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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 January and September 2022.

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Pathophysiology Studies

Circulating Polyunsaturated Fatty Acids, Pressure Pain Thresholds, and Nociplastic Pain Conditions.

Sanders AE, Weatherspoon ED, Ehrmann BM, Soma PS, Shaikh SR, Preisser JS, Ohrbach R, Fillingim RB, Slade GD.

Prostaglandins Leukot Essent Fatty Acids. 2022 Sep;184:102476. doi: 10.1016/j.plefa.2022.102476. Epub 2022 Jul 23. PMID: 35908377.

Objective: Polyunsaturated fatty acids (PUFAs) play a role in pain regulation. This study sought to determine whether free PUFAs found in red blood cells also play a role in nociceptive processing. We examined associations between circulating PUFAs and nociceptive thresholds to noxious mechanical stimuli. We also determined whether nociceptive thresholds were associated with nociplastic pain conditions. Methods: This cross-sectional study used stored red bloods cells and data from 605 adult participants in the OPPERA-2 study of chronic overlapping pain conditions. In OPPERA-2 adults completed quantitative sensory testing in which pressure algometry measured deep muscular tissue sensitivity at six anatomical sites. Standardized protocols classified adults for presence or absence of five nociplastic pain conditions: temporomandibular disorder, headache, low back pain, irritable bowel syndrome and fibromyalgia. Liquid chromatography tandem mass spectroscopy quantified erythrocyte PUFAs. We conducted three sets of analyses. First, a multivariable linear regression model assessed the association between n-6/n-3 PUFA ratio and the number of overlapping nociplastic pain conditions. Second, a series of 36 multivariable linear regression models assessed covariate-adjusted associations between PUFAs and nociceptive thresholds at each of six anatomical sites. Third, a series of 30

multivariable linear regression models assessed covariate-adjusted associations between nociceptive thresholds at six anatomical sites and each of five pain conditions. Results: In multiple linear regression, each unit increase in n-6/n-3 PUFA ratio was associated with more pain conditions (β = 0.30, 95% confidence limits: 0.07, 0.53, p = 0.012). Omega-6 linoleic acid and arachidonic acid were negatively associated with lower nociceptive thresholds at three and at five, respectively, anatomical sites. In contrast, omega-3 alpha-linolenic acid, eicosapentaenoic acid, docosahexaenoic acid and the n-6/n-3 PUFA ratio were not associated with nociceptive thresholds at any site. Pain cases had significantly lower nociceptive thresholds than non-case controls at all anatomical sites. Conclusion: A higher n-6/n-3 PUFA ratio was associated with more pain conditions. Omega-6 PUFAs may promote a generalized upregulation of nociceptive processing.

Brain Structure, Psychosocial, and Physical Health in Acute and Chronic Back Pain: a UK Biobank Study.
Tagliaferri SD, Fitzgibbon BM, Owen PJ, Miller CT, Bowe SJ, Belavy DL.
Pain. 2022 Jul 1;163(7):1277-1290. doi: 10.1097/j.pain.0000000000002524. Epub 2021 Oct 26. PMID: 34711762.

Brain structure, psychosocial, and physical factors underpin back pain conditions; however, less is known about how these factors differ based on pain duration and location. We examined, cross-sectionally, 11,106 individuals from the UK Biobank who (1) were pain-free (n = 5616), (2) had acute back pain (n = 1746), (3) had chronic localised back pain (CBP; n = 1872), or (4) had chronic back pain and additional chronic pain sites (CWP; n = 1872). We found differences in structural brain measures in the chronic pain groups alone. Both CBP and CWP groups had lower primary somatosensory cortex {CBP mean difference (MD) (95% confidence interval [CI]): -250 (-393, -107) mm3, P < 0.001; CWP: -170 (-313, -27)mm3, P = 0.011} and higher caudate gray matter volumes (CBP: 127 [38,216]mm3, P = 0.001; CWP: 122 [33,210]mm3, P = 0.002) compared with pain-free controls. The CBP group also had a lower primary motor cortex volume (-215 [-382, -50]mm3, P = 0.005), whereas the CWP group had a lower amygdala gray matter volume (-27 [-52, -3]mm3, P = 0.021) compared with pain-free controls. Differences in gray matter volumes in some regions may be moderated by sex and body mass index. Psychosocial factors and body mass index differed between all groups and affected those with widespread pain the most (all, P < 0.001), whereas grip strength was only compromised in individuals with widespread pain (-1.0 [-1.4, -0.5] kg, P < 0.001) compared with pain-free controls. Longitudinal research is necessary to confirm these interactions to determine the process of pain development in relation to assessed variables and covariates. However, our results suggest that categorised pain duration and the number of pain sites warrant consideration when assessing markers of brain structure, psychosocial, and physical health.

The Role of Neuro-Immune Interaction in Chronic Pain Conditions; Functional Somatic Syndrome, Neurogenic Inflammation, and Peripheral Neuropathy.
Meade E, Garvey M.
Int J Mol Sci. 2022 Aug 2;23(15):8574. doi: 10.3390/ijms23158574. PMID: 35955708; PMCID: PMC9369187.

Functional somatic syndromes are increasingly diagnosed in chronically ill patients presenting with an array of symptoms not attributed to physical ailments. Conditions such as chronic fatigue syndrome, fibromyalgia syndrome, or irritable bowel syndrome are common disorders that belong in this broad category. Such syndromes are characterised by the presence of one or multiple chronic symptoms including widespread musculoskeletal pain, fatigue, sleep disorders, and abdominal pain, amongst other issues. Symptoms are believed to relate to a complex interaction of biological and psychosocial factors, where a definite aetiology has not been established. Theories suggest causative pathways between the immune and nervous systems of affected individuals with several risk factors identified in patients presenting with one or more functional syndromes. Risk factors including stress and childhood trauma are now recognised as important contributors to chronic pain conditions. Emotional, physical, and sexual abuse during childhood is considered a severe stressor having a high prevalence in functional somatic syndrome suffers. Such trauma permanently alters the biological stress response of the suffers leading to neuroexcitatory and other nerve issues associated with chronic pain in adults. Traumatic and chronic stress results in epigenetic changes in stress response genes, which ultimately leads to dysregulation of the hypothalamic-pituitary axis, the autonomic nervous system, and the immune system manifesting in a broad array of symptoms. Importantly, these systems are known to be dysregulated in patients suffering

from functional somatic syndrome. Functional somatic syndromes are also highly prevalent co-morbidities of psychiatric conditions, mood disorders, and anxiety. Consequently, this review aims to provide insight into the role of the nervous system and immune system in chronic pain disorders associated with the musculoskeletal system, and central and peripheral nervous systems.

Interactions between the Painful Disorders and the Autonomic Nervous System.
Arslan D, Ünal Çevik I.
Agri. 2022 Jul;34(3):155-165. English. doi: 10.14744/agri.2021.43078. PMID: 35792695.

The autonomic nervous system (ANS) controls the heart rate, blood pressure, digestion, respiration, pupillary reactivity, sweating, urination, sexual arousal, and regulates the functions of internal organs. This system provides the homeostasis of the cells, tissues, and organs throughout the body and protects against the disturbances imposed by the external and internal stressors. The ANS has three main divisions: The sympathetic nervous system (SNS), the parasympathetic nervous system (PNS), and the enteric nervous system. In general, the SNS and PNS have opposing effects. Each region belonging to the 'pain matrix' interacts with ANS. The descending system regulates pain and creates a regulatory effect by the contribution of aminergic neurotransmitters. Hypothalamus, amygdala, and periaqueductal gray are the main structures of this regulatory system. Dysfunction of the ANS is frequently observed in pain patients. The SNS induce, facilitate, or potentiate chronic pain. Increased responsiveness of injured sensory nerves to catecholamines, increased expression of α-1 adrenoreceptors on the primary afferent nociceptors and hyperalgesic skin, central sensitization rendering Aβ mechanoreceptors, enhanced discharge and sympathetic sprouting in dorsal root ganglia, central sensitization, and dysfunction of the pain modulation is proposed mechanisms. In this review, the anatomical, physiological and pathological aspects of ANS and pain, and laboratory tests to evaluate autonomic functions will be discussed. Pathophysiological role of ANS in migraine, trigeminal autonomic cephalgias, trigeminal neuralgia, peripheral nerve injuries, small fiber neuropathies, myofascial pain syndrome, fibromyalgia, painful joint diseases, visceral pain, phantom limb pain, complex regional pain syndrome, and spinal cord injury will be discussed.

The Role of Depressive Disorders in Autonomic Cardiovascular Dysregulation in Fibromyalgia.
Reyes Del Paso GA, Contreras-Merino AM, Duschek S.
Psychosom Med. 2022 Sep 1;84(7):793-802. doi: 10.1097/PSY.0000000000001097. Epub 2022 Jun 22. PMID: 35796593.

Objective: Previous research revealed aberrances in autonomic cardiovascular regulation in fibromyalgia, which may be relevant to symptoms genesis and the increased risk of cardiovascular disorders in individuals with fibromyalgia. This study investigated the role of comorbid depression in autonomic cardiovascular dysregulations in fibromyalgia.
Methods: Cardiovascular recordings were obtained in 53 participants with fibromyalgia who also had depression (n = 27), in participants with fibromyalgia without depression (n = 26), and in 29 healthy controls, at rest and during a cold pressor test and an arithmetic task. Assessed parameters included interbeat interval, blood pressure, heart rate variability, baroreflex sensitivity, stroke volume, preejection period, left ventricular ejection time, Heather index, and total peripheral resistance. Results: Participants with both fibromyalgia and depression displayed lower tonic interbeat interval, baroreflex sensitivity, and heart rate variability compared with participants with fibromyalgia without depression and controls (p values < .012, d values = 0.71-1.06). Participants with fibromyalgia but without depression did not differ from controls in these variables. Moreover, participants with fibromyalgia who also had depression, but not those without depression, exhibited lower Heather index, stroke volume, and left ventricular ejection time compared with controls (p values < .013, d values = 0.62-0.78). No group differences arose for preejection period or total peripheral resistance. Stress reactivity was reduced in participants with fibromyalgia, independently of depression, for diastolic blood pressure, interbeat interval, left ventricular ejection time, and heart rate variability, than in controls. Conclusions: The role of depression in the autonomic dysregulation in fibromyalgia involves chronotropic cardiac control rather than adrenergic influences on contractility and vascular tone. Blunted cardiovascular reactivity may be ascribable to pathological factors inherent to fibromyalgia. These results underline the importance of diagnostics and treatment of comorbid depressive disorders in the management of fibromyalgia.

Interplay of Oral, Mandibular, and Facial Disorders and Migraine.
Teruel A, Romero-Reyes M.
Curr Pain Headache Rep. 2022 Jul;26(7):517-523. doi: 10.1007/s11916-022-01054-6. Epub 2022 May 14. PMID: 35567662.

Purpose of the review: Migraine and other primary headache disorders can be localized in the face resembling facial or dental pain, indicating the influence of the trigeminovascular system in the structures innervated by the maxillary (V2) and mandibulary (V3) branches of the trigeminal nerve. Disorders of oral and craniofacial structures may influence primary headache disorders. In the current article, we review the potential links of this interplay. Recent findings: This interplay may be related to anatomy, with the trigeminal pathway and the involvement of both peripheral and central mechanisms, and the presence of calcitonin gene-related peptide (CGRP), a key mediator in migraine pathophysiology. CGRP is also involved in the pathophysiology of temporomandibular disorders (TMD) and their comorbidity with migraine and is also implicated in dental and periodontal pathology. Inflammatory and pathological processes of these structures and their trigeminal nociceptive pathways may influence the trigeminovascular system and consequently may exacerbate or even potentially trigger migraine.

Neuroimmune Signatures in Chronic Low Back Pain Subtypes.
Alshelh Z, Brusaferri L, Saha A, Morrissey E, Knight P, Kim M, Zhang Y, Hooker JM, Albrecht D, Torrado-Carvajal A, Placzek MS, Akeju O, Price J, Edwards RR, Lee J, Sclocco R, Catana C, Napadow V, Loggia ML.
Brain. 2022 Apr 29;145(3):1098-1110. doi: 10.1093/brain/awab336. PMID: 34528069; PMCID: PMC9128369.

We recently showed that patients with different chronic pain conditions (such as chronic low back pain, fibromyalgia, migraine and Gulf War illness) demonstrated elevated brain and/or spinal cord levels of the glial marker 18-kDa translocator protein (TSPO), which suggests that neuroinflammation might be a pervasive phenomenon observable across multiple aetiologically heterogeneous pain disorders. Interestingly, the spatial distribution of this neuroinflammatory signal appears to exhibit a degree of disease specificity (e.g. with respect to the involvement of the primary somatosensory cortex), suggesting that different pain conditions may exhibit distinct 'neuroinflammatory signatures'. To explore this hypothesis further, we tested whether neuroinflammatory signal can characterize putative aetiological subtypes of chronic low back pain patients based on clinical presentation. Specifically, we explored neuroinflammation in patients whose chronic low back pain either did or did not radiate to the leg (i.e. 'radicular' versus 'axial' back pain). Fifty-four patients with chronic low back pain, 26 with axial back pain [43.7 ± 16.6 years old (mean ± SD)] and 28 with radicular back pain (48.3 ± 13.2 years old), underwent PET/MRI with 11C-PBR28, a second-generation radioligand for TSPO. 11C-PBR28 signal was quantified using standardized uptake values ratio (validated against volume of distribution ratio; n = 23). Functional MRI data were collected simultaneously to the 11C-PBR28 data (i) to functionally localize the primary somatosensory cortex back and leg subregions; and (ii) to perform functional connectivity analyses (in order to investigate possible neurophysiological correlations of the neuroinflammatory signal). PET and functional MRI measures were compared across groups, cross-correlated with one another and with the severity of 'fibromyalgianess' (i.e. the degree of pain centralization, or 'nociplastic pain'). Furthermore, statistical mediation models were used to explore possible causal relationships between these three variables. For the primary somatosensory cortex representation of back/leg, 11C-PBR28 PET signal and functional connectivity to the thalamus were: (i) higher in radicular compared to axial back pain patients; (ii) positively correlated with each other; (iii) positively correlated with fibromyalgianess scores, across groups; and finally (iv) fibromyalgianess mediated the association between 11C-PBR28 PET signal and primary somatosensory cortex-thalamus connectivity across groups. Our findings support the existence of 'neuroinflammatory signatures' that are accompanied by neurophysiological changes and correlate with clinical presentation (in particular, with the degree of nociplastic pain) in chronic pain patients. These signatures may contribute to the subtyping of distinct pain syndromes and also provide information about interindividual variability in neuroimmune brain signals, within diagnostic groups, that could eventually serve as targets for mechanism-based precision medicine approaches.

Transcriptional and Cellular Signatures of Cortical Morphometric Remodeling in Chronic Pain.
Martins D, Dipasquale O, Veronese M, Turkheimer F, Loggia ML, McMahon S, Howard MA, Williams SCR.

Pain. 2022 Jun 1;163(6):e759-e773. doi: 10.1097/j.pain.0000000000002480. Epub 2021 Sep 23. PMID: 34561394; PMCID: PMC8940732.

Chronic pain is a highly debilitating and difficult to treat condition, which affects the structure of the brain. Although the development of chronic pain is moderately heritable, how disease-related alterations at the microscopic genetic architecture drive macroscopic brain abnormalities is currently largely unknown. Here, we examined alterations in morphometric similarity (MS) and applied an integrative imaging transcriptomics approach to identify transcriptional and cellular correlates of these MS changes, in 3 independent small cohorts of patients with distinct chronic pain syndromes (knee osteoarthritis, low back pain, and fibromyalgia) and age-matched and sex-matched pain-free controls. We uncover a novel pattern of cortical MS remodeling involving mostly small-to-medium MS increases in the insula and limbic cortex (none of these changes survived stringent false discovery rate correction for the number of regions tested). This pattern of changes is different from that observed in patients with major depression and cuts across the boundaries of specific pain syndromes. By leveraging transcriptomic data from Allen Human Brain Atlas, we show that cortical MS remodeling in chronic pain spatially correlates with the brain-wide expression of genes related to pain and broadly involved in the glial immune response and neuronal plasticity. Our findings bridge levels to connect genes, cell classes, and biological pathways to in vivo imaging correlates of chronic pain. Although correlational, our data suggest that cortical remodelling in chronic pain might be shaped by multiple elements of the cellular architecture of the brain and identifies several pathways that could be prioritized in future genetic association or drug development studies.

A Distinctive Profile of Family Genetic Risk Scores in a Swedish National Sample of Cases of Fibromyalgia, Irritable Bowel Syndrome, and Chronic Fatigue Syndrome Compared to Rheumatoid Arthritis and Major Depression.

Kendler KS, Rosmalen JGM, Ohlsson H, Sundquist J, Sundquist K.
Psychol Med. 2022 Mar 31:1-8. doi: 10.1017/S0033291722000526. Epub ahead of print. PMID: 35354508.

BACKGROUND: Functional somatic disorders (FSD) feature medical symptoms of unclear etiology. Attempts to clarify their origin have been hampered by a lack of rigorous research designs. We sought to clarify the etiology of the FSD by examining the genetic risk patterns for FSD and other related disorders. METHODS: This study was performed in 5 829 186 individuals from Swedish national registers. We quantified familial genetic risk for FSD, internalizing disorders, and somatic disorders in cases of chronic fatigue syndrome (CFS), fibromyalgia (FM), and irritable bowel syndrome (IBS), using a novel method based on aggregate risk in first to fifth degree relatives, adjusting for cohabitation. We compared these profiles with those of a prototypic internalizing psychiatric - major depression (MD) - and a somatic/autoimmune disorder: rheumatoid arthritis (RA). RESULTS: Patients with FM carry substantial genetic risks not only for FM, but also for pain syndromes and internalizing, autoimmune and sleep disorders. The genetic risk profiles for IBS and CFS are also widely distributed although with lower average risks. By contrast, genetic risk profiles of MD and RA are much more restricted to related conditions. CONCLUSION: Patients with FM have a relatively unique family genetic risk score profile with elevated genetic risk across a range of disorders that differs markedly from the profiles of a classic autoimmune disorder (RA) and internalizing disorder (MD). A similar less marked pattern of genetic risks was seen for IBS and CFS. FSD arise from a distinctive pattern of genetic liability for a diversity of psychiatric, autoimmune, pain, sleep, and functional somatic disorders.

Genetic Overlap Analysis of Endometriosis and Asthma Identifies Shared Loci Implicating Sex Hormones and Thyroid Signaling Pathways.

Adewuyi EO, Mehta D; International Endogene Consortium (IEC); 23andMe Research Team, Nyholt DR.
Hum Reprod. 2022 Jan 28;37(2):366-383. doi: 10.1093/humrep/deab254. PMID: 35472084; PMCID: PMC8804329.

STUDY QUESTION: Is there a shared genetic or causal association of endometriosis with asthma or what biological mechanisms may underlie their potential relationships? SUMMARY ANSWER: Our results confirm a significant but non-causal association of endometriosis with asthma implicating shared genetic susceptibility and biological pathways in the mechanisms of the disorders, and potentially, their co-occurrence. WHAT IS KNOWN ALREADY: Some observational studies have reported a pattern of co-occurring relationship between endometriosis and asthma; however, there is conflicting evidence and the aetiology, as well

as the underlying mechanisms of the relationship, remain unclear. STUDY DESIGN, SIZE, DURATION: We applied multiple statistical genetic approaches in the analysis of well-powered, genome-wide association study (GWAS) summary data to comprehensively assess the relationship of endometriosis with asthma. Endometriosis GWAS from the International Endogene Consortium (IEC, 17 054 cases and 191 858 controls) and asthma GWAS from the United Kingdom Biobank (UKB, 26 332 cases and 375 505 controls) were analysed. Additional asthma data from the Trans-National Asthma Genetic Consortium (TAGC, 19 954 cases and 107 715 controls) were utilized for replication testing. PARTICIPANTS/MATERIALS, SETTING, METHODS: We assessed single-nucleotide polymorphism (SNP)-level genetic overlap and correlation between endometriosis and asthma using SNP effect concordance analysis (SECA) and linkage disequilibrium score regression analysis (LDSC) methods, respectively. GWAS meta-analysis, colocalization (GWAS-PW), gene-based and pathway-based functional enrichment analysis methods were applied, respectively, to identify SNP loci, genomic regions, genes and biological pathways shared by endometriosis and asthma. Potential causal associations between endometriosis and asthma were assessed using Mendelian randomization (MR) methods. MAIN RESULTS AND THE ROLE OF CHANCE: SECA revealed significant concordance of SNP risk effects across the IEC endometriosis and the UKB asthma GWAS. Also, LDSC analysis found a positive and significant genetic correlation (rG = 0.16, P = 2.01 × 10-6) between the two traits. GWAS meta-analysis of the IEC endometriosis and UKB asthma GWAS identified 14 genome-wide significant (Pmeta-analysis < 5.0 × 10-8) independent loci, five of which are putatively novel. Three of these loci were consistently replicated using TAGC asthma GWAS and reinforced in colocalization and gene-based analyses. Additional shared genomic regions were identified in the colocalization analysis. MR found no evidence of a significant causal association between endometriosis and asthma. However, combining gene-based association results across the GWAS for endometriosis and asthma, we identified 17 shared genes with a genome-wide significant Fisher's combined P-value (FCPgene) <2.73 × 10-6. Additional analyses (independent gene-based analysis) replicated evidence of gene-level genetic overlap between endometriosis and asthma. Biological mechanisms including 'thyroid hormone signalling', 'abnormality of immune system physiology', 'androgen biosynthetic process' and 'brain-derived neurotrophic factor signalling pathway', among others, were significantly enriched for endometriosis and asthma in a pathway-based analysis. LARGE SCALE DATA: The GWAS for endometriosis data were sourced from the International Endogen Consortium (IEC) and can be accessed by contacting the consortium. The GWAS data for asthma are freely available online at Lee Lab (https://www.leelabsg.org/resources) and from the Trans-National Asthma Genetic Consortium (TAGC). LIMITATIONS, REASONS FOR CAUTION: Given we analysed GWAS datasets from mainly European populations, our results may not be generalizable to other ancestries. WIDER IMPLICATIONS OF THE FINDINGS: This study provides novel insights into mechanisms underpinning endometriosis and asthma, and potentially their observed relationship. Findings support a co-occurring relationship of endometriosis with asthma largely due to shared genetic components. Agents targeting 'selective androgen receptor modulators' may be therapeutically relevant in both disorders. Moreover, SNPs, loci, genes and biological pathways identified in our study provide potential targets for further investigation in endometriosis and asthma.

Spatial Transcriptomics of Dorsal Root Ganglia Identifies Molecular Signatures of Human Nociceptors.

Tavares-Ferreira D, Shiers S, Ray PR, Wangzhou A, Jeevakumar V, Sankaranarayanan I, Cervantes AM, Reese JC, Chamessian A, Copits BA, Dougherty PM, Gereau RW 4th, Burton MD, Dussor G, Price TJ.

Sci Transl Med. 2022 Feb 16;14(632):eabj8186. doi: 10.1126/scitranslmed.abj8186. Epub 2022 Feb 16. PMID: 35171654; PMCID: PMC9272153.

Nociceptors are specialized sensory neurons that detect damaging or potentially damaging stimuli and are found in the dorsal root ganglia (DRG) and trigeminal ganglia. These neurons are critical for the generation of neuronal signals that ultimately create the perception of pain. Nociceptors are also primary targets for treating acute and chronic pain. Single-cell transcriptomics on mouse nociceptors has transformed our understanding of pain mechanisms. We sought to generate equivalent information for human nociceptors with the goal of identifying transcriptomic signatures of nociceptors, identifying species differences and potential drug targets. We used spatial transcriptomics to molecularly characterize transcriptomes of single DRG neurons from eight organ donors. We identified 12 clusters of human sensory neurons, 5 of which are C nociceptors, as well as 1 C low-threshold mechanoreceptors (LTMRs), 1 Aβ nociceptor, 2 Aδ, 2 Aβ, and 1 proprioceptor subtypes. By

focusing on expression profiles for ion channels, G protein-coupled receptors (GPCRs), and other pharmacological targets, we provided a rich map of potential drug targets in the human DRG with direct comparison to mouse sensory neuron transcriptomes. We also compared human DRG neuronal subtypes to nonhuman primates showing conserved patterns of gene expression among many cell types but divergence among specific nociceptor subsets. Last, we identified sex differences in human DRG subpopulation transcriptomes, including a marked increase in calcitonin-related polypeptide alpha (CALCA) expression in female pruritogen receptor-enriched nociceptors. This comprehensive spatial characterization of human nociceptors might open the door to development of better treatments for acute and chronic pain disorders.

Irritable Bowel Syndrome and Basal Serum Tryptase: Correlation between Subtype, Severity, and Comorbidities. A Pilot Study.

Ciriza de Los Ríos C, Castel de Lucas I, Canga Rodríguez-Valcárcel F, Diéguez Pastor MDC, de Las Cuevas Moreno N, Rey Díaz-Rubio E.

Rev Esp Enferm Dig. 2022 Jan;114(1):22-27. doi: 10.17235/reed.2021.7697/2020. PMID: 33562988.

INTRODUCTION: the activation of mast cells causes alterations in epithelial and neuromuscular function and is involved in visceral hypersensitivity and dysmotility in gastrointestinal functional disorders. OBJECTIVES: primary: to evaluate differences in basal serum tryptase (BST) between patients with irritable bowel syndrome (IBS) and healthy controls. Secondary: BST depending on IBS subtype (diarrhea: IBS-D; constipation: IBS-C), comorbidities and correlation with IBS severity and quality of life. MATERIAL AND METHODS: a prospective control-case study in IBS patients (Rome IV criteria). BST (ImmunoCAP-Phadia, Sweden®), IBS Severity Score (IBSSS), pain, bloating and flatulence analogue scales, IBS quality of life (IBSQOL), and patient health status (PHQ-9) were determined. BST is the primary variable to achieve the primary endpoint. RESULTS: thirty-two patients were included, 21 (65.6 %) with IBS-D and 11 (34.4 %) with IBS-C; 32 controls were also included. Mean IBSSSS: 326.6 (± 71.4), IBSQOL: 76 (± 20.3), and PHQ9: 10.2 (± 5.9). BST was 4.8 ± 2.6 in IBS and 4.7 ± 2.6 in controls (p = 0.875). There were no differences in BST between IBS subtypes (4.7 ± 2.9 in IBS-D and 5 ± 1.8 in IBS-C; p = 0.315) or IBS severity (p = 0.662). However, BST was higher in patients with IBS and extraintestinal comorbidities compared to other patients and controls (p = 0.029). This subgroup also has more severe bloating (p = 0.021). There was no correlation between BST, quality of life (p = 0.9260), and health status (p = 0.3985). CONCLUSION: BST does not discriminate between IBS patients and controls. However, BST was higher in patients with IBS with extraintestinal comorbidities, which had more severe bloating. This finding is worthy of investigation.

Multisensory Sensitivity Differentiates between Multiple Chronic Pain Conditions and Pain-Free Individuals.

Wang D, Frey-Law LA.

Pain. 2022 May 19. doi: 10.1097/j.pain.0000000000002696. Epub ahead of print. PMID: 35588150.

Multisensory sensitivity (MSS) to non-painful stimuli has been identified as a risk factor for the presence of coexisting chronic pain conditions (COPCs). However, it remains unclear whether MSS can differentiate pain phenotypes involving different levels of central sensitivity. Both pain-free and those with chronic pain, particularly fibromyalgia (FM), migraine or low back pain (LBP) were recruited, with pain co-morbidities assessed. MSS was highest in FM, followed by migraine, then LBP, and lowest in pain-free individuals (adjusted between condition Cohen's d = 0.32 - 1.2, p ≤ 0.0007). However, when secondly grouping patients by total number of pain comorbidities reported, those with a single pain condition (but not FM) did not have significantly elevated MSS versus pain-free individuals (adj d= 0.17, p = 0.18). Elevated MSS scores produced increased odds of having 2 or more pain comorbidities; OR [95%CI] =2.0 [1.15, 3.42] without, and 5.6 [2.74, 11.28], with FM (p ≤ 0.0001). Further, those with low MSS levels were 55% - 87% less likely to have ≥ 2 pain comorbidities with or without FM (OR 0.45 [0.22, 0.88] to 0.13 [0.05, 0.39]; p ≤ 0.0001). Our findings support that MSS can differentiate between pain phenotypes with different degrees of expected central mechanism involvement, and also serves as a risk and resilience marker for total COPCs. This supports the use of MSS as a marker of heightened central nervous system processing, and thus may serve as a clinically feasible assessment to better profile pain phenotypes with the goal of improving personalized treatment.

Sex Differences in Pain Along the Neuraxis.

Presto P, Mazzitelli M, Junell R, Griffin Z, Neugebauer V.
Neuropharmacology. 2022 Jun 1;210:109030. doi: 10.1016/j.neuropharm.2022.109030. Epub 2022 Mar 21. PMID: 35331712; PMCID: PMC9354808.

Despite the overwhelming female-predominance in chronic pain disorders, preclinical pain studies have historically excluded females as research subjects. Male-biased explanations of pathological pain mechanisms may not fully translate to pain processes in females, necessitating the exploration of pain processing and modulation in both sexes at the preclinical and clinical levels. This review highlights historical trends in the study of sex differences within the pain field and examines the current literature regarding new techniques for the mechanistic analysis of pain modulation in males and females. A large body of evidence suggests that sex differences exist at the molecular, cellular, and systems levels of pain processing, likely influenced by a combination of genetic, hormonal, and neuroimmune factors that may differ at distinct levels of the neuraxis.

Sensory Thresholds and Peripheral Nerve Responses in Chronic Tension-Type Headache and Neuropsychological Correlation.
Romero-Godoy R, Romero-Godoy SR, Romero-Acebal M, Gutiérrez-Bedmar M.
J Clin Med. 2022 Mar 29;11(7):1905. doi: 10.3390/jcm11071905. PMID: 35407512; PMCID: PMC8999240.

Chronic tension-type headache (CTTH) is a common disease with no fully defined pathophysiological processes. We designed a study to value electrophysiological responses in these patients and their correlation with possible psychopathological manifestations in order to deepen understanding of central and peripheral mechanisms of CTTH. In 40 patients with CTTH and 40 healthy controls, we used electrical stimulation to determine sensory threshold (SPT) and pain perception threshold (PPT) and the characteristics of the electrophysiological sensory nerve action potential (SNAP): initial sensory response (ISR) and supramaximal response (SMR). We then calculated the intensity differences between thresholds (IDT), namely SPT-PPT, ISR-SMR and SMR-PPT, and correlated these IDTs with psychological characteristics: trait and state anxiety, depression, and emotional regulation. The SPT, together with the ISR and SMR thresholds, were higher (p < 0.01) in CTTH patients. The SMR-PPT IDT was smaller and correlated with significantly higher indicators of depression, state and trait anxiety, and poorer cognitive reappraisal. CTTH patients have less capacity to recognize non-nociceptive sensory stimuli, greater tendency toward pain facilitation, and a poor central pain control requiring higher stimulation intensity thresholds to reach the start and the peak amplitude of the SNAP. This is consistent with relative hypoexcitability of the Aβ nerve fibers in distant regions from the site of pain, and therefore, it could be considered a generalized dysfunction with a focal expression. Pain facilitation is directly associated with psychological comorbidity.

Altered Metabolome and Microbiome Features Provide Clues in Understanding Irritable Bowel Syndrome and Depression Comorbidity.
Han L, Zhao L, Zhou Y, Yang C, Xiong T, Lu L, Deng Y, Luo W, Chen Y, Qiu Q, Shang X, Huang L, Mo Z, Huang S, Huang S, Liu Z, Yang W, Zhai L, Ning Z, Lin C, Huang T, Cheng C, Zhong LLD, Li S, Bian Z, Fang X.
ISME J. 2022 Apr;16(4):983-996. doi: 10.1038/s41396-021-01123-5. Epub 2021 Nov 8. PMID: 34750528; PMCID: PMC8940891.

Irritable bowel syndrome (IBS) is one of the functional gastrointestinal disorders characterized by chronic and/or recurrent symptoms of abdominal pain and irregular defecation. Changed gut microbiota has been proposed to mediate IBS; however, contradictory results exist, and IBS-specific microbiota, metabolites, and their interactions remain poorly understood. To address this issue, we performed metabolomic and metagenomic profiling of stool and serum samples based on discovery (n = 330) and validation (n = 101) cohorts. Fecal metagenomic data showed moderate dysbiosis compared with other diseases, in contrast, serum metabolites showed significant differences with greater power to distinguish IBS patients from healthy controls. Specifically, 726 differentially abundant serum metabolites were identified, including a cluster of fatty acyl-CoAs enriched in IBS. We further identified 522 robust associations between differentially abundant gut bacteria and fecal metabolites, of which three species including Odoribacter splanchnicus, Escherichia coli, and Ruminococcus gnavus were strongly associated with the low abundance of dihydropteroic acid. Moreover, dysregulated tryptophan/serotonin metabolism was found to be correlated with the severity of IBS depression in both fecal and serum metabolomes, characterized by a shift in tryptophan metabolism towards kynurenine production. Collectively, our study revealed serum/fecal

metabolome alterations and their relationship with gut microbiome, highlighted the massive alterations of serum metabolites, which empower to recognize IBS patients, suggested potential roles of metabolic dysregulation in IBS pathogenesis, and offered new clues to understand IBS depression comorbidity. Our study provided a valuable resource for future studies, and would facilitate potential clinical applications of IBS featured microbiota and/or metabolites.

Genetic Overlap between Temporomandibular Disorders and Primary Headaches: A Systematic Review.
Cruz D, Monteiro F, Paço M, Vaz-Silva M, Lemos C, Alves-Ferreira M, Pinho T.
Jpn Dent Sci Rev. 2022 Nov;58:69-88. doi: 10.1016/j.jdsr.2022.02.002. Epub 2022 Feb 23. PMID: 35242249; PMCID: PMC8881721.

Primary headache disorders (PHD), specifically migraine, are strongly associated with temporomandibular disorders (TMD), sharing some patterns of orofacial pain. Both disorders have significant genetic contributions already studied. PRISMA guidelines were followed to conduct this systematic review, which comprehensively summarize and discuss the genetic overlap between TMD and PHD to aid future research in potential therapy targets. This review included eight original articles published between 2015 and 2020, written in English and related to either TMD and/or PHD. The genes simultaneously assessed in PHD and TMD studies were COMT, MTHFR, and ESR1. COMT was proved to play a critical role in TMD pathogenesis, as all studies have concluded about its impact on the occurrence of the disease, although no association with PHD was found. No proof on the impact of MTHFR gene regulation on either TMD or PHD was found. The most robust results are concerning the ESR1 gene, which is present in the genetic profile of both clinical conditions. This novel systematic review highlights not only the need for a clear understanding of the role of ESR1 and COMT genes in pain pathogenesis, but it also evaluates their potential as a promising therapeutic target to treat both pathologies.

Identifying Functional Brain Abnormalities in Migraine and Depression Comorbidity.
Yang Y, Wei K, Zhang H, Hu H, Yan L, Gui W, Liu Y, Chen X.
Quant Imaging Med Surg. 2022 Apr;12(4):2288-2302. doi: 10.21037/qims-21-667. PMID: 35371950; PMCID: PMC8923836.

BACKGROUND: Migraine and major depressive disorder (MDD) are both highly prevalent brain disorders and are often comorbid. However, the common and distinctive neural mechanisms underlying these disorders and the brain function alterations associated with their comorbidity are largely unknown. We aimed to explore the functional abnormalities of the brain associated with the co-occurrence of migraine and depression. METHODS: High-resolution T1-weighted and resting-state functional magnetic resonance images (MRI) were acquired from 93 well-matched patients with comorbid migraine and depression, patients with migraine, patients with MDD, and healthy controls. Voxel-wise analysis of variance (ANOVA) and a two-sample t-test of multiple functional variables were performed among the groups. Furthermore, correlation analysis was conducted to detect the clinical significance of the altered functional regions in the brain. RESULTS: Migraine patients with and without depression revealed widely shared regional networks of functional changes. Brain function changes in the right paracentral lobule and fusiform were specific to patients with comorbid migraine and depression [$P<0.05$, cluster-level familywise error (FWE)-corrected], while changes in the left thalamus, medial orbital of superior frontal gyrus and triangular part of the inferior frontal gyrus were specific to patients with migraine ($P<0.05$, cluster-level FWE-corrected). Importantly, the brain activity of the right paracentral lobule, left calcarine, and left dorsolateral superior frontal gyrus was associated with emotional symptoms in the pooled migraine data ($P<0.05$). CONCLUSIONS: These findings help to identify the neural correlates underlying patients with migraine and those with comorbid migraine and depression. These shared and distinct brain changes could be used as potential image markers to decipher the comorbidity of the 2 disorders.

In Schizophrenia, Chronic Fatigue Syndrome- and Fibromyalgia-Like Symptoms are Driven by Breakdown of the Paracellular Pathway with Increased Zonulin and Immune Activation-Associated Neurotoxicity.
Maes M, Andrés-Rodríguez L, Vojdani A, Sirivichayakul S, Barbosa DS, Kanchanatawan B.
CNS Neurol Disord Drug Targets. 2022 Aug 6. doi: 10.2174/1871527321666220806100600. Epub ahead of print. PMID: 35946099.

Background: A meaningful part of schizophrenia patients suffer from physiosomatic

symptoms (formerly named psychosomatic) which are reminiscent of chronic fatigue syndrome and fibromyalgia (FF) and are associated with signs of immune activation and increased levels of tryptophan catabolites (TRYCATs). Aims: To examine whether FF symptoms in schizophrenia are associated with breakdown of the paracellular pathway, zonulin, lowered natural IgM responses to oxidative specific epitopes (OSEs); and whether FF symptoms belong to the behavioral-cognitive-physical-psychosocial-(BCPS)-worsening index consisting of indices of a general cognitive decline (G-CoDe), symptomatome of schizophrenia, and quality of life (QoL)-phenomenome. Methods: FF symptoms were assessed using the Fibromyalgia and Chronic Fatigue Rating scale in 80 schizophrenia patients and 40 healthy controls and serum cytokines/chemokines, IgA levels to TRYCATs, IgM to OSEs, zonulin and transcellular/paracellular (TRANS/PARA) molecules were assayed using ELISA methods. Results: A large part (42.3%) of the variance in the total FF score was explained by the regression on the PARA/TRANS ratio, pro-inflammatory cytokines, IgM to zonulin, IgA to TRYCATs (all positively) and IgM to OSEs (inversely). There were highly significant correlations between the total FF score and G-CoDe, symtopmatome, QoL phenomenome and BCPS-worsening score. FF symptoms belong to a common core shared by G-CoDe, symtopmatome, and QoL phenomenome. Discussion: The physio-somatic symptoms of schizophrenia are driven by various pathways including increased zonulin, breakdown of the paracellular tight-junctions pathway, immune activation with induction of the TRYCAT pathway, and consequent neurotoxicity. It is concluded that FF symptoms are part of the phenome of schizophrenia and BCPS-worsening as well.

The Gut Microbiota: A Double Edge Sword in Endometriosis.
Talwar C, Singh V, Kommagani R.
Biol Reprod. 2022 Jul 25:ioac147. doi: 10.1093/biolre/ioac147. Epub ahead of print. PMID: 35878972.

Endometriosis that afflicts 1 in 10 women of reproductive age is characterized by growth of endometrial tissue in the extra-uterine sites and encompasses metabolic-, immunologic- and endocrine-disruption. Importantly, several comorbidities are associated with endometriosis, especially autoimmune disorders such as inflammatory bowel disease. Primarily thought of as a condition arising from retrograde menstruation, emerging evidence uncovered a functional link between the gut microbiota and endometriosis. Specifically, recent findings revealed altered gut microbiota profiles in endometriosis and in turn this altered microbiota appears to be causal in the disease progression, implying a bi-directional crosstalk. In this review, we discuss the complex etiology and pathogenesis of endometriosis emphasizing on this recently recognized role of gut microbiome. We review the gut microbiome structure and functions and its complex network of interactions with the host for maintenance of homeostasis that is crucial for disease prevention. We highlight the underlying mechanisms on how some bacteria promotes disease progression and others protects against endometriosis. Further, we highlight the areas that require future emphases in the gut microbiome-endometriosis nexus and the potential microbiome-based therapies for amelioration of endometriosis.

Ectopic Endometriosis in the Pelvic Cavity Evokes Bladder Hypersensitivity via Transient Receptor Potential Ankyrin 1 Hyperexpression in Rats.
Hayashi N, Kawamorita N, Ishizuka Y, Kimura S, Satake Y, Ito A.
Int Urogynecol J. 2022 Aug 30. doi: 10.1007/s00192-022-05335-x. Epub ahead of print. PMID: 36040506.

Introduction and hypothesis: In women with chronic pelvic pain (CPP), interstitial cystitis/bladder pain syndrome (IC/BPS) and endometriosis frequently coexist. The mechanism of these diseases coexisting is explained by cross-sensitization between endometriosis and IC/BPS. The overlapped symptoms may be related to cross-sensitization with transient receptor potential vanilloid 1 (TRPV1) and/or transient receptor potential ankyrin 1 (TRPA1) hyperexpression. This study was aimed at exploring whether bladder hypersensitivity is evoked in the surgically induced ectopic endometriosis rat and whether TRPV1 and/or TRPA1 play a vital role. Methods: A total of 63 Sprague-Dawley female rats were divided into two groups, 39 for physiological examination and 24 for molecular analysis. Surgical induction of ectopic endometriosis (ENDO, n=27), surgical sham treatment (n=18), and treatment for endometriosis by GnRH analog (ENDO-G) (n=18) were performed. Bladder function was investigated by cystometry (for TRPV1 in the sham [n=6] and ENDO [n=9] groups and for TRPA1 in the sham [n=6], ENDO [n=9], and ENDO+G [n=9] groups), and TRPV1 and TRPA1 mRNA expressions were measured using real-time qPCR in the bladder and dorsal root ganglia (DRGs). Results: On cystometry, the relative intercontraction interval

(ICI) after/before resiniferatoxin (RTx; TRPV1 activator) infusion to the bladder showed no significant difference between the two groups, whereas relative ICI after/before allyl isothiocyanate (AITC; TRPA1 activator) infusion was significantly lower in the ENDO group than in the sham group. TRPA1 mRNA expression in the bladder and L5 DRG was considerably higher in the ENDO group than in the sham group on real-time qPCR. TRPA1 mRNA hyperexpression and bladder hypersensitivity after AITC infusion were reduced in the ENDO-G group. Conclusions: Bladder cross-sensitization in ENDO rats occurs in association with hyperexpression of TRPA1 at both the DRG and the bladder mucosa. This can be understood by the "cross-sensitization of endometriosis to bladder" theory explaining overlapping symptoms among BPS/IC and ectopic endometriosis.

Sex Differences in the Amygdaloid Projections to the Ventrolateral Periaqueductal Gray and their Activation during Inflammatory Pain in the Rat.
Cantu DJ, Kaur S, Murphy AZ, Averitt DL.
J Chem Neuroanat. 2022 Oct;124:102123. doi: 10.1016/j.jchemneu.2022.102123. Epub 2022 Jun 20. PMID: 35738454.

Preclinical and clinical studies have reported sex differences in pain and analgesia. These differences may be linked to anatomical structures of the central nervous system pain modulatory circuitry, and/or hormonal milieu. The midbrain periaqueductal gray (PAG) is a critical brain region for descending inhibition of pain. The PAG projects to the rostral ventromedial medulla (RVM), which projects bilaterally to the spinal cord to inhibit pain. In addition to pain, this descending circuit (or pathway) can be engaged by endogenous opioids (i.e., endorphins) or exogenous opioids (i.e., morphine), and we have previously reported sex differences in the activation of this circuit during pain and analgesia. Forebrain structures, including the amygdala, project to and engage the PAG-RVM circuit during persistent inflammatory pain. However, there are limited studies in females detailing this amygdalar-PAG pathway and its involvement during persistent inflammatory pain. The objective of the present study was to delineate the neural projections from the amygdala to the PAG in male and female rats to determine if they are sexually distinct in their anatomical organization. We also examined the activation of this pathway by inflammatory pain and the co-localization of receptors for estrogen. Injection of the retrograde tracer fluorogold (FG) into the ventrolateral PAG (vlPAG) resulted in dense retrograde labeling in both the central amygdala (CeA) and medial amygdala (MeA). While the number of CeA-vlPAG neurons were comparable between the sexes, there were more MeA-vlPAG neurons in females. Inflammatory pain resulted in greater activation of the amygdala in males; however, females displayed higher Fos expression within CeA-vlPAG projection neurons. Females expressed higher ERα in the MeA and CeA and the same was true of the projection neurons. Together, these data indicate that although the MeA-vlPAG projections are denser in females, inflammatory pain does not significantly activate these projections. In contrast, inflammatory pain resulted in a greater activation of the CeA-vlPAG pathway in females. As females experience a greater number of chronic pain syndromes, the CeA-vlPAG pathway may play a facilitatory (and not inhibitory) role in pain modulation.

Sex-Specific Characteristics of Cells Expressing the Cannabinoid 1 Receptor in the Dorsal Horn of the Lumbar Spinal Cord.
Zhang Y, Ke J, Zhou Y, Liu X, Huang T, Wang F.
J Comp Neurol. 2022 Oct;530(14):2451-2473. doi: 10.1002/cne.25342. Epub 2022 May 17. PMID: 35580011.

It is becoming increasingly clear that robust sex differences exist in the processing of acute and chronic pain in both rodents and humans. However, the underlying mechanism has not been well characterized. The dorsal horn of the lumbar spinal cord is the fundamental building block of ascending and descending pain pathways. It has been shown that numerous neurotransmitter and neuromodulator systems in the spinal cord, including the endocannabinoid system and its main receptor, the cannabinoid 1 receptor (CB_1 R), play vital roles in processing nociceptive information. Our previous findings have shown that CB_1 R mRNA is widely expressed in the brain in sex-dependent patterns. However, the sex-, lamina-, and cell-type-specific characteristics of CB_1 R expression in the spinal cord have not been fully described. In this study, the CB_1 R-iCre-EGFP mouse strain was generated to label and identify CB_1 R-positive (CB_1 R^{GFP}) cells. We reported no sex difference in CB_1 R expression in the lumbar dorsal horn of the spinal cord, but a dynamic distribution within superficial laminae II and III in female mice between estrus and nonestrus phases. Furthermore, the cell-type-specific CB_1 R expression pattern in the dorsal horn was similar in

both sexes. Over 50% of CB_1 R^{GFP} cells were GABAergic neurons, and approximately 25% were glycinergic and 20-30% were glutamatergic neurons. The CB_1 R-expressing cells also represented a subset of spinal projection neurons. Overall, our work indicates a highly consistent distribution pattern of CB_1 R^{GFP} cells in the dorsal horn of lumbar spinal cord in males and females.

Upregulation of P2X3 Receptors in Primary Afferent Pathways Involved in Colon-to-Bladder Cross-sensitization in Rats.
Dong X, Yang Y, Luo S, Deng X, Tang W.
Front Physiol. 2022 Sep 8;13:920044. doi: 10.3389/fphys.2022.920044. PMID: 36160872; PMCID: PMC9493003.

Background: Clinical investigation indicates a high level of co-morbidity between bladder overactivity and irritable bowel syndrome. The cross-sensitization of afferent pathways has been demonstrated to be the main reason for the cross-organ sensitization, but the underlying mechanism is unclear. Methods: A single dose of 2, 4, 6-trinitrobenzene sulfonic acid (TNBS) was applied to induce the colitis rat models by intracolonic administration. All rats were randomly divided into three groups: control, TNBS-3-day, and TNBS-7-day groups. Western blot and immunofluorescent staining were performed to detect the expression of the P2X3 receptor. The spontaneous contractions of the detrusor strip were measured to evaluate the detrusor contractility function. The micturition function was measured by a cystometry experiment. The intercontractile interval (ICI) and maximum bladder pressure (BP) were recorded. Results: The distal colon from colitis showed serious tissue damage or chronic inflammation after TNBS instillation ($p < 0.01$). However, there were no detectable histological changes in bladder among groups ($p > 0.05$). TNBS-induced colitis significantly increased P2X3 receptor expression on the myenteric and submucosal plexus of the distal colon and urothelium of the bladder, especially at day 3 post-TNBS ($p < 0.05$). Meanwhile, the expression of the P2X3 receptor on DRG neurons was increased in TNBS-induced colitis ($p < 0.01$). The detrusor strip of rats exhibited detrusor overactivity after days 3 and 7 of TNBS administration ($p < 0.01$), but inhibition of the P2X3 receptor had no effect ($p > 0.05$). Moreover, the rats with colitis exhibited the micturition pattern of bladder overactivity, manifested by decreased ICI and increased maximum BP ($p < 0.05$). Interestingly, inhibition of the P2X3 receptor by intrathecal injection of A-317491 alleviated bladder overactivity evoked by TNBS-induced colitis ($p < 0.05$). Conclusion: The upregulation of the P2X3 receptor in an afferent pathway involved in bladder overactivity evoked by TNBS-induced colonic inflammation, suggesting that the P2X3 receptor antagonist may be an available and novel strategy for the control of bladder overactivity.

A Syngeneic Inoculation Mouse Model of Endometriosis that Develops Multiple Comorbid Visceral and Cutaneous Pain Like Behaviours.
Maddern J, Grundy L, Harrington A, Schober G, Castro J, Brierley SM.
Pain. 2022 Aug 1;163(8):1622-1635. doi: 10.1097/j.pain.0000000000002552. Epub 2021 Dec 15. PMID: 35050959.

Endometriosis is a chronic and debilitating condition, commonly characterised by chronic pelvic pain (CPP) and infertility. Chronic pelvic pain can be experienced across multiple pelvic organs, with comorbidities commonly effecting the bowel, bladder, and vagina. Despite research efforts into endometriosis pathophysiology, little is known about how endometriosis induces CPP, and as such, therapeutic interventions are lacking. The aim of this study was to characterise a syngeneic mouse model of endometriosis that mimics naturally occurring retrograde menstruation, thought to precede endometriosis development in patients, and determine whether these mice exhibit signs of CPP and altered behaviour. We characterised the development of endometriosis over 10 weeks following uterine tissue inoculation, measured in vivo and ex vivo hypersensitivity to mechanical stimuli across multiple visceral organs, and assessed alterations in animal spontaneous behaviour. We confirmed that inoculated uterine horn tissue formed into endometriosis lesions throughout the peritoneal cavity, with significant growth by 8 to 10 weeks post inoculation. Additionally, we found that mice with fully developed endometriosis displayed hypersensitivity evoked by (1) vaginal distension, (2) colorectal distension, (3) bladder distension, and (4) cutaneous thermal stimulation, compared to their sham counterparts. Moreover, endometriosis mice displayed alterations in spontaneous behaviour indicative of (5) altered bladder function and (6) anxiety. This model creates a foundation for mechanistical studies into the diffuse CPP associated with endometriosis and the development of targeted therapeutic interventions to improve the quality of life of women with endometriosis.

Oxytocin Inhibits Hindpaw Hyperalgesia Induced by Orofacial Inflammation Combined with Stress.
Li YX, Li JH, Guo Y, Tao ZY, Qin SH, Traub RJ, An H, Cao DY.
Mol Pain. 2022 Jan-Dec;18:17448069221089591. doi: 10.1177/17448069221089591. PMID: 35266833; PMCID: PMC9047792.

Oxytocin (OT) is recognized as a critical neuropeptide in pain-related disorders. Chronic pain caused by the comorbidity of temporomandibular disorder (TMD) and fibromyalgia syndrome (FMS) is common, but whether OT plays an analgesic role in the comorbidity of TMD and FMS is unknown. Female rats with masseter muscle inflammation combined with 3-day forced swim (FS) stress developed somatic hypersensitivity, which modeled the comorbidity of TMD and FMS. Using this model, the effects of spinal OT administration on mechanical allodynia and thermal hyperalgesia in hindpaws were examined. Furthermore, the protein levels of OT receptors and 5-HT2A receptors in the L4-L5 spinal dorsal horn were analyzed by Western blot. The OT receptor antagonist atosiban and 5-HT2A receptor antagonist ritanserin were intrathecally injected prior to OT injection in the separate groups. Intrathecal injection of 0.125 μg and 0.5 μg OT attenuated the hindpaw hyperalgesia. The expression of OT receptors and 5-HT2A receptors in the L4-L5 spinal dorsal horn significantly increased following intrathecal injection of 0.5 μg OT. Intrathecal administration of either the OT receptor antagonist atosiban or 5-HT2A receptor antagonist ritanserin blocked the analgesic effect of OT. These results suggest that OT may inhibit hindpaw hyperalgesia evoked by orofacial inflammation combined with stress through OT receptors and/or 5-HT2A receptors, thus providing a therapeutic prospect for drugs targeting the OT system and for patients with comorbidity of TMD and FMS.

Kappa Opioid Receptor Blockade in the Amygdala Mitigates Pain Like-Behaviors by Inhibiting Corticotropin Releasing Factor Neurons in a Rat Model of Functional Pain.
Yakhnitsa V, Ji G, Hein M, Presto P, Griffin Z, Ponomareva O, Navratilova E, Porreca F, Neugebauer V.
Front Pharmacol. 2022 May 25;13:903978. doi: 10.3389/fphar.2022.903978. PMID: 35694266; PMCID: PMC9177060.

Functional pain syndromes (FPS) occur in the absence of identifiable tissue injury or noxious events and include conditions such as migraine, fibromyalgia, and others. Stressors are very common triggers of pain attacks in various FPS conditions. It has been recently demonstrated that kappa opioid receptors (KOR) in the central nucleus of amygdala (CeA) contribute to FPS conditions, but underlying mechanisms remain unclear. The CeA is rich in KOR and encompasses major output pathways involving extra-amygdalar projections of corticotropin releasing factor (CRF) expressing neurons. Here we tested the hypothesis that KOR blockade in the CeA in a rat model of FPS reduces pain-like and nocifensive behaviors by restoring inhibition of CeA-CRF neurons. Intra-CeA administration of a KOR antagonist (nor-BNI) decreased mechanical hypersensitivity and affective and anxiety-like behaviors in a stress-induced FPS model. In systems electrophysiology experiments in anesthetized rats, intra-CeA application of nor-BNI reduced spontaneous firing and responsiveness of CeA neurons to peripheral stimulation. In brain slice whole-cell patch-clamp recordings, nor-BNI increased feedforward inhibitory transmission evoked by optogenetic and electrical stimulation of parabrachial afferents, but had no effect on monosynaptic excitatory transmission. Nor-BNI decreased frequency, but not amplitude, of spontaneous inhibitory synaptic currents, suggesting a presynaptic action. Blocking KOR receptors in stress-induced FPS conditions may therefore represent a novel therapeutic strategy.

Sex Differences in Kappa Opioid Receptor Antinociception is Influenced by the Number of X Chromosomes in Mouse.
Taylor AMW, Chadwick CI, Mehrabani S, Hrncir H, Arnold AP, Evans CJ.
J Neurosci Res. 2022 Jan;100(1):183-190. doi: 10.1002/jnr.24704. Epub 2020 Jul 30. PMID: 32731302; PMCID: PMC8452150.

Kappa opioid receptor (KOR) agonists produce robust analgesia with minimal abuse liability and are considered promising pharmacological agents to manage chronic pain and itch. The KOR system is also notable for robust differences between the sexes, with females exhibiting lower analgesic response than males. Sexually dimorphic traits can be due to either the influence of gonadal hormones during development or adulthood, or due to the complement of genes expressed on the X or Y chromosome. Previous studies examining sex differences in KOR antinociception have relied on surgical or pharmacological manipulation of the gonads

to determine whether sex hormones influence KOR function. While there are conflicting reports whether gonadal hormones influence KOR function, no study has examined these effects in context with sex chromosomes. Here, we use two genetic mouse models, the four core genotypes and XY*, to isolate the chromosomal and hormonal contributions to sex differences in KOR analgesia. Mice were treated with systemic KOR agonist (U50,488H) and thermal analgesia measured in the tail withdrawal assay. We found that KOR antinociception was influenced predominantly by the number of the X chromosomes. These data suggest that the dose and/or parental imprint on X gene(s) contribute significantly to the sexually dimorphism in KOR analgesia.

Spinal CCK1 Receptors Contribute to Somatic Pain Hypersensitivity Induced by Malocclusion via a Reciprocal Neuron-Glial Signaling Cascade.
Xiang T, Li JH, Su HY, Bai KH, Wang S, Traub RJ, Cao DY.
J Pain. 2022 Oct;23(10):1629-1645. doi: 10.1016/j.jpain.2022.05.009. Epub 2022 Jun 10. PMID: 35691467; PMCID: PMC9560966.

Recent studies have shown that the incidence of chronic primary pain (CPP) including temporomandibular disorders (TMD) and fibromyalgia syndrome (FMS) often exhibit comorbidities. We recently reported that central sensitization and descending facilitation system contributed to the development of somatic pain hypersensitivity induced by orofacial inflammation combined with stress. The purpose of this study was to explore whether TMD caused by unilateral anterior crossbite (UAC) can induce somatic pain hypersensitivity, and whether the cholecystokinin (CCK) receptor-mediated descending facilitation system promotes hypersensitivity through neuron-glia cell cascade signaling. UAC evoked thermal and mechanical pain hypersensitivity of the hind paws from day 5 to 70 that peaked at week 4 post UAC. The expression levels of CCK1 receptors, IL-18 and IL-18 receptors (IL-18R) were significantly up-regulated in the L4-L5 spinal dorsal horn at 4 weeks post UAC. Intrathecal injection of CCK1 and IL-18 receptor antagonists blocked somatic pain hypersensitivity. IL-18 mainly co-localized with microglia, while IL-18R mainly co-localized with astrocytes and to a lesser extent with neurons. These findings indicate that the signaling transduction between neurons and glia at the spinal cord level contributes to the descending pain facilitation through CCK1 receptors during the development of the comorbidity of TMD and FMS. Perspective: CCK1 receptor-dependent descending facilitation may mediate central mechanisms underlying the development of widespread somatic pain via a reciprocal neuron-glial signaling cascade, providing novel therapeutic targets for the clinical treatment of TMD and FMS comorbidities.

Inhibition of CXCR4 in Spinal Cord and DRG with AMD3100 Attenuates Colon-Bladder Cross-Organ Sensitization.
Zhang H, Dong X, Yang Z, Zhao J, Lu Q, Zhu J, Li L, Yi S, Xu J.
Drug Des Devel Ther. 2022 Jan 6;16:67-81. doi: 10.2147/DDDT.S336242. PMID: 35023903; PMCID: PMC8747645.

BACKGROUND: Cross-sensitization of pelvic organs is one theory for why symptoms of gut sickness and interstitial cystitis/bladder pain syndrome overlap. Experimental colitis has been shown to trigger bladder hyperactivity and hyperalgesia in rats. The chemokine receptor CXCR4 plays a key role in bladder function and central sensitization. We aim to study the role of CXCR4 and its inhibitor AMD3100 in colon-bladder cross-organ sensitization. METHODS: The colitis model was established by rectal infusion of trinitrobenzene sulfonic acid. Western blot and immunofluorescence were used to assess the expression and distribution of CXCR4. Intrathecal injection of AMD3100 (a CXCR4 inhibitor) and PD98059 (an ERK inhibitor) were used to inhibit CXCR4 and downstream extracellular signal-regulated kinase (ERK) in the spinal cord and dorsal root ganglion (DRG). Intravesical perfusion of resiniferatoxin was performed to measure the pain behavior counts of rats, and continuous cystometry was performed to evaluate bladder voiding function. RESULTS: Compared to the control group, CXCR4 was expressed more in bladder mucosa and colon mucosa, L6-S1 dorsal root ganglion (DRG), and the corresponding segment of the spinal dorsal horn (SDH) in rats with colitis. Moreover, intrathecal injection of the AMD3100 suppressed bladder overactivity, bladder hyperalgesia, and mastocytosis symptoms caused by colitis. Furthermore, AMD3100 effectively inhibited ERK activation in the spinal cord induced by experimental colitis. Finally, treatment with PD98059 alleviated bladder overactivity and hyperalgesia caused by colitis. CONCLUSION: Increased CXCR4 in the DRG and SDH contributes to colon inflammation-induced bladder overactivity and hyperalgesia partly via the phosphorylation of spinal ERK. Treatment targeting the CXCR4/ERK pathway might provide a potential new approach for the

comorbidity between the digestive system and the urinary system.

SAHA Inhibits Somatic Hyperalgesia Induced by Stress Combined with Orofacial Inflammation Through Targeting Different Spinal 5-HT Receptor Subtypes.
Tao ZY, Qiu XY, Wei SQ, Bai G, Li JF, Cao DY.
Neurochem Res. 2022 May;47(5):1405-1418. doi: 10.1007/s11064-022-03540-0. Epub 2022 Jan 29. PMID: 35092569.

Epigenetic regulation of gene expression has been implicated in the development of chronic pain. However, little is known about whether this regulation is involved in the development and treatment of chronic pain comorbidities such as fibromyalgia syndrome (FMS) and temporomandibular disorder (TMD), a comorbidity predominantly occurring among women. Here we explored the impact of the histone deacetylase (HDAC) inhibitor suberoylanilide hydroxamic acid (SAHA) on somatic hyperalgesia induced by stress or stress combined with orofacial inflammation, which mimicked the comorbidity of FMS and TMD in rats. Our data showed that somatic thermal hyperalgesia and mechanical allodynia induced by both conditions were completely prevented by intrathecal injection of SAHA, which upregulated 5-HT2C receptors but downregulated 5-HT3 receptors in the spinal dorsal horn. Subsequent spinal administration of RS102221 to inhibit 5-HT2C receptors or SR57227 to activate 5-HT3 receptors reversed the analgesic effect of SAHA under both conditions. These results indicate that SAHA attenuates the pro-nociceptive effects of stress combined with orofacial inflammation and the effects of stress alone. This likely occurs through epigenetic regulation of spinal 5-HT2C and 5-HT3 receptor expression, suggesting that SAHA has potential therapeutic value in FMS or comorbid FMS-TMD patients with somatic hyperalgesia.

Clinical Studies

Clinical Phenotyping for Pain Mechanisms in Urologic Chronic Pelvic Pain Syndromes: A MAPP Research Network Study.
Schrepf A, Gallop R, Naliboff B, Harte SE, Afari N, Lai HH, Pontari M, McKernan LC, Strachan E, Kreder KJ, As-Sanie SA, Rodriguez LV, Griffith JW, Williams DA; Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network.
J Pain. 2022 Sep;23(9):1594-1603. doi: 10.1016/j.jpain.2022.03.240. Epub 2022 Apr 25. PMID: 35472518.

PERSPECTIVE: This article presents differences in clinical characteristics based on a simple self-report method of classifying pain mechanisms for Urologic Chronic Pelvic Pain Syndrome patients. This method can be easily applied to other chronic pain conditions and may be useful for exploring pathophysiology in pain subtypes. DISCLOSURES: Funding for the MAPP Research Network was obtained under a cooperative agreement from National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH) [DK082315 (Andriole, G; Lai, H), DK082316 (Landis, J), DK082325 (Buchwald, D), DK082333 (Lucia, M), DK082342 (Klumpp, D; Schaeffer A), DK082344 (Kreder, K), DK082345 (Clauw, D; Clemens, JQ), DK082370 (Mayer, E; Rodriguez L), DK103227 (Moses, M), DK103260 (Anger, J; Freeman, M), DK103271 (Nickel, J)]. Three categories of pain mechanisms are recognized as contributing to pain perception: nociceptive, neuropathic, and nociplastic (i.e., central nervous system augmented pain processing). We use validated questionnaires to identify pain mechanisms in Urologic Chronic Pelvic Pain Syndrome (UCCPS) patients (n=568, female=378, male= 190) taking part in the Symptom Patterns Study of the Multidisciplinary Approach to the study of chronic Pelvic Pain Research Network. A cutoff score of 12 on the painDETECT questionnaire (-1-38) was used to classify patients into the neuropathic category while the median score of 7 on the fibromyalgia survey criteria (0-31) was used to classify patients into the nociplastic category. Categories were compared on demographic, clinical, psychosocial, psychophysical and medication variables. At baseline, 43% of UCPPS patients were classified as nociceptive-only, 8% as neuropathic only, 27% as nociceptive+nociplastic, and 22% as neuropathic+nociplastic. Across outcomes nociceptive-only patients had the least severe symptoms and neuropathic+nociplastic patients the most severe. Neuropathic pain was associated with genital pain/sensitivity on pelvic exam, while nociplastic pain was associated with comorbid pain conditions, psychosocial difficulties, and increased pressure pain sensitivity outside the pelvis. A self-report method classifying individuals on pain mechanisms reveals clinical differences that could inform clinical trials and novel targets for treatment.

Reliability and Validity of Pain and Urinary Symptom Severity Assessment in Urological

Chronic Pelvic Pain: A MAPP Network Analysis.
Naliboff BD, Locke K Jr, Schrepf AD, Griffith JW, Moldwin R, Krieger JN, Rodriguez LV, Clemens JQ, Lai HH, Sutcliffe S, Taple BJ, Williams D, Pontari MA, Mullins C, Landis JR.
J Urol. 2022 Jun;207(6):1246-1255. doi: 10.1097/JU.0000000000002438. Epub 2022 Jan 21. PMID: 35060778.

PURPOSE: We assessed the reliability and validity of an efficient severity assessment for pelvic pain and urinary symptoms in urological chronic pelvic pain syndrome, which consists of interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome. MATERIALS AND METHODS: A total of 578 patients were assessed using brief, empirically derived self-report scales for pelvic pain severity (PPS) and urinary symptom severity (USS) 4 times during a 1-month period and baseline clinic visit that included urological, pain and illness-impact measures. Mild, moderate and severe categories on each dimension were examined for measurement stability and construct validity. RESULTS: PPS and USS severity categories had adequate reliability and both discriminant validity (differential relationships with specific clinical and self-report measures) and convergent validity (common association with nonurological somatic symptoms). For example, increasing PPS was associated with pelvic tenderness and widespread pelvic pain, whereas USS was associated with urgency during a bladder filling test and increased sensory sensitivity. PPS and USS categories were independently associated with nonurological pain and emotional distress. A descriptive analysis identified higher likelihood characteristics associated with having moderate to severe PPS or USS or both. Lack of sex interactions indicated that the measures are comparable in interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome. CONCLUSIONS: Women and men with urological chronic pelvic pain syndrome can be reliably subgrouped using brief self-report measures of mild, moderate or severe pelvic pain and urinary symptoms. Comparisons with a broad range of clinical variables demonstrate the validity and potential clinical utility of these classifications, including use in clinical trials, health services and biological research.

Approach to Diagnosis and Management of Chronic Pelvic Pain in Women: Incorporating Chronic Overlapping Pain Conditions in Assessment and Management.
Till SR, Nakamura R, Schrepf A, As-Sanie S. Approach to Diagnosis and Management of Chronic Pelvic Pain in Women: Incorporating Chronic Overlapping Pain Conditions in Assessment and Management. Obstet Gynecol Clin North Am. 2022 Jun;49(2):219-239. doi: 10.1016/j.ogc.2022.02.006. PMID: 35636805; PMCID: PMC9297339.

Chronic pelvic pain (CPP) is multifactorial in etiology and heterogeneous in presentation. Identification of all pain contributors is essential for successful management. Chronic overlapping pain conditions (COPCs) are a specified group of chronic pain conditions that commonly co-occur in patients. We briefly review individual COPCs and highlight risk factors and mechanisms that appear to be applicable across COPCs. We review evaluation and communication strategies that may help establish a productive therapeutic relationship between clinicians and patients. Management should include treatment of peripheral pain generators as well as co-occurring psychological conditions and central sensitization when present.

Examining Vaginal and Vulvar Health and Sexual Dysfunction in Patients with Interstitial Cystitis (UNICORN-1 Study).
Okui N, Okui M, Gambacciani M.
Int Urogynecol J. 2022 Sep;33(9):2493-2499. doi: 10.1007/s00192-022-05220-7. Epub 2022 May 11. PMID: 35543734.

Introduction and hypothesis: The Vaginal Health Index Score (VHIS) and vulvodynia swab tests are used to assess vaginal health and vulvodynia. However, few studies have used these tests in patients with interstitial cystitis/bladder pain syndrome (IC/BPS). IC/BPS is a chronic, debilitating disorder, characterised by urinary frequency, urinary urgency and pelvic pain. It adversely affects organs adjacent to the urinary system, leading to complications of sexual dysfunction. This study was aimed at understanding sexual dysfunction in patients with IC/BPS, as well as deterioration of vaginal health and vulvodynia. Methods: This study compared the vaginal health of IC/BPS patients with that of asymptomatic control individuals. The Pain Urgency Frequency (PUF) score, Female Sexual Function Index (FSFI), VHIS, and vulvodynia swab tests, were used as tools. The PUF and FSFI are questionnaire-based surveys of bladder symptoms and sexual function respectively. VHIS evaluation and vulvodynia swab tests are performed by physicians. The PUF was used to assess baseline

IC/BPS symptoms to validate the patient population, and FSFI, vulvodynia swab tests and VHIS were used to determine between-group differences. Results: Thirty-seven patients were recruited in each group. The IC/BPS group had a higher PUF score (18.19±3.51 vs 3.56±2.35; p<0.05), worse total FSFI (15.72±4.46 vs 26.3±4.93; p<0.05), and worse vulvodynia swab test and total VHIS (11.59±2.87 vs 22.05±3.05; p<0.05) scores than those of the control group. Conclusions: Asian women with IC/BPS experienced greater sexual dysfunction, worsened vaginal health and increased vulvodynia compared with control individuals. Information on vaginal and vulva health is very useful in evaluating IC/BPS patients.

Investigation of Temporomandibular Disorders in Patients with Fibromyalgia Syndrome: A Case-control Study.
Sahbaz T, Karacay BC.
J Stomatol Oral Maxillofac Surg. 2022 Sep 21:S2468-7855(22)00285-3. doi: 0.1016/j.jormas.2022.09.017. Epub ahead of print. PMID: 36152974.

Introduction: The aim of this study is to compare the frequency of temporomandibular disorders and to examine the temporomandibular pain and functionality levels between healthy female participants and female patients diagnosed with fibromyalgia. Materials and methods: Our study included 300 participants. Patients were evaluated according to the Diagnostic Criteria for Temporomandibular Disorders: Assessment Instruments (DC/TMD). While evaluating the patients using DC/TMD, TMD Pain Screener and Symptom questionnaire were used within the scope of Axis I, and Graded Chronic Pain Scale, Jaw Functional Limitation Scale-8 (JFLS-8), Patient Health Questionnaire (PHQ-4) and Oral Behaviors Checklist were applied. Results: Bruxism, tooth grinding and masseter hypertrophy were found to be significantly higher in fibromyalgia patients compared to healthy volunteers (p<0.001). The pain screener, JFLS-8, PHQ-4 and OBC scores and GCPS levels were found to be increased in the fibromyalgia group compared to healthy individuals (p<0.001). Considering the post-examination diagnoses of the participants, the diagnoses of myalgia (p=0.022) and disc displacement with reduction (p<0.001) were significantly higher than healthy individuals. Conclusions: Fibromyalgia is a common pathology, therefore, TMD symptoms, which are more difficult to diagnose and often missed, should be questioned in fibromyalgia patients and should be kept in mind in the management of fibromyalgia patients.

A Rose by Another Name? Characteristics that Distinguish Headache Secondary to Temporomandibular Disorder from Headache that is Comorbid with TMD.
Sharma S, Slade G, Fillingim R, Ohrbach R.
Pain. 2022 Aug 30. doi: 10.1097/j.pain.0000000000002770. Epub ahead of print. PMID: 36048529.

Co-occurring pain conditions that affect overlapping body regions are complicated by the distinction between primary versus secondary pain conditions. We investigate the occurrence of headache and painful temporomandibular disorder (TMD) in a community-based, cross-sectional study of U.S. adults in the Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA-II) study. A specific goal was to determine if headache attributed to TMD is separable from primary headache. Using DC/TMD and ICHD-3 criteria, three groups of individuals were created: a) headache without TMD; b) headache comorbid with TMD; and c) headache attributed to TMD. Regression models compared study groups according to demographic and comorbid characteristics, and post-hoc contrasts tested for differences. Descriptive statistics and Cohen's d effect size were computed, by group, for each predictor variable. Differences in continuous predictors were analyzed using one-way ANOVA. Nearly all demographic and comorbid variables distinguished the combined headache and TMD groups from the group with headache alone. Relative to the reference group with primary headache alone, markers related to headache, TMD, somatic pain processing, psychosocial, and health conditions were substantially greater in both headache comorbid with TMD and headache attributed to TMD, attesting to their qualitative similarities. However, effect sizes relative to the reference group were large for headache comorbid with TMD and larger again for headache attributed to TMD, attesting to their separability in quantitative terms. In summary, the presence of overlapping painful TMD and headache adds substantially to the biopsychosocial burden of headache and points to the importance of comprehensive assessment and differential management.

Temporomandibular Disorders and Neck Pain in Primary Headache Patients: A Retrospective Machine Learning Study.

Ferrillo M, Migliario M, Marotta N, Fortunato F, Bindi M, Pezzotti F, Ammendolia A, Giudice A, Foglio Bonda PL, de Sire A.
Acta Odontol Scand. 2022 Jul 29:1-7. doi: 10.1080/00016357.2022.2105945. Epub ahead of print. PMID: 35906722.

Objectives: To evaluate the linkage underpinning different clinical conditions as painful TMD and neck pain in patients affected by primary headaches. Materials and methods: In this machine learning study, data from medical records of patients with headaches as migraine, tension-type headache (TTH) and other primary ones, referring to a University Hospital over a 10-year period were analysed. VAS was used to evaluate the intensity of the TMD and neck pain. Moreover, the magnetic resonance imaging was used to supplement the clinical data. Results: A total of 300 patients (72 male, 228 female), mean aged 37.78 ± 5.11 years, were included. Higher TMD and neck pain VAS in migraine patients were reported. The machine learning analysis focussed on type of primary headache demonstrated that a higher TMD VAS was correlated to migraine, whereas a higher neck pain VAS was correlated to TTH or migraine. Concerning the TMD type, arthrogenous and mixed TMD were correlated to mild-moderate TMD pain (depending on neck pain intensity), whereas myogenic TMD was correlated to moderate-severe TMD pain. Conclusions: Machine-learning approach highlighted the complexity of diagnosis process and demonstrated that neck pain might be an influential variable on the belonging to different group of headaches in TMD patients.

Back and Neck Pain: A Comparison between Acute and Chronic Pain-Related Temporomandibular Disorders.
Botros J, Gornitsky M, Samim F, der Khatchadourian Z, Velly AM.
Can J Pain. 2022 Jul 1;6(1):112-120. doi: 10.1080/24740527.2022.2067032. PMID: 35799959; PMCID: PMC9255212.

Background: Temporomandibular disorders (TMDs) are common and cause persistent pain. Comorbidities are associated with TMDs and can affect the effectiveness of their treatments. The literature is lacking enough evidence on the difference between acute and chronic pain, particularly in TMDs. Investigating this difference could highlight potential risk factors for the transition from acute to chronic pain-related TMDs. Aim: To compare the likelihood of back and neck pain (BP, NP) between acute and chronic pain-related TMDs (AP-TMD, CP-TMD) as defined by pain duration and pain-related disability. Methods: Participants with AP-TMDs (≤3 months) and CP-TMDs (>3 months) were recruited according to the diagnostic criteria and research diagnostic criteria of TMD. BP and NP were assessed using a self-reported checklist. CP-TMDs defined by disability (chronic disability) and depression and anxiety symptoms were assessed using validated instruments. Logistic regression analyses were employed. Results: This study enrolled 487 adults with AP-TMD (*n* = 118) and CP-TMD (*n* = 369). Relative to AP-TMD, participants with CP-TMD had twice the odds of reporting NP (odds ratio [OR] = 2.17, 95% CI 1.27-3.71) but not BP (OR = 0.96, 95% CI 0.57-1.64). Participants with chronic disability were twice as likely to report NP (OR = 1.95, 95% CI 1.20-3.17) but not BP (OR = 1.13, 95% CI 0.69-1.82) compared to those without. All analyses were adjusted for age, sex, and anxiety and depression symptoms. Conclusions: Within the limitations of this study, results suggest that central dysregulation or trigeminocervical convergence mechanisms are implicