS symptoms holistically.

Creation of a Multispecialty Clinic for Patients with Central Sensitization-Based Chronic Pain Conditions.

Loftus CG, Ebbert JO, Aakre CA, Caine NA, DeZutter MA, Eastman RJ, Fischer SM, Gilman EA, Johnson MG, Luedtke CA, Mohabbat AB, Reinschmidt KJ, Roellinger DL, Sanchez W, Philpot LM.

Mayo Clin Proc Innov Qual Outcomes. 2021 Dec 23;6(1):45-54. doi: 10.1016/j.mayocpiqo.2021.11.003. PMID: 35005437; PMCID: PMC8715289.

OBJECTIVE: To design and evaluate, through a human-centered design approach, a multispeciality clinic for patients with central sensitization syndromes that combined virtual previsit consultations, traditional face-to-face appointments, and technology-enabled educational programming. PATIENTS AND METHODS: Patients with suspected fibromyalgia and chronic abdominal pain were seen in a multispecialty practice, and the performance of the clinic was evaluated against a contemporary cohort. Quantitative and qualitative evaluation measures included team estimates of time spent on care-related tasks, physician rank of alignment of patient need with clinic design, major appointment changes, and nonvisit care tasks. Members of the care team also evaluated strengths, weaknesses, opportunities, and threats to the success of the clinic. RESULTS: The pilot clinic was operated from April 1, 2020, to April 30, 2021, and included 34 patients with suspected fibromyalgia/chronic abdominal pain. During the pilot period, physicians ranked the value of the virtual previsit consultations in providing care as 7.5 on a scale of 0 to 10 and reported an average of 50 minutes in preparation for the appointment, execution of the appointment, and postvisit documentation. We did not observe substantial differences in the number of added appointments or messages received within the patient portal when compared with a comparison cohort. Patients who participated in the combination nurse educator-led and digital education program provided positive feedback about their experience. CONCLUSION: Our clinic model provides a framework for the treatment of patients with debilitating centrally sensitized conditions and future expansion of virtual care delivery models to better meet patient care and educational needs.

Diagnosis and Management of Migraine in Ten Steps.

Eigenbrodt AK, Ashina H, Khan S, Diener HC, Mitsikostas DD, Sinclair AJ, Pozo-Rosich P, Martelletti P, Ducros A, Lantéri-Minet M, Braschinsky M, Del Rio MS, Daniel O, Özge A, Mammadbayli A, Arons M, Skorobogatykh K, Romanenko V, Terwindt GM, Paemeleire K, Sacco S, Reuter U, Lampl C, Schytz HW, Katsarava Z, Steiner TJ, Ashina M.

Nat Rev Neurol. 2021 Aug;17(8):501-514. doi: 10.1038/s41582-021-00509-5. Epub 2021 Jun 18. PMID: 34145431; PMCID: PMC8321897.

Migraine is a disabling primary headache disorder that directly affects more than one billion people worldwide. Despite its widespread prevalence, migraine remains under-diagnosed and under-treated. To support clinical decision-making, we convened a European panel of experts to develop a ten-step approach to the diagnosis and management of migraine. Each step was established by expert consensus and supported by a review of current literature, and the Consensus Statement is endorsed by the European Headache Federation and the European Academy of Neurology. In this Consensus Statement, we introduce typical clinical features, diagnostic criteria and differential diagnoses of migraine. We then emphasize the value of patient centricity and patient education to ensure treatment adherence and

satisfaction with care provision. Further, we outline best practices for acute and preventive treatment of migraine in various patient populations, including adults, children and adolescents, pregnant and breastfeeding women, and older people. In addition, we provide recommendations for evaluating treatment response and managing treatment failure. Lastly, we discuss the management of complications and comorbidities as well as the importance of planning long-term follow-up.

COVID-19 Pandemic and the Psyche, Bruxism, Temporomandibular Disorders Triangle.
Colonna A, Guarda-Nardini L, Ferrari M, Manfredini D.
Cranio. 2021 Oct 15:1-6. doi: 10.1080/08869634.2021.1989768. Epub ahead of print. PMID: 34652252.

OBJECTIVE: To investigate the effect of the Coronavirus pandemic on the report of psychological status, bruxism, and TMD symptoms. METHODS: An online survey was drafted to report the presence of psychological status, bruxism activities, and reported symptoms of TMDs perceived during the COVID-19 pandemic in a population of 506 individuals. RESULTS: Mental health is not positive during the Coronavirus pandemic: almost half the subjects reported an increase in bruxism behaviors, while up to one-third reported an increase in their symptoms involving the TMJ and jaw muscles. Specifically, 36% and 32.2% of participants reported increased pain in the TMJ and facial muscles, respectively, and almost 50% of the subjects also reported more frequent migraines and/or headaches. CONCLUSION: Increased psychosocial distress during the COVID-19 pandemic can increase the frequency of TMD symptoms and bruxism behaviors, which, in turn, constitute a triangle of mutually interacting factors with the psychological and emotional status.

Myofascial Pain in Temporomandibular Disorders: Updates on Etiopathogenesis and Management.
Kalladka M, Young A, Khan J.
J Bodyw Mov Ther. 2021 Oct;28:104-113. doi: 10.1016/j.jbmt.2021.07.015. Epub 2021 Aug 8. PMID: 34776126.

OBJECTIVES: Temporomandibular disorders (TMDs) are an umbrella term encompassing disorders of both the temporomandibular joint (TMJD) and masticatory musculature (MMD). The objective of this review is to provide an overview of the etiopathogenesis, clinical features and diagnosis of MMD, and to summarize the current trends in the therapeutic management. METHODS: A review of the literature was performed from 1985 to 2020. The keywords included were "temporomandibular disorders OR temporomandibular joint disorders" AND "myofascial pain OR masticatory myofascial pain OR trigger point". A total of 983 articles were screened with abstracts and approximately 500 full text articles were included in the review based on their relevance to the topic. RESULTS: MMD's present significant challenges in diagnosis and treatment. Effective treatment requires a clear diagnosis based on an understanding of pathophysiologic mechanisms, a detailed history with assessment of predisposing local and systemic factors, perpetuating factors, a comprehensive clinical evaluation and a diagnostic workup. CONCLUSION: A thorough history and clinical examination are the gold standards for diagnosis of MMD. Serological testing may help identify underlying co-morbidities. Recent diagnostic modalities including ultrasound sonoelastography and magnetic resonance elastography (MRE) have shown promising results. The treatment goals for MMD are to control pain, restore mandibular function and facilitate the return to normal daily activity and improve the overall quality of life of a patient. Conservative modalities including home care regimens, pharmacotherapy, intraoral appliance therapy, local anesthetic trigger point injections, physiotherapy and complementary modalities may be beneficial in patients with MMD's.

Impact of Psychological Comorbidity on the Prognosis of Irritable Bowel Syndrome.
Goodoory VC, Mikocka-Walus A, Yiannakou Y, Houghton LA, Black CJ, Ford AC. Am J Gastroenterol. 2021 Jul 1;116(7):1485-1494. doi: 10.14309/ajg.0000000000001247. PMID: 33840729.

INTRODUCTION: Psychological comorbidities are associated with irritable bowel syndrome (IBS), but little is known about their cumulative effect on its prognosis. We examined this issue in a longitudinal 12-month follow-up study. METHODS: We collected complete demographic, symptom, and psychological comorbidity data (anxiety, depression, somatic symptom disorder, perceived stress, and gastrointestinal symptom-specific anxiety) at baseline from 807 adults who met Rome IV criteria for IBS. At 12 months, we collected data regarding IBS symptom severity and impact, consultation behavior, and treatments

commenced from 452 individuals successfully followed up. We examined the cumulative effects of psychological comorbidities at baseline on subsequent IBS disease behavior. RESULTS: At baseline, among the 807 participants, 177 (21.9%) had 1, 139 (17.2%) 2, 103 (12.8%) 3, 89 (11.0%) 4, and 54 (6.7%) 5 psychological comorbidities. IBS symptom severity at baseline increased significantly with the number of psychological comorbidities (72.2% of those with 5 psychological comorbidities reported severe symptoms, vs 29.1% of those with none, P < 0.001). Among 452 (56.0%) participants followed up at 12 months, those with a higher number of psychological comorbidities at baseline were significantly more likely to have seen a gastroenterologist (33.3% of those with 5 psychological comorbidities, vs 21.4% of those with none, P = 0.001), cycle through more treatments (P < 0.0001), to report more severe IBS symptoms (66.7% with 5, vs 24.4% with none, P < 0.001) and continuous abdominal pain (22.1% with none, vs 61.9% with 5, P < 0.001), and to report that symptoms impacted on daily activities ≥50% of the time (90.5% with 5, vs 41.2% with none, P < 0.001). DISCUSSION: The prognosis of individuals with Rome IV-defined IBS worsens according to incremental increases in psychological comorbidity. This has important clinical and research implications.

Psychological Impact of COVID-19 Pandemic on TMD Subjects.
Di Giacomo P, Serritella E, Imondi F, Di Paolo C.
Eur Rev Med Pharmacol Sci. 2021 Jul;25(13):4616-4626. doi: 10.26355/eurrev_202107_26254. PMID: 34286503.

OBJECTIVE: The aim of the study was to assess the psychological impact of COVID-19 pandemic on subjects with temporomandibular disorders (TMD), as for symptomatology and presence of parafunctions and sleep disorders. PATIENTS AND METHODS: Two hundred fourteen subjects completed an online questionnaire, including Perceived Stress Scale (PSS), a temporomandibular screening and a specific item about the impact of such event on the psycho-physical side. Non-parametric tests - Mann-Whitney and Kruskal-Wallis - were performed to compare sex and age groups, as for PSS and "COVID-19 pandemic impact score (CpIS)", and the groups Improved/stationary and worsened in symptomatology as for the "CpIS". Data of subjects undergoing gnathological therapy and not were compared, using Chi-squared test. Orofacial symptomatology values before and during pandemic were compared. The level of statistical significance was set at p<0.05. RESULTS: The most prevalent category of perceived stress was the one of "moderate stress". Participants on average attributed to the pandemic a medium-low impact. The reported symptomatology actually showed a significant negative trend only as for neck pain. The intensity of orofacial symptomatology during pandemic was lower than before. Differences between age groups were statistically significant, as for CpIS. Subjects belonging to the group worsened in one or more fields examined - TMD symptoms, comorbidities, sleep disturbances and fatigue - reported a significantly higher CpIS (p<0.0001). Awake and sleep bruxism, dental grinding, alteration in the quality and quantity of sleep and fatigue increased. Gnathological therapy was not a protective factor. CONCLUSIONS: The most evident fact during pandemic was the increase of parafunctions and sleep disorders. The trend of symptoms was more variable and complex.

Evaluation of Temporomandibular Joint Disorder in Headache Patients.
Memmedova F, Emre U, Yalın OÖ, Doğan OC.
Neurol Sci. 2021 Nov;42(11):4503-4509. doi: 10.1007/s10072-021-05119-z. PMID: 33604763.

OBJECTIVE: The present study is aimed at determining the percentage of temporomandibular joint disorder (TMD) in patients admitted to the neurology outpatient clinic with a headache complaint and to evaluate the association of TMD with the presence of bruxism and headache traits. MATERIALS AND METHODS: A total of 349 headache patients were included in the study. The headache type, characteristics of the headache (incidence, duration, and severity of attacks), and the scores of the migraine disability scale (MIDAS) and Allodynia Symptom Scale (ASC-12T) were examined considering the presence of sleep bruxism. The International Classification of Headache Disorders (ICHD-3 Beta) criteria were used for diagnosing headaches. The presence of TMD was evaluated by using the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD). All patients diagnosed with TMD and/or bruxism were evaluated by a dentist. RESULTS: A total of 349 patients, 259 females and 90 males, were included in the study. The mean age of the patients was 36 years. Primary and secondary headaches were diagnosed in 317 (90.80%) and 32 (9.20%) patients, respectively. In the primary headache group, there were 227 migraines (182

females, 45 males), 74 tension-type headaches (TTH) (48 females, 26 males), and 15 trigeminal autonomic cephalalgias (TACs) (7 females, 8 males) patients. The remaining patients were diagnosed with other types of diagnoses. The rate of patients with chronic headache was 86.50%. TMD was detected in 89 (25.50%) of the patients while sleep bruxism was present in 80 (23.30%) patients. TMD was detected in 68 (30.0%) migraine patients and 13 (17.60%) TTH patients. The rate of TMD was statistically significantly higher in migraine patients compared to the TTH patients (p=0.037). CONCLUSION: Our cross-sectional outpatient-based study determined the incidence of TMD in headache patients as 25%. Among the primary headaches, the incidence of TMD was higher in migraine patients compared to the other diagnoses. Considering these data, the presence of TMD is a clinical condition that should be considered in the pathophysiology of headache, primarily migraine, and especially in cases of non-response to treatment.

Transitioning to Chronic Temporomandibular Disorder Pain: A Combination of Patient Vulnerabilities and Iatrogenesis.
Greene CS, Manfredini D.
J Oral Rehabil. 2021 Sep;48(9):1077-1088. doi: 10.1111/joor.13180. PMCID: PMC8453911.

BACKGROUND: Based on a variety of studies conducted in recent years, some of the factors that might contribute to the negative treatment responses of some TMD patients have been elucidated. METHODS: This paper describes known vulnerability factors that make individuals susceptible to developing temporomandibular disorders (TMDs), as well as those that contribute to the perpetuation of such problems. In addition, the topic of iatrogenesis is discussed as a major contributor to the negative outcomes that can be seen in this field. RESULTS: At the patient level, anatomical, psychosocial and genetic factors may contribute to individual vulnerability. The anatomy and pathophysiology of muscles, joints, disc and nerves may all be involved in predisposing to TMD symptoms, especially when the patients have pain elsewhere in the body. Among the psychosocial factors, some features may be elucidated by the DC/TMD axis II, while others (eg illness behaviour, Munchausen syndrome, lack of acceptance of non-mechanical approaches) require careful evaluation by trained clinicians. Genetic predisposition to first onset TMDs and to chronification of symptoms has been identified for individuals with certain psychological traits, presence of comorbid conditions and certain abnormal clinical manifestations. Regarding iatrogenesis, sins of omission may influence the clinical picture, with the main ones being misdiagnosis and undertreatment. Joint repositioning strategies, occlusal modifications, abuse of oral appliances, use of diagnostic technologies, nocebo effect and complications with intracapsular treatments are the most frequent sins of commission that may contribute to chronification of TMDs. The patients who present with massive occlusal and jaw repositioning changes combined with persistent severe orofacial pain are not a rarity within TMD and orofacial pain canters; these patients are the most difficult ones to manage because of this horrific combination of negative factors. CONCLUSIONS: The information presented in this paper will help clinicians to understand better why some individuals develop temporomandibular disorders, why some of them will progress to becoming chronic patients, and what the appropriate responses may be.

Phenotype of Cluster Headache: Clinical Variability, Persisting Pain Between Attacks, and Comorbidities-An Observational Cohort Study in 825 Patients.
Göbel CH, Karstedt S, Heinze A, Koch B, Göbel H.
Pain Ther. 2021 Dec;10(2):1121-1137. doi: 10.1007/s40122-021-00267-8. Epub 2021 May 4. PMID: 33945123; PMCID: PMC8586113.

INTRODUCTION: Cluster headaches can occur with considerable clinical variability. The inter- and intra-individual variability could contribute to the fact that the clinical headache phenotype is not captured by too strict diagnostic criteria, and that the diagnosis and the effective therapy are thereby delayed. The aim of the study was to analyze the severity and extent of the clinical symptoms of episodic and chronic cluster headaches with regard to their variability and to compare them with the requirements of the International Classification of Headache Disorders 3rd edition (ICHD-3) diagnostic criteria. METHODS: The study was carried out as a cross-sectional analysis of 825 patients who had been diagnosed with cluster headaches by their physician. Using an online questionnaire, standardized questions on sociodemographic variables, clinical features of the cluster headache according to ICHD-3, and accompanying clinical symptoms were recorded. RESULTS: The majority of patients with cluster headaches have clinical features that are mapped by the diagnostic criteria of ICHD-3. However, due to the variability of the symptoms, there is a significant proportion of clinical

phenotypes that are not captured by the ICHD-3 criteria for cluster headaches. In addition, change in the side of the pain between the cluster episodes, pain location, as well as persisting pain between the attacks is not addressed in the ICHD-3 criteria. In the foreground of the comorbidities are psychological consequences in the form of depression, sleep disorders, and anxiety. CONCLUSIONS: The variability of the phenotype of cluster headaches can preclude some patients from receiving an appropriate diagnosis and effective therapy if the diagnostic criteria applied are too strict. The occurrence of persisting pain between attacks should also be diagnostically evaluated due to its high prevalence and severity as well as psychological strain. When treating patients with cluster headaches, accompanying psychological illnesses should carefully be taken into account.

Multitargeting the Sleep-Pain Interaction with Pharmacological Approaches: A Narrative Review with Suggestions on New Avenues of Investigation.
Herrero Babiloni A, Beetz G, Bruneau A, Martel MO, Cistulli PA, Nixdorf DR, Conway JM, Lavigne GJ.
Sleep Med Rev. 2021 Oct;59:101459. doi: 10.1016/j.smrv.2021.101459. Epub 2021 Jan 28. PMID: 33601274.

The multimorbidity formed by sleep disturbances and pain conditions is highly prevalent and has a significant impact in global health and in the socioeconomic system. Although different approaches have been directed toward its management, evidence regarding an optimal treatment is lacking, and pharmacological options are often preferred. Health professionals (e.g., pain and sleep clinicians) tend to focus on their respective expertise, targeting a single symptom with a single drug. This may increase polypharmacy and the risk of drug interactions, adverse events, and mortality. Hence, the use of medications that can directly or indirectly improve sleep, pain, and other possible accompanying conditions without exacerbating them becomes especially relevant. The objectives of this comprehensive review are to: a) describe the beneficial or deleterious effects that some commonly used medications to manage pain have on sleep and sleep disorders; and b) describe the beneficial or deleterious effects that frequently prescribed medications for sleep may have on pain. Moreover, medications targeting some specific sleep-pain interactions will be suggested and future directions for improving sleep and alleviating pain of these patients will be provided with clinical and research perspectives.

Mechanisms and Pathways of Pain Photobiomodulation: A Narrative Review.
Cheng K, Martin LF, Slepian MJ, Patwardhan AM, Ibrahim MM.
J Pain. 2021 Jul;22(7):763-777. doi: 10.1016/j.jpain.2021.02.005. Epub 2021 Feb 23. PMID: 33636371; PMCID: PMC8277709.

A growing body of evidence supports the modulation of pain by light exposure. As such, phototherapy is being increasingly utilized for the management of a variety of pain conditions. The modes of delivery, and hence applications of phototherapy, vary by wavelength, intensity, and route of exposure. As such, differing mechanisms of action exist depending upon those parameters. Cutaneous application of red light (660 nm) has been shown to reduce pain in neuropathies and complex regional pain syndrome-I, whereas visual application of the same wavelength of red light has been reported to exacerbate migraine headache in patients and lead to the development of functional pain in animal models. Interestingly visual exposure to green light can result in reduction in pain in variety of pain conditions such as migraine and fibromyalgia. Cutaneous application typically requires exposure on the order of minutes, whereas visual application requires exposure on the order of hours. Both routes of exposure elicit changes centrally in the brainstem and spinal cord, and peripherally in the dorsal root ganglia and nociceptors. The mechanisms of photobiomodulation of pain presented in this review provide a foundation in furtherance of exploration of the utility of phototherapy as a tool in the management of pain. PERSPECTIVE: This review synopsizes the pathways and mechanisms through which light modulates pain and the therapeutic utility of different colors and exposure modalities of light on pain. Recent advances in photobiomodulation provide a foundation for understanding this novel treatment for pain on which future translational and clinical studies can build upon.

Epidemiology Studies

Association of Multimorbidity on Healthcare Expenditures Among Older United States Adults with Pain.
Marupuru S, Axon DR.

J Aging Health. 2021 Oct;33(9):741-750. doi: 10.1177/08982643211011841. PMID: 33881371

Objectives: This cross-sectional study compared the healthcare expenditures associated with multimorbidity (having ≥2 chronic conditions) versus no multimorbidity among older United States (US) adults (aged ≥ 50 years) with self-reported pain in the past 4 weeks. Methods: This research used data from the 2018 Medical Expenditure Panel Survey. Adjusted linear regression models evaluated group differences in various annual healthcare expenditures. Results: Descriptive statistics indicated multimorbidity was associated with all personal characteristics ($p < 0.05$) except gender and smoking status ($p > 0.05$). Multimorbidity had 75.8% greater annual total health expenditures ($p = 0.0083$), 40.6% greater office-based expenditures ($p = 0.0224$), 100.6% greater prescription medication costs, ($p = 0.0268$), yet 47.3% lower inpatient expenditures ($p = 0.0158$), and 56.6% lower home healthcare expenditures ($p < 0.0001$) than no multimorbidity. Discussion: This study found greater healthcare expenditures among older US adults with pain and multimorbidity, which captures the financial burden of comorbidity in this population.

Inequalities in Developing Multimorbidity Over Time: A Population-based Cohort Study from an Urban, Multi-ethnic Borough in the United Kingdom.

Bisquera A, Turner EB, Ledwaba-Chapman L, Dunbar-Rees R, Hafezparast N, Gulliford M, Durbaba S, Soley-Bori M, Fox-Rushby J, Dodhia H, Ashworth M, Wang Y.
Lancet Reg Health Eur. 2021 Nov 4;12:100247. doi: 10.1016/j.lanepe.2021.100247. PMID: 34901910; PMCID: PMC8640725.

BACKGROUND: Social and material deprivation accelerate the development of multimorbidity, yet the mechanisms which drive multimorbidity pathways and trajectories remain unclear. We aimed to examine the association between health inequality, risk factors and accumulation or resolution of LTCs, taking disease sequences into consideration. METHODS: We conducted a retrospective cohort of adults aged 18 years and over, registered between April 2005 and May 2020 in general practices in one inner London borough (n = 826,936). Thirty-two long term conditions (LTCs) were selected using a consensus process, based on a definition adapted to the demographic characteristics of the local population. The development and resolution of these LTCs were examined according to sociodemographic and clinical risk factors (hypertension; moderate obesity (BMI 30·0-39·9 kg/m2), high cholesterol (total cholesterol > 5 mmol/L), smoking, high alcohol consumption (>14 units per week), and psychoactive substance use), through the application of multistate Markov chain models. FINDINGS: Participants were followed up for a median of 4.2 years (IQR = 1·8 - 8·4); 631,760 (76%) entered the study with no LTCs, 121,424 (15%) with 1 LTC, 41,720 (5%) with 2 LTCs, and 31,966 (4%) with three or more LTCs. At the end of follow-up, 194,777 (24%) gained one or more LTCs, while 45,017 (5%) had resolved LTCs and 27,021 (3%) died. In multistate models, deprivation (hazard ratio [HR] between 1·30 to 1·64), female sex (HR 1·13 to 1·20), and Black ethnicity (HR 1·20 to 1·30; vs White) were independently associated with increased risk of transition from one to two LTCs, and shorter time spent in a healthy state. Substance use was the strongest risk factor for multimorbidity with an 85% probability of gaining LTCs over the next year. First order Markov chains identified consistent disease sequences including: chronic pain or osteoarthritis followed by anxiety and depression; alcohol and substance dependency followed by HIV, viral hepatitis, and liver disease; and morbid obesity followed by diabetes, hypertension, and chronic pain. INTERPRETATION: We examined the relations among 32 LTCs, taking the order of disease occurrence into consideration. Distinctive patterns for the development and accumulation of multimorbidity have emerged, with increased risk of transitioning from no conditions to multimorbidity and mortality related to ethnicity, deprivation and gender. Musculoskeletal disorders, morbid obesity and substance abuse represent common entry points to multimorbidity trajectories.

Prevalence of Chronic Pain in LTCs and Multimorbidity: A Cross-Sectional Study using UK Biobank.

McQueenie R, Jani BD, Siebert S, McLoone P, McCowan C, Macdonald S, Mair FS, Nicholl BI.
J Multimorb Comorb. 2021 Dec 21;11:26335565211005870. doi: 10.1177/26335565211005870. PMID: 35004337; PMCID: PMC8728767.

OBJECTIVES: Chronic pain is often experienced alongside other long-term conditions (LTCs), yet our understanding of this, particularly in relation to multimorbidity (≥2 LTCs) is poor. We aimed to examine associations between the presence/extent of chronic pain with type/number of LTCs experienced. METHODS: We examined the relationship between

number/type of LTCs (N = 45) in UK Biobank participants (n = 500,295) who self-reported chronic pain lasting ≥3 months in seven body sites or widespread. Relative risk ratios (RRR) for presence/extent of chronic pain sites were compared using logistic regression adjusted for sociodemographic (sex/age/socioeconomic status) and lifestyle factors (smoking/alcohol intake/BMI/physical activity). RESULTS: 218,648 participants self-reported chronic pain. Of these, 69.1% reported ≥1 LTC and 36.2% reported ≥2 LTCs. In 31/45 LTCs examined, >50% of participants experienced chronic pain. Chronic pain was common with migraine/headache and irritable bowel syndrome where pain is a primary symptom, but also with mental health conditions and diseases of the digestive system. Participants with >4 LTCs were over three times as likely to have chronic pain (RRR 3.56, 95% confidence intervals (CIs) 3.44-3.68) and 20 times as likely to have widespread chronic pain (RRR 20.13, 95% CI 18.26-22.19) as those with no LTCs. CONCLUSIONS: Chronic pain is extremely common across a wide range of LTCs. People with multimorbidity were at higher risk of having a greater extent of chronic pain. These results show that chronic pain is a key factor for consideration in the management of patients with LTCs or multimorbidity.

Prevalence and Characteristics of Chronic Pain in the Chinese Community-dwelling Elderly: A Cross-sectional Study.
Li X, Zhu W, Li J, Huang C, Yang F.
BMC Geriatr. 2021 Oct 7;21(1):534. doi: 10.1186/s12877-021-02432-2. PMID: 34620105; PMCID: PMC8499479.

BACKGROUND: Chronic pain adversely affects health and daily life in the elderly. Gaining insight into chronic pain that affects the community-dwelling elderly is crucial for pain management in China, which possesses the largest elderly population in the world. METHODS: This is a cross-sectional design study that followed the STROBE Guideline. A randomized cluster sampling method was used to recruit participants in the Sichuan Province from Dec 2018 to May 2019. In addition, face-to-face interviews were conducted to collect socio-demographic data, characteristics and health-seeking behaviors of chronic pain through a self-designed questionnaire. RESULTS: A total of 1381 older adults participated in this study. Among these participants, 791 (57.3%) had chronic pain. Here, prevalence and pain intensity were both found to increase from the 60-69 group to the 70-79 group, which then decreased in the ≥80 group with no significant differences in sex ($p > 0.05$). The most common pain locations were observed in the legs/feet (53.5%), head (23.6) and abdomen/pelvis (21.1%). Among the elderly suffering from chronic pain, 29.4% sought medical help, 59.2% received medication and 59.7% adopted non-drug therapy. CONCLUSION: Chronic pain is a common health concern in the Chinese community-dwelling elderly, which possesses different characteristics than other countries' populations. Therefore, easier access to medication assistance and provision of scientific guidance for non-drug therapy may serve as satisfactory approaches in improving pain management.

Functional Limitations in People with Multimorbidity and the Association with Mental Health Conditions: Baseline Data from the Canadian Longitudinal Study on Aging (CLSA).
Fisher K, Griffith LE, Gruneir A, Kanters D, Markle-Reid M, Ploeg J.
PLoS One. 2021 Aug 11;16(8):e0255907. doi: 10.1371/journal.pone.0255907. PMID: 34379653; PMCID: PMC8357170.

INTRODUCTION: Increasing multimorbidity is often associated with declining physical functioning, with some studies showing a disproportionate impact on functioning when mental health conditions are present. More research is needed because most multimorbidity studies exclude mental health conditions. OBJECTIVES: This study aims to improve our understanding of the association between functional limitation and multimorbidity, including a comparison of those with multimorbidity that includes versus excludes mental health conditions. METHODS: This is a population-based, cross-sectional analysis of data from The Canadian Longitudinal Study on Aging. Functional limitation was defined as the presence of any of 14 activities of daily living (ADLs) or instrumental activities of daily living (IADLs). Multimorbidity, measured by the number of chronic conditions, included mood and anxiety disorders. Logistic regression explored the association between multimorbidity (with and without mental health conditions) and functional limitation. Factor analysis identified common condition clusters to help understand clinical complexity in those with mood/anxiety disorders and the potential influences on functional limitation. RESULTS: There were 51,338 participants, with a similar proportion of men and women (49% versus 51%) and 42% age 65 years or older. Fifteen percent (15%) had no chronic conditions and 17% had 5+. Ten percent (10%) reported at least one ADL or IADL limitation. Odds ratios (ORs) for functional limitation

increased with multimorbidity and were generally higher for those with versus without mental health conditions (e.g., ORs from 1 to 5+ chronic conditions increased .9 to 15.8 for those with mood/anxiety disorders versus 1.8 to 10.2 for those without). Factor analysis showed that mood/anxiety conditions clustered with somatic conditions (e.g., migraines, bowel/gastrointestinal disorders). CONCLUSION: This study found higher odds of functional limitation for those with multimorbidity that included versus excluded mental health conditions, at all levels of multimorbidity. It highlights the need for concurrent management of mental and physical comorbidities to prevent functional limitations and future decline. This approach is aligned with the NICE clinical assessment and management guidelines for people with multimorbidity.

Pain Conditions and Suicide Attempts in Military Veterans: A Case-Control Design.
Boska RL, Bishop TM, Ashrafioun L.
Pain Med. 2021 Dec 11;22(12):2846-2850. doi: 10.1093/pm/pnab287. PMID: 34550391

OBJECTIVE: Specific pain conditions such as back pain and migraines are associated with increased risk of suicide mortality after accounting for key covariates. The purpose of the current study was to assess the associations of specific pain conditions with suicide attempts. DESIGN: Case-control. SETTING: Veterans Health Administration (VHA). SUBJECTS: Individuals who utilized VHA services with a record of a suicide attempt (N = 30,051) in Fiscal Years 2013 and 2014 were identified and propensity score matched with controls with no such record (N = 30,051). METHODS: Data on pain condition diagnoses (back pain, arthritis, migraine, headaches, psychogenic pain, neuropathy, fibromyalgia) psychiatric diagnoses, medical comorbidity, and demographics were extracted from VHA medical record and suicide surveillance datasets. RESULTS: Unadjusted logistic regression analyses found that each of the pain conditions were associated with suicide attempts (e.g., back pain: Odds ratio [OR]=3.25, 95% Confidence Interval [CI]=3.12-3.39). After adjusting for mental health conditions, medical comorbidity, and each of the pain conditions, the effects were attenuated across pain conditions; however, remained significant for each of the pain conditions except for fibromyalgia. Specifically, back pain (OR = 1.25, 95% CI = 1.19-1.32), migraines (OR = 1.29, 95% CI = 1.14-1.46), headaches (OR = 1.33, 95% CI = 1.19-1.48), and neuropathic pain (OR = 1.52, 95% CI = 1.33-1.74) were each associated with increased odds of a suicide attempt. Fibromyalgia was the only pain condition associated with re-attempt status (OR = 1.25, 95% CI = 1.08-1.45). CONCLUSIONS: Specific pain conditions are associated with increased odds of suicide attempts even after including key covariates. LIMITATIONS: Limitations of the study include the retrospective study design and lack of examination into additional variables including prescription opioid use, pain intensity, and pain duration. The case-control design also limits the ability to draw causal or temporal conclusions.

Irritable Bowel Syndrome and Migraine: Evidence from Mendelian Randomization Analysis in the UK Biobank.
Chen J, Chen X, Xie Y, Sun Y, Wang X, Hesketh T.
Expert Rev Gastroenterol Hepatol. 2021 Oct;15(10):1233-1239. doi: 10.1080/17474124.2021.1949290. Epub 2021 Jul 19. PMID: 34176420.

BACKGROUND: Irritable Bowel Syndrome (IBS) and Migraine are two diseases featuring high prevalence. Previous studies have suggested a relationship between IBS and migraine, although the causal association remains unclear. The authors sought to explore the causal association between IBS and migraine, and to show the importance of migraine prevention in IBS patients. METHODS: This study conducted a Mendelian randomization analysis to explore the association of IBS with migraine. Genetic association with migraine was acquired from the UK Biobank (UKB) genetic databases (cases: 1,072; controls: 360,122). The authors performed estimation using Inverse Variance Weighting (IVW), along with Maximum Likelihood, MR-RAPS, MR-Egger, and Weighted Median for sensitivity analysis. Considering possible bias, they also conducted polymorphism, heterogeneity, and directional analysis. RESULTS: The IVW estimation genetically predicted the causal association between IBS and migraine (OR = 1.09, 95% CI 1.01 to 1.17, p = 0.03). Neither statistical horizontal pleiotropy (MR Egger p = 0.42; MR-PRESSO p = 0.78) nor possible heterogeneity (IVW Q = 26.15, p = 0.80) was found. Reverse causation was also not detected (p steiger <0.01). CONCLUSION: Mendelian randomization analysis supported a potential causal association between IBS and migraine, providing enlightenment for disease prevention and control.

Migraine and Gastrointestinal Disorders in Middle and Old Age: A UK Biobank Study.
Welander NZ, Olivo G, Pisanu C, Rukh G, Schiöth HB, Mwinyi J.

Brain Behav. 2021 Aug;11(8):e2291. doi: 10.1002/brb3.2291. Epub 2021 Jul 21. PMID: 34291601; PMCID: PMC8413796.

INTRODUCTION: Migraine is a prevalent condition causing a substantial level of disability worldwide. Despite this, the pathophysiological mechanisms are not fully understood. Migraine often co-occurs with gastrointestinal disorders, but the direction of a potential causal link is unclear. The aim of this project was to investigate the associations between migraine and several gastrointestinal disorders in the same cohort in order to determine the relative strengths of these associations. METHODS: This cross-sectional study examined whether migraine is associated with irritable bowel syndrome (IBS), peptic ulcers, Helicobacter pylori (HP) infections, celiac disease, Crohn's disease and ulcerative colitis. Baseline data covering 489,753 UK Biobank participants (migraine group: n = 14,180) were analyzed using Pearson's chi-square tests and adjusted binary logistic regression models. RESULTS: Migraine was significantly associated with IBS (odds ratio [OR] 2.24, 95% confidence interval [CI] 2.08-2.40, p <.001) and peptic ulcers (OR 1.55, 95% CI 1.35-1.77, p <.001). Migraine was not associated with HP infection (OR 1.34, 95% CI 1.04-1.73, p = .024), celiac disease (OR 1.29, 95% CI 1.04-1.60, p = .023), Crohn's disease (OR 1.08, 95% CI 0.80-1.45, p = .617) or ulcerative colitis (OR 1.00, 95% CI 0.79-1.27, p = .979) after adjusting for multiple testing. CONCLUSIONS: Migraine was associated with IBS and peptic ulcers in this large population-based cohort. The associations with HP infection, celiac disease, Crohn's disease, and ulcerative colitis did not reach significance, suggesting a weaker link between migraine and autoimmune gastrointestinal conditions or HP infection.

Comorbid Conditions in Temporomandibular Disorders Myalgia and Myofascial Pain Compared to Fibromyalgia.

Barjandi G, Kosek E, Hedenberg-Magnusson B, Velly AM, Ernberg M.
J Clin Med. 2021 Jul 16;10(14):3138. doi: 10.3390/jcm10143138. PMID: 34300304; PMCID: PMC8306531.

The impact of comorbidities in fibromyalgia (FM) and temporomandibular disorders (TMD) have been well documented, but whether TMD sub-diagnoses myalgia (MYA) and myofascial pain with referral (MFP) differ regarding comorbidity is unclear. We aimed to elucidate this by studying the presence and associations of comorbidities in FM, MFP and MYA. An extended version of the Diagnostic Criteria for TMD axis II questionnaire was used to examine demographics, pain and comorbidities in 81 patients with FM, 80 with MYA, and 81 with MFP. Patients with MFP and FM reported a higher percentage of irritable bowel syndrome (IBS), depression, anxiety, somatic symptoms, perceived stress, and insomnia compared to MYA. Patients with FM had more IBS, depression, and somatic symptom disorder versus MFP. After adjusting for confounding variables, participants with anxiety, somatic symptoms disorder, pain catastrophizing, and perceived stress, as well as a greater number of comorbidities, were more likely to have MFP than MYA, whereas FM participants were more associated with IBS, somatic symptoms and insomnia compared to MFP. The number of comorbidities was significantly associated with widespread pain but not pain duration, body mass index or being on sick leave. In conclusion, patients with MFP were more similar to those with FM regarding comorbidity and should be differentiated from MYA in clinical settings and pain management.

Social Position and Functional Somatic Disorders: The DanFunD Study.

Schovsbo SU, Dantoft TM, Thuesen BH, Leth-Møller KB, Eplov LF, Petersen MW, Jørgensen T, Osler M.
Scand J Public Health. 2021 Nov 19:14034948211056752. doi: 10.1177/14034948211056752. PMID: 34796745.

BACKGROUND AND AIM: It is generally accepted that functional somatic disorders (FSDs) are a product of biological, psychological, and social factors. Social position might be part of this complex, but the literature on this issue is currently heterogeneous and inconsistent. The aim of the present study was - in a population-based cohort - to test the hypothesis that lower social position would be associated with higher a risk of FSD. METHOD: The association between social position and FSD was examined in a cross-sectional study with various measures of social position (education as measured by vocational training; employment; cohabitation; subjective social status) and delimitations of FSD (irritable bowel syndrome, chronic fatigue syndrome, fibromyalgia, bodily distress syndrome, and symptom profiles). The associations were analyzed using logistic regressions to calculate odds ratios and 95% confidence intervals. Each social measure was analyzed independently and was adjusted for age and sex. RESULTS: Lower levels of vocational training, being unemployed, and living

alone were associated with higher risk of FSD, regardless of the FSD delimitation. There was also a significant negative association between subjective evaluated social status and FSD. The associations remained after multiple adjustments, and seemed to be strongest for the more severe FSD-types. CONCLUSIONS: Lower social position is associated with higher risk of FSD, especially the more severe FSD delimitations, which might constitute an especially vulnerable group. However, the mechanisms behind the relations remain unknown.

Co-occurrence of Immune-Mediated Conditions and Endometriosis among Adolescents and Adult Women.
Shafrir AL, Palmor MC, Fourquet J, DiVasta AD, Farland LV, Vitonis AF, Harris HR, Laufer MR, Cramer DW, Terry KL, Missmer SA. Am J Reprod Immunol. 2021 Jul;86(1):e13404. doi: 10.1111/aji.13404. PMID: 33583078; PMCID: PMC8243788.

PROBLEM: Associations between immune dysfunction conditions (eg, systemic lupus erythematous, rheumatoid arthritis) and endometriosis have been observed in adult women, but not assessed among a younger population. We investigated the association between immune-mediated conditions and endometriosis among young women. METHOD OF STUDY: This cross-sectional analysis in the Women's Health Study: From Adolescence to Adulthood included 551 participants with surgically diagnosed endometriosis (median age=19) and 652 controls without endometriosis (median age=24). Participants completed an expanded Endometriosis Phenome and Biobanking Harmonization Project questionnaire. We used logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) to investigate the associations between autoimmune/inflammatory, atopic, chronic pain/fatigue, and endocrine disorders with endometriosis, adjusting for confounders. RESULTS: Participants with any autoimmune and/or inflammatory condition had an increased odds of co-occurring endometriosis (OR: 1.87; CI: 0.92-3.80), as did participants with allergies (OR: 1.76; CI: 1.32-2.36), asthma (OR: 1.35; CI: 0.97-1.88), chronic fatigue syndrome and/or fibromyalgia (OR: 5.81; CI: 1.89-17.9), or previous mononucleosis (OR: 1.75; CI: 1.14-2.68). Odds of endometriosis were lower among participants with eczema (OR: 0.68; CI: 0.44-1.04). We observed a positive trend between the number of immune-mediated conditions and the odds of endometriosis (p-trend=0.0002). Endocrine disorders were not associated with endometriosis. CONCLUSIONS: Among this population of adolescents and adult women, endometriosis was more likely among participants with autoimmune and/or inflammatory diseases, allergies, asthma, previous mononucleosis infection, and chronic fatigue and/or fibromyalgia. We observed that an increasing number of immune-mediated conditions were positively associated with endometriosis risk. It is important for clinicians who care for adolescents and women with these conditions to consider endometriosis as a comorbidity.

Increased Occurrence of Temporomandibular Joint Disorders in COVID-19 Confirmed Patients.
Tirrell M, Katz J.
Am J Dent. 2021 Dec;34(6):313-316. PMID: 35051318.

PURPOSE: To examine the prevalence of temporomandibular joint disorders (TMJD) in COVID-19 confirmed patients before and after adjustments for risk factors such as fibromyalgia, nocturnal bruxism, and anxiety disorders. METHODS: The i2b2 database was used to query searches of patient records at University of Florida Health Centers. Queries were submitted for the number of total hospital patients, TMJD cases, COVID-19 cases, and TMJD with COVID-19 cases from December 2019 to July 2021. Additional searches excluded fibromyalgia, nocturnal bruxism, and anxiety to examine their prevalence as risk factors. RESULTS: Out of the 548,646 total hospital patients, 86 had a diagnosis of both COVID-19 and TMJD, 14,836 had only COVID-19, and 1,856 had only TMJD. The odds ratio (OR) for having TMJD with COVID-19 was 1.7, with around 80% of TMJD occurring in young adult females. Excluding fibromyalgia and nocturnal bruxism did not change the OR. Anxiety was present in 37% of COVID-19 with TMJD cases and exclusion of this population significantly diminished the odds ratio to 1.08. These results demonstrate a correlation between COVID-19 and TMJD that dissolves when adjusting for stress. Thus, anxiety is a significant factor in the prevalence of TMJD in COVID-19 patients. CLINICAL SIGNIFICANCE: COVID-19 positive patients demonstrate an increased risk of developing TMJD, with a correlation to stress and anxiety that should be addressed during treatment.

Suicidal Behavior in Fibromyalgia Patients: Rates and Determinants of Suicide Ideation, Risk, Suicide, and Suicidal Attempts-A Systematic Review of the Literature and Meta-Analysis of Over 390,000 Fibromyalgia Patients.
Adawi M, Chen W, Bragazzi NL, Watad A, McGonagle D, Yavne Y, Kidron A, Hodadov H,

Amital D, Amital H. Front Psychiatry. 2021 Nov 19;12:629417. doi: 10.3389/fpsyt.2021.629417. PMID: 34867495; PMCID: PMC8640182.

Background: Suicide is a leading cause of death worldwide, affecting ~800,000 people every year. Fibromyalgia is an extremely prevalent rheumatic disease with a predisposition for comorbid anxiety and depression, which are known risk factors for suicidal behavior. Suicidality and relevant risk factors for suicidal behavior have not been thoroughly studied in patients with fibromyalgia. Objectives: To investigate the risk of suicidal ideation and attempts in patients with fibromyalgia. Methods: A systematic review and meta-analysis was conducted and reported according to the "Preferred Reporting Items for Systematic reviews and Meta-analyses" (PRISMA) standards. Also, the gray literature was extensively searched. Results: Thirteen studies were included in the present systematic review and meta-analysis, including 394,087 fibromyalgia patients. Sample size ranged from 44 to 199,739 subjects, mean age ranged from 45.8 to 54.5 years while the female percentage with fibromyalgia ranged from 17.1 to 100.0%. The overall suicide ideation prevalence was 29.57% (95%CI 1.84-72.07), with an OR 9.12 of (95%CI 1.42-58.77), ranging from 2.34 (95%CI 1.49-3.66) to 26.89 (95%CI 5.72-126.42). Pooled suicide attempt prevalence was 5.69% [95%CI 1.26-31.34], with an OR of 3.12 [95%CI 1.37-7.12]. Suicide risk was higher with respect to the general population with an OR of 36.77 (95%CI 15.55-96.94), as well as suicide events with an HR of 1.38 (95%CI 1.17-1.71). Determinants of suicidality were found to be: employment status, disease severity, obesity and drug dependence, chronic pain and co-morbidities, in particular depression, anxiety, poor sleep, and global mental health. However, in some cases, after adjusting for psychiatric conditions, the threshold of statistical significance was not achieved. Conclusion: Fibromyalgia patients are particularly prone to suicide, in terms of ideation, attempt, risk and events, warranting a pre-emptive screening of their mental health status. Given the few studies available, the high amount of heterogeneity, the evidence of publications bias and the lack of statistical significance when adjusting for underlying psychiatric co-morbidities, further high-quality studies should be conducted. Clinical Trial Registration: ClinicalTrial.gov, identifier 10.17605/OSF.IO/Y4BUE.

Incidence and Predictors of Persistent Pelvic Pain Following Hysterectomy in Women with Chronic Pelvic Pain.

As-Sanie S, Till SR, Schrepf AD, Griffith KC, Tsodikov A, Missmer SA, Clauw DJ, Brummett CM. Incidence and predictors of persistent pelvic pain following hysterectomy in women with chronic pelvic pain. Am J Obstet Gynecol. 2021 Nov;225(5):568.e1-568.e11. doi: 10.1016/j.ajog.2021.08.038. PMID: 34464585; PMCID: PMC9297195.

BACKGROUND: Chronic pelvic pain is a debilitating problem that afflicts 15% to 20% of women in the United States. Although more than 200,000 hysterectomies are performed annually for the treatment of chronic pelvic pain, previous studies indicate that 1 in 4 women undergo the discomfort and morbidity of hysterectomy without the relief of pain. The factors that predict treatment failure remain poorly characterized. OBJECTIVE: To describe the incidence of persistent pelvic pain 6 months following hysterectomy in women with chronic pelvic pain and determine whether a simple, self-reported measure of central sensitization is associated with a greater risk of persistent pelvic pain following hysterectomy. STUDY DESIGN: We conducted a prospective, observational cohort study of women undergoing hysterectomy at an academic tertiary care center for a benign indication. Patients with preoperative chronic pelvic pain, defined as average pelvic pain ≥3 on a 0 to 10 numeric rating scale for >3 months before hysterectomy, were included in this analysis. The patients completed validated assessments of pain, anxiety, depression, and centralized pain (using the 2011 Fibromyalgia Survey Criteria, 0-31 points) preoperatively and 6 months after hysterectomy. The demographic information, surgical history, intraoperative findings, and surgical pathology were abstracted from the electronic medical records. Multivariate logistic regression was used to identify the independent predictors of persistent pelvic pain 6 months following hysterectomy, defined as <50% improvement in pelvic pain severity. RESULTS: Among 176 participants with pelvic pain before hysterectomy, 126 (71.6%) were retained at 6 months, and 15 (11.9%) reported persistent pelvic pain. There was no difference in age (P=.46), race (P=.55), average pain severity during menses (P=.68), average overall pelvic pain (P=.10), or pain duration (P=.80) in those with and without persistent pelvic pain. Whereas intraoperative findings of endometriosis (P=.05) and uterine fibroids (P=.03) were associated with a higher incidence of persistent pain on univariate analysis, the surgical route (P=.46), pelvic adhesions (0.51), uterine weight (P=.66), and adenomyosis on histopathology (P=.27) were not related to the risk of persistent pain. Higher preoperative centralized pain scores (P=.01) but not depression (P=.64) or anxiety (P=.45) were more common in women

with persistent pelvic pain. Multivariate logistic regression adjusting for age, preoperative pain severity, anxiety, depression, and operative findings of endometriosis and fibroids indicated that every 1-point increase in centralized pain before hysterectomy was associated with a 27% increase in the odds of persistent pelvic pain (odds ratio, 1.27; 95% confidence interval, 1.03-1.57) 6 months after surgery. CONCLUSION: Although the majority of women with chronic pelvic pain report considerable improvement in pain following hysterectomy, higher degrees of centralized pain before hysterectomy is a robust predictor of persistent pelvic pain.

Frequency of Irritable Bowel Syndrome in Patients with Brugada Syndrome and Drug-Induced Type 1 Brugada Pattern.
Sarica AS, Bor S, Orman MN, Barajas-Martinez H, Juang JJ, Antzelevitch C, Hasdemir C.
Am J Cardiol. 2021 Jul 15;151:51-56. doi: 10.1016/j.amjcard.2021.04.010. PMCID: PMC9148266

Irritable bowel syndrome (IBS) is one of the most widely recognized functional bowel disorders (FBDs) with a genetic component. SCN5A gene and SCN1B loci have been identified in population-based IBS cohorts and proposed to have a mechanistic role in the pathophysiology of IBS. These same genes have been associated with Brugada syndrome (BrS). The present study examines the hypothesis that these two inherited syndromes are linked. Prevalence of FBDs over a 12 months period were compared between probands with BrS/drug-induced type 1 Brugada pattern (DI-Type 1 BrP) (n = 148) and a control group (n = 124) matched for age, female sex, presence of arrhythmia and co-morbid conditions. SCN5A/SCN1B genes were screened in 88 patients. Prevalence of IBS was 25% in patients with BrS/DI-Type 1 BrP and 8.1% in the control group ($p = 2.34 \times 10\text{-}4$). On stepwise logistic regression analysis, presence of current and/or history of migraine (OR of 2.75; 95% CI: 1.08 to 6.98; $p = 0.033$) was a predictor of underlying BrS/DI-Type 1 BrP among patients with FBDs. We identified 8 putative SCN5A/SCN1B variants in 7 (12.3%) patients with BrS/DI-Type 1 BrP and 1 (3.2%) patient in control group. Five out of 8 (62.5%) patients with SCN5A/SCN1B variants had FBDs. In conclusion, IBS is a common co-morbidity in patients with BrS/DI-Type 1 BrP. Presence of current and/or history of migraine are a predictor of underlying BrS/DI-Type 1 BrP among patients with FBDs. Frequent co-existence of IBS and BrS/DI-Type 1 BrP necessitates cautious use of certain drugs among the therapeutic options for IBS that are known to exacerbate the Brugada phenotype.

Migraine and the Development of Additional Psychiatric and Pain Disorders in the Transition from Adolescence to Adulthood.
Gerstl L, Tadych N, Heinen F, Kainz C, Bonfert MV, Hannibal I, Huss K, Ruscheweyh R, Straube A, Obermeier V, von Kries R, Landgraf MN.
Cephalalgia. 2021 Nov;41(13):1342-1347. doi: 10.1177/03331024211021792. Epub 2021 Jun 23. PMID: 34162254; PMCID: PMC8592111.

INTRODUCTION: The transition from childhood to adolescence and from adolescence to adulthood are vulnerable phases in life. In these phases, late or insufficient treatment of diseases may lead to chronification and favor development of additional disorders. In adolescents, migraine often has a highly negative impact on school performance and everyday life. The hypothesis of the present study was that adolescents with migraine have a higher risk for developing additional disorders such as psychiatric disorders or other pain syndromes in the course of the disease. MATERIALS AND METHODS: In this study, we analyzed health insurance data of 56,597 German adolescents at the age of 15 years in the year 2006. By using the International Classification of Diseases (ICD 10), we determined a group with migraine diagnosis in the year 2006 and a control group without any headache diagnosis in 2006. We then compared both groups regarding the development of additional disorders (based on the ICD 10) during the following 10 years (2007 to 2016). RESULTS: Adolescents with migraine had a 2.1 fold higher risk than persons without migraine diagnosis to develop an additional affective or mood disorder, a 1.8 fold higher risk to obtain neurotic, stress-related and somatoform disorders, a 1.8 fold higher risk to subsequently suffer from behavioral syndromes, a 1.6 higher risk to get back pain and a 1.5 fold higher risk for irritable bowel syndrome during the next 10 years. CONCLUSION: Adolescents with migraine are at risk for developing additional disorders later. Considering and addressing the patient's risks and potential medical and psychosocial problems might improve the long-term outcome significantly.

High rate of Dyspareunia and Probable Vulvodynia in Ehlers-Danlos Syndromes and Hypermobility Spectrum Disorders: An Online Survey.

Glayzer JE, McFarlin BL, Castori M, Suarez ML, Meinel MC, Kobak WH, Steffen AD, Schlaeger JM.
Am J Med Genet C Semin Med Genet. 2021 Dec;187(4):599-608. doi: 10.1002/ajmg.c.31939. Epub 2021 Nov 7. PMID: 34747110; PMCID: PMC8665058.

Vulvodynia is debilitating vulvar pain accompanied by dyspareunia (pain with sexual intercourse). Ehlers-Danlos syndromes (EDS) and hypermobility spectrum disorders (HSD) may represent a predisposing factor for vulvodynia given a high rate of dyspareunia in these conditions. We conducted an online survey of women with EDS or HSD to assess rates of dyspareunia and estimate rates of vulvodynia, report rates of comorbid conditions common to EDS or HSD and vulvodynia, and examine rates of conditions contributing to dyspareunia in women with EDS or HSD. Women with EDS or HSD (N = 1,146) recruited via social media were 38.2 ± 11.5 years old, primarily White (94.4%), and resided in the United States (78.5%). 63.7% of participants reported dyspareunia and 50% screened positive for vulvodynia. The rate of comorbid conditions common to EDS or HSD and vulvodynia were: irritable bowel syndrome, 6.5%; fibromyalgia, 40.0%; temporomandibular joint dysfunction, 56.4%; migraine, 6.7%; interstitial cystitis, 1.7%; and mast cell activation syndrome, 10.2%. Participants reporting dyspareunia also reported ovarian cysts, fibroids, or abdominal or pelvic scars, 47.5%; endometriosis, 26.5%; and genital lacerations, 19.3%. Women with EDS or HSD may have a higher rate of vulvodynia (50.0%) than women in the U.S. population at large (8%) and should be assessed for dyspareunia and vulvodynia.

Comorbidities and Quality of Life in Women Undergoing First Surgery for Endometriosis: Differences Between Chinese and Italian Population.
Chen H, Vannuccini S, Capezzuoli T, Ceccaroni M, Mubiao L, Shuting H, Wu Y, Huang H, Petraglia F.
Reprod Sci. 2021 Aug;28(8):2359-2366. doi: 10.1007/s43032-021-00487-5. Epub 2021 Mar 9. PMID: 33751460; PMCID: PMC8289763.

An observational cross-sectional study was conducted in a group (n = 371) of fertile age women with endometriosis, by administering a structured questionnaire, in order to evaluate the incidence of gynecological and systemic comorbidities and the impact on quality of life (QoL) in two different groups of Italian and Chinese patients affected by endometriosis. Chinese (n = 175) and Italian (n = 196) women were compared regarding systemic (inflammatory, autoimmune, and mental) and gynecological comorbidities, pain symptoms, and QoL, by using the Short Form 12 (SF-12). Italian patients resulted younger at the diagnosis and suffered more frequently from severe pain than Chinese ones. Deep infiltrating endometriosis (DIE) and mixed phenotypes were more frequent in Italian patients, whereas ovarian (OMA) and superficial endometriosis (SUP) were more common in the Chinese. The Italian group showed more systemic comorbidities, and those disorder were already present before the diagnosis of endometriosis. Furthermore, the Italian group showed lower SF-12 physical and mental scores, suggesting a worse health-related QoL in Italian endometriotic patients. A number of differences has been observed between Italian and Chinese women with endometriosis in terms of comorbidities and QoL, which may be related to the ethnicity, the different health system organization and the social and cultural background.

Risk of Rheumatoid Arthritis in Patients with Endometriosis: A Nationwide Population-Based Cohort Study.
Chen SF, Yang YC, Hsu CY, Shen YC.
J Womens Health (Larchmt). 2021 Aug;30(8):1160-1164. doi: 10.1089/jwh.2020.8431. Epub 2020 Nov 18. PMID: 33211602.

Background: Abnormalities in the immune system of endometriosis has been demonstrated and may reflect the chronic inflammatory response or the autoimmune reaction to the presence of ectopic endometrial tissue. Rheumatoid arthritis (RA) is a chronic inflammatory joint disease of an autoimmune nature. The study aimed to investigate the risk of incident RA in patients with endometriosis. Materials and Methods: A total of 17,913 patients with endometriosis and 17,913 unaffected controls matched by age, index year, and Charlson Comorbidity Index (CCI) score were enrolled between 2000 and 2012. Patients were followed until the end of 2013 using Taiwan's National Health Insurance Research Database, at which time participants who developed RA were identified. Cox regression analysis was used to calculate the hazard ratio (HR) with a 95% confidence interval (CI) of RA incidence rate between patients with endometriosis and unaffected controls. Results: Patients with endometriosis were associated with an increased risk of incident RA compared with unaffected controls after adjusting for age, CCI score, and hormonal and surgical treatments

(3.56 vs. 1.30 per 10,000 person-years, HR: 3.71, 95% CI: 2.91-5.73). Among these adjusted variables, hormonal and surgical treatments were treated as time-dependent covariates. Stratification analyses also revealed similar risk associations linking endometriosis to subsequent RA in all stratified age and CCI score subgroups (adjusted HR all >1, although not all were significant) Conclusions: Patients with endometriosis was associated with an increased risk of incident RA. Additional prospective studies that take into account genetic vulnerability and environmental exposures are warranted to confirm this relationship.

Increased Risk of Rheumatoid Arthritis Among Patients with Endometriosis: A Nationwide Population-Based Cohort Study.
Xue YH, You LT, Ting HF, Chen YW, Sheng ZY, Xie YD, Wang YH, Chiou JY, Wei JC.
Rheumatology (Oxford). 2021 Jul 1;60(7):3326-3333. doi: 10.1093/rheumatology/keaa784. PMID: 33331948

OBJECTIVES: Autoimmunity may play a role in endometriosis. The association between endometriosis and RA remains unknown. This study was conducted to identify any evidence for this relationship. METHODS: This 13-year, nationwide, population-based, retrospective cohort study analysed the risk of RA in a cohort of individuals with endometriosis. We investigated the incidence of RA among patients with endometriosis using data from the Longitudinal Health Insurance Database 2000, which is maintained by the Taiwan National Health Research Institutes. We used propensity scores to match comorbidities in the two cohorts. Kaplan-Meier analysis and Cox proportional hazard model were employed to analyse the association between endometriosis and RA among patients with different potential risks. RESULTS: Patients with endometriosis [adjusted hazard ratio (HR) 1.75, 95% CI 1.27, 2.41], aged ≥45 years (adjusted HR 1.50, 95% CI 1.06-2.13) and with autoimmune disease (adjusted HR 6.99, 95% CI 2.84-17.21) had a significantly higher risk of RA. The analyses also showed that when stratified by age, comorbidities and medication use, the risk of RA in patients with endometriosis was also higher than in those without endometriosis. CONCLUSIONS: This 14-year, nationwide, population-based retrospective cohort study revealed that patients with endometriosis have a higher risk of RA. In the clinical management of patients with RA, rheumatologists should be especially mindful of the possibility of underlying endometriosis.

Functional Somatic Syndromes and Joint Hypermobility: A Systematic Review and Meta-Analysis.
Chen G, Olver JS, Kanaan RA.
J Psychosom Res. 2021 Sep;148:110556. doi: 10.1016/j.jpsychores.2021.110556. PMID: 34237584

OBJECTIVE: There have been multiple reports of increased joint hypermobility (JH) in functional somatic syndromes (FSS). We sought to evaluate the evidence for an association. METHODS: A systematic search of the databases Medline and PsycINFO was conducted to identify all controlled studies from inception to February 2020 measuring the association of an FSS and JH. Records were identified and screened, and full-text articles assessed for eligibility by two independent authors. Meta-analysis was performed using random-effects modelling with the DerSimonian and Laird method. RESULTS: We found 220 studies initially, which yielded 11 studies for inclusion in the qualitative review and 10 in the quantitative analysis - 5 studies on fibromyalgia, 3 on chronic fatigue syndrome and 3 on functional gastrointestinal disorder. Nine of the 11 studies found increased rates of JH in FSS compared to controls, though most studies were fair to poor in quality. Meta-analysis showed a weighted summary effect odds ratio of 3.27 (95% CI: 1.83, 5.84; $p < 0.001$) of JH in FSS, suggesting greater odds of FSS in individuals with JH than in those without. CONCLUSIONS: There is some evidence for an association between FSS and JH, but this is limited by the generally poor quality of studies and the narrow range of FSS studied. Better research is needed to confirm these findings as well as evaluate causation using prospective cohort studies.

Comorbidities in a Nationwide, Heterogenous Population of Veterans with Interstitial Cystitis/Bladder Pain Syndrome.
Laden BF, Bresee C, De Hoedt A, Dallas KB, Scharfenberg A, Saxena R, Senechal JF, Barbour KE, Kim J, Freedland SJ, Anger JT.
Urology. 2021 Oct;156:37-43. doi: 10.1016/j.urology.2021.04.015. Epub 2021 Apr 23. PMID: 33901534; PMCID: PMC8536792.

OBJECTIVE: To examine the prevalence of comorbid conditions in a nationwide population of

men and women with IC/BPS utilizing a more heterogeneous sample than most studies to date. METHODS: Using the Veterans Affairs Informatics and Computing Infrastructure, we identified random samples of male and female patients with and without an ICD-9/ICD-10 diagnosis of IC/BPS. Presence of comorbidities (NUAS [chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome, migraines], back pain, diabetes, and smoking) and psychosocial factors (alcohol abuse, post-traumatic stress disorder, sexual trauma, and history of depression) were determined using ICD-9 and ICD-10 codes. Associations between these variables and IC/BPS status were evaluated while adjusting for the potential confounding impact of race/ethnicity, age, and gender. RESULTS: Data was analyzed from 872 IC/BPS patients (355 [41%] men, 517 [59%] women) and 558 non-IC/BPS patients (291 [52%] men, 267 [48%] women). IC/BPS patients were more likely than non-IC/BPS patients to have a greater number of comorbidities (2.72+/-1.77 vs 1.73+/-1.30, P < 0.001), experience one or more NUAS (chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome, and migraines) (45% [388/872] vs. 18% [101/558]; P < 0.001) and had a higher prevalence of at least one psychosocial factor (61% [529/872] v. 46% [256/558]; P < 0.001). Differences in the frequencies of comorbidities between patients with and without IC/BPS were more pronounced in female patients. CONCLUSION: These findings validate the findings of previous comorbidity studies of IC/BPS in a more diverse population.

Comorbidities of Primary Headache Disorders: A Literature Review with Meta-Analysis.
Caponnetto V, Deodato M, Robotti M, Koutsokera M, Pozzilli V, Galati C, Nocera G, De Matteis E, De Vanna G, Fellini E, Halili G, Martinelli D, Nalli G, Serratore S, Tramacere I, Martelletti P, Raggi A; European Headache Federation School of Advanced Studies (EHF-SAS).
J Headache Pain. 2021 Jul 14;22(1):71. doi: 10.1186/s10194-021-01281-z. PMID: 34261435; PMCID: PMC8278743.

BACKGROUND: Primary headache disorders are common and burdensome conditions. They are associated to several comorbidities, such as cardiovascular or psychiatric ones, which, in turn, contribute to the global burden of headache. The aim of this study is to provide a comprehensive description of the pooled prevalence of comorbidities of primary headache disorders using a meta-analytical approach based on studies published between 2000 and 2020. METHODS: Scopus was searched for primary research (clinical and population studies) in which medical comorbidities were described in adults with primary headache disorders. Comorbidities were extracted using a taxonomy derived from the Global Burden of Disease (GBD) study. We compared prevalence of comorbidities among headache sufferers against general population using GBD-2019 estimates, and compared comorbidities' proportions in clinical vs. population studies, and by age and gender. RESULTS: A total of 139 studies reporting information on 4.19 million subjects with primary headaches were included: in total 2.75 million comorbidities were reported (median per subject 0.64, interquartile range 0.32-1.07). The most frequently addressed comorbidities were: depressive disorders, addressed in 51 studies (pooled proportion 23 %, 95 % CI 20-26 %); hypertension, addressed in 48 studies (pooled proportion 24 %, 95 % CI 22-26 %); anxiety disorders addressed in 40 studies (pooled proportion 25 %, 95 % CI 22-28 %). For conditions such as anxiety, depression and back pain, prevalence among headache sufferers was higher than in GBD-2109 estimates. Associations with average age and female prevalence within studies showed that hypertension was more frequent in studies with higher age and less females, whereas fibromyalgia, restless leg syndrome, and depressive disorders were more frequent in studies with younger age and more female. CONCLUSIONS: Some of the most relevant comorbidities of primary headache disorders - back pain, anxiety and depression, diabetes, ischemic heart disease and stroke - are among the most burdensome conditions, together with headache themselves, according to the GBD study. A joint treatment of headaches and of these comorbidities may positively impact on headache sufferers' health status and contribute to reduce the impact of a group of highly burdensome diseases.

Fibromyalgia: A New Facet of the Post-COVID-19 Syndrome Spectrum? Results from a Web-Based Survey.
Ursini F, Ciaffi J, Mancarella L, Lisi L, Brusi V, Cavallari C, D'Onghia M, Mari A, Borlandelli E, Faranda Cordella J, La Regina M, Viola P, Ruscitti P, Miceli M, De Giorgio R, Baldini N, Borghi C, Gasbarrini A, Iagnocco A, Giacomelli R, Faldini C, Landini MP, Meliconi R.
RMD Open. 2021 Aug;7(3):e001735. doi: 10.1136/rmdopen-2021-001735. PMID: 34426540; PMCID: PMC8384499.

OBJECTIVE: Postacute COVID-19 syndrome (PACS) is an emerging entity characterised by

a large array of manifestations, including musculoskeletal complaints, fatigue and cognitive or sleep disturbances. Since similar symptoms are present also in patients with fibromyalgia (FM), we decided to perform a web-based cross-sectional survey aimed at investigating the prevalence and predictors of FM in patients who recovered from COVID-19. METHODS: Data were anonymously collected between 5 and 18 April 2021. The collection form consisted of 28 questions gathering demographic information, features and duration of acute COVID-19, comorbid diseases, and other individual's attributes such as height and weight. The American College of Rheumatology (ACR) Survey Criteria and the Italian version of the Fibromyalgia Impact Questionnaire completed the survey. RESULTS: A final sample of 616 individuals (77.4% women) filled the form 6±3 months after the COVID-19 diagnosis. Of these, 189 (30.7%) satisfied the ACR survey criteria for FM (56.6% women). A multivariate logistic regression model including demographic and clinical factors showed that male gender (OR: 9.95, 95% CI 6.02 to 16.43, p<0.0001) and obesity (OR: 41.20, 95% CI 18.00 to 98.88, p<0.0001) were the strongest predictors of being classified as having post-COVID-19 FM. Hospital admission rate was significantly higher in men (15.8% vs 9.2%, p=0.001) and obese (19.2 vs 10.8%, p=0.016) respondents. CONCLUSION: Our data suggest that clinical features of FM are common in patients who recovered from COVID-19 and that obesity and male gender affect the risk of developing post-COVID-19 FM.

Healthcare Spending and Utilization for Pediatric Irritable Bowel Syndrome in a Commercially Insured Population.

Beinvogl B, Palmer N, Kohane I, Nurko S.
Neurogastroenterol Motil. 2021 Nov;33(11):e14147. doi: 10.1111/nmo.14147. Epub 2021 Apr 5. PMID: 33818857.

BACKGROUND: Pediatric Irritable Bowel Syndrome (IBS) is common and can be associated with disabling gastrointestinal symptoms. Comprehensive data regarding utilization and cost of pediatric IBS are lacking. Our aim was to determine the annual all-cause spending and healthcare utilization in pediatric IBS. METHODS: Cross-sectional cohort study using a national claims database of commercially insured individuals. 932,592 members, age 8-18 years, were included. Members were selected based on PheWas codes and continuous enrollment in 2014. Linear and binomial regression models were used to calculate healthcare spending and compare comorbidities between IBS subjects and controls. KEY RESULTS: 1215 members with claims for IBS (68.4% female) and 931,377 controls (55.7% female) were included. Mean age was 15.03 ± 2.83 (median 16) years in the IBS group and 13.14 ± 3.12 (median 13) years in controls. Mental health and chronic pain comorbidities were more prevalent in the IBS cohort. Healthcare spending: The mean annual all-cause incremental spending of members with IBS was $6,364.60 compared to controls when adjusting for age and gender. Healthcare utilization: Members with IBS had increased healthcare utilization including higher rates of inpatient, outpatient, and emergency room visits, and higher rates of health service utilization including medical care, radiology/laboratory services, surgery, anesthesia, mental health, and physical therapy. General pediatrics was more frequently consulted by controls. All subspecialty consultations, with the exception of dental medicine and endocrinology, were sought more frequently by IBS patients. CONCLUSION: Patients with IBS incur significant annual spending through increased healthcare utilization.

Association Between Type 2 Diabetes and Chronic Low Back Pain in General Practices in Germany.

Jacob L, Rathmann W, Koyanagi A, Haro JM, Kostev K.
BMJ Open Diabetes Res Care. 2021 Jul;9(1):e002426. doi: 10.1136/bmjdrc-2021-002426. PMID: 34266855; PMCID: PMC8286747.

INTRODUCTION: There are conflicting results on the association between type 2 diabetes and chronic low back pain (CLBP). Therefore, the goal was to investigate the relationship between type 2 diabetes and CLBP in individuals followed in general practices in Germany. RESEARCH DESIGN AND METHODS: Adults diagnosed for the first time with type 2 diabetes in 809 general practices in Germany between 2005 and 2018 (index date) were included. Adults without type 2 diabetes were matched (1:1) to those with type 2 diabetes by sex, age, index year, and the annual number of medical consultations (index date: a randomly selected visit date). The association between type 2 diabetes and the 10-year incidence of CLBP was analyzed in conditional Cox regression models adjusted for a wide range of comorbidities, including hypertension, lipid metabolism disorders, and obesity. RESULTS: There were 139 002 individuals included in this study (women: 58.0%; mean (SD) age 62.5 (13.4) years). There was a positive association between type 2 diabetes and the incidence of

CLBP in the overall sample (HR=1.23, 95% CI: 1.13 to 1.35). Sex-stratified analyses showed a higher risk of CLBP in women (HR=1.68, 95% CI: 1.43 to 1.90) and a lower risk in men with than in their counterparts without type 2 diabetes (HR=0.83, 95% CI: 0.71 to 0.97). CONCLUSIONS: Newly diagnosed type 2 diabetes was associated with an increased risk of CLBP. There were important sex differences in the type 2 diabetes-CLBP relationship, and more research is warranted to investigate the underlying factors explaining these differences.

Interstitial Cystitis/Bladder Pain Syndrome Patient is Associated with Subsequent Increased Risks of Outpatient Visits and Hospitalizations: A population-based Study.
Hsieh sieh KL, Chin HY, Lo TS, Long CY, Ho CH, Huang SK, Chuang YC, Wu MP.
PLoS One. 2021 Sep 7;16(9):e0256800. doi: 10.1371/journal.pone.0256800. PMID: 34492065; PMCID: PMC8423233.

Interstitial cystitis/bladder pain syndrome (IC/BPS) is not only a chronic urinary bladder pain syndrome but is also associated with multifactorial etiology. Our study aimed to test the hypothesis that IC/BPS is associated with subsequent increased risks of outpatient visits and hospitalizations. Using nationwide database, the diagnoses were based on the International Classification Codes (ICD-9-CM) (595.1) of at least three outpatient services during 2002-2008, (n = 27,990) and cystoscopic finding Hunner type and/or glomerulation with pre-audit criteria. All recruited cases monitored for subsequent outpatient visits and hospitalizations for 2 years, including all-cause and specialty-specific departments, were classified according to medical specialty and age group (<40, 40-60, ≥60 years of age). IC/BPS patients have more overall outpatient department (OPD) visits and an overall adjusted incidence rate ratio (IRR) of 1.64. As for specialty, IRRs were higher in psychiatry (2.75), Chinese medicine (2.01), and emergency medicine (2.00), besides urology and gynecology. The IRRs decreased as age advanced (2.01, 1.71, and 1.44, respectively), except for gynecology (2.42, 2.52, and 2.81). A similar phenomenon happens in hospitalization with IRR of 1.69. Due to claim data characteristics, whether ulcer type IC/BPS findings can be deductive to non-ulcer type remains inclusive. Current results indicate the impacts of healthcare burden in broad spectrum about IC/PBS patients. IC/BPS has been suggested to be associated with lower threshold of healthcare visits and some coexisting disease and is comprised of systemic dysregulation, and is beyond the scope of local bladder-urethra disease. Adequate recognition of associated or comorbid factors and possible recommendation or referral for IC/BPS patients can help provide better healthcare quality.

Bidirectional Relationship between Temporomandibular Disorder and Ankylosing Spondylitis: A Population-based Cohort Study.
Huang YF, Chang CT, Muo CH, Chiu KM, Tsai CH, Liu SP.
Clin Oral Investig. 2021 Nov;25(11):6377-6384. doi: 10.1007/s00784-021-03938-0. PMID: 33855657.

OBJECTIVES: This study aimed to determine the relation between temporomandibular disorder (TMD) and ankylosing spondylitis (AS) bidirectionally and ascertain the important comorbidities for AS occurrence in TMD patients. MATERIALS AND METHODS: We conducted this population-based cohort study through Longitudinal Health Insurance Database, Taiwan. Study 1 investigated the risk of TMD in AS patients. Study 2 assessed the risk of AS in TMD patients. RESULTS: In total, 3204 AS patients and 12,816 age-matched and gender-matched comparisons were enrolled in study 1. The TMD incidence in the AS cohort was 2.88-fold higher when compared with the comparisons (1.54 vs. 0.53 per 10,000 person-years). After adjusting for age, gender, and comorbidity, the AS cohort had a 2.66-fold (95% CI = 1.79-3.97) increased risk of TMD occurrence (P < 0.0001). The second study recruited 4998 TMD patients and 19,991 age-matched and gender-matched comparisons. Both TMD and comparison cohorts showed similar AS risk (HR = 1.49, 95% CI = 0.91-2.43, P = 0.1108) in the adjusted model. Study 2 identified a 3.66-fold increased risk of AS occurrence in TMD patients with comorbidity, including parapsoriasis, rheumatoid arthritis, osteoporosis, Cushing's syndrome, and climacteric arthritis (P < 0.012). CONCLUSIONS: AS appears to significantly impact the occurrence of TMD. TMD might play a synergic role in AS development. CLINICAL RELEVANCE: Clinicians have to be vigilant about the increased risk of TMD in AS patients and take care of AS disease activity and prognosis. The symptoms and signs of TMD could be a predictor of AS in patients with the aforementioned comorbidities.

Prevalence of Signs and Symptoms of Temporomandibular Disorder in Patients with Sleep Apnea.
Alessandri-Bonetti A, Scarano E, Fiorita A, Cordaro M, Gallenzi P.

Sleep Breath. 2021 Dec;25(4):2001-2006. doi: 10.1007/s11325-021-02337-9. PMID: 33674964.

PURPOSE: The aim of the present study was to detect the prevalence of temporomandibular disorders (TMD) in patients with untreated obstructive sleep apnea (OSA) and to compare the results with healthy controls, matched for sex and age. METHODS: Forty-one consecutive patients with OSA were prospectively recruited from the Department of Otorhinolaryngology at the A. Gemelli Hospital prior to undergoing any treatment for OSA and independently of OSA severity. All patients underwent a complete TMD examination according to the diagnostic criteria for temporomandibular disorders (DC/TMD) protocol. The same examination was performed on 41 healthy controls matched for sex and age. Chi-squared test was used to compare results between the two groups. RESULTS: Of the 41 patients with OSA, 21 (51%) presented signs and/or symptoms of TMD compared to 13 of 41 subjects (32%) from the control group. Headache attributed to TMD and disc displacement with reduction were the most common diagnoses, with a statistically significant difference between the two groups ($p<0.05$). CONCLUSIONS: The prevalence of TMD signs and symptoms is significantly higher in untreated patients with OSA compared to healthy controls.

The Impact of Coexisting Fibromyalgia Syndrome on Disease Activity in Patients with Psoriatic Arthritis and Rheumatoid Arthritis: A Cross-sectional Study.
Mülkoğlu C, Ayhan FF.
Mod Rheumatol. 2021 Jul;31(4):827-833. doi: 10.1080/14397595.2020.1823069. Epub 2020 Oct 2. PMID: 32924689.

BACKGROUND/OBJECTIVE: This study aims to assess the coexistence of fibromyalgia syndrome (FMS) and impact of possible FMS on disease activity in patients with psoriatic arthritis (PsA) and rheumatoid arthritis (RA). METHODS: A total of 126 patients, aged 18-65 years old, who were being followed up with PsA (n = 64) and RA (n = 62) diagnoses were included. The Fibromyalgia Rapid Screening Tool (FiRST) was administered for screening FMS. Patients were divided according to the presence of FMS; PsA patients with FMS, patients with PsA without FMS, patients with both RA and FMS and patients with RA without FMS. Disease Activity Score 28 (DAS28) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) were recorded. RESULTS: FMS was detected in 26.5% of the patients with PsA and 17.7% of the patients with RA ($p = .04$). A statistically significant higher DAS28 and BASDAI scores were found in patients with FMS ($p < .05$). There was statistically significant correlation between FiRST with DAS28 and BASDAI scores ($p < .001$, $p = .03$, respectively) in PsA patients. No significant correlation was found between FiRST score with age, disease duration, CRP and DAS28 in patients with RA ($p > .05$). CONCLUSION: The patients with concomitant FMS had higher disease activity parameters (DAS28 and BASDAI) than those without FMS.

Fifteen-Years Follow-Up in a Cohort of Children with Functional Gastrointestinal Disorders: Prevalence and Risk Factors to Develop Neuropsychiatric Disorders and Other Comorbidities.
Zanchi C, Pintaldi S, Di Leo G, Ronfani L, Zamagni G, Viel M, Barbi E, Cozzi G.
Children (Basel). 2021 Sep 24;8(10):838. doi: 10.3390/children8100838. PMID: 34682103; PMCID: PMC8534479.

BACKGROUND: Functional gastrointestinal disorders (FGIDs) are chronic and recurrent disorders, which affect up to 23% of children and adolescents and represent 50% of gastroenterological accesses. The association between FGIDs diagnosed at paediatric age and the onset of migraine or headache and neuropsychiatric diseases in adolescence and adulthood is widely reported in the literature. However, there is still limited knowledge about the long-term prognosis and risk factors for neuropsychiatric pathologies and other comorbidities. AIM: The aim is to assess the prevalence and persistence of FGIDs as well as the occurrence of migraine or headache and neuropsychiatric disorders in a cohort of patients diagnosed with FGIDs 15 years ago compared with a control group of peers. MATERIALS AND METHODS: We enrolled a group of patients diagnosed with FGIDs at paediatric age, at least 10 years ago (FGIDs group, n = 79; median age 23), and control subjects (control group, n = 201; median age 23). In both groups, an online questionnaire created explicitly for the study was submitted in order to investigate the presence of chronic intestinal diseases, migraine, headache or neuropsychiatric disorders. RESULTS: 45.6% (36 out of 79) of patients previously diagnosed with FGIDs still suffer from FGIDs versus 12% (24 out of 201) of healthy controls ($p < 0.0001$). The prevalence of chronic organic gastrointestinal disorders was comparable in the two groups (2.5% in FGIDs group versus 1% in healthy group, p =

0.3). Thirty-three percent (26 out of 79) of FGIDs patients reported headache or migraine versus 13% (26 out of 201) of healthy peers ($p < 0.001$). No differences were found regarding the prevalence of anxiety and depression. CONCLUSION: The outcome at 15 years of FGIDs was characterized by a high prevalence of persisting functional symptoms along with a significant incidence of headaches and migraines.

Temporal Relationship between Osteoarthritis and Comorbidities: A Combined Case Control and Cohort Study in the UK Primary Care Setting.
Swain S, Coupland C, Mallen C, Kuo CF, Sarmanova A, Bierma-Zeinstra SMA, Englund M, Prieto-Alhambra D, Doherty M, Zhang W.
Rheumatology (Oxford). 2021 Sep 1;60(9):4327-4339. doi: 10.1093/rheumatology/keab067. PMID: 33506862; PMCID: PMC8410005.

OBJECTIVE: To determine the burden of comorbidities in OA and their temporal relationships in the UK. METHODS: The Clinical Practice Research Datalink (CPRD) GOLD was used to identify people with incident OA and age, gender and practice matched non-OA controls from UK primary care. Controls were assigned the same index date as matched cases (date of OA diagnosis). Associations between OA and 49 individual comorbidities and multimorbidities (two or more comorbidities excluding OA) both before and after OA diagnosis were estimated, adjusting for covariates, using odds ratios (aORs) and hazard ratios (aHRs), respectively. RESULTS: During 1997-2017, we identified 221 807 incident OA cases and 221 807 matched controls. Of 49 comorbidities examined, 38 were associated with OA both prior to and following the diagnosis of OA and 2 (dementia and systemic lupus erythematosus) were associated with OA only following the diagnosis of OA. People with OA had a higher risk of developing heart failure [aHR 1.63 (95% CI 1.56, 1.71)], dementia [aHR 1.62 (95% CI 1.56, 1.68)], liver diseases [aHR 1.51 (95% CI 1.37, 1.67)], irritable bowel syndrome [aHR 1.51 (95% CI 1.45, 1.58)], gastrointestinal bleeding [aHR 1.49 (95% CI 1.39, 1.59)], 10 musculoskeletal conditions and 25 other conditions following OA diagnosis. The aOR for multimorbidity prior to the index date was 1.71 (95% CI 1.69, 1.74), whereas the aHR for multimorbidity after the index date was 1.29 (95% CI 1.28, 1.30). CONCLUSIONS: People with OA are more likely to have other chronic conditions both before and after the OA diagnosis. Further study on shared aetiology and causality of these associations is needed.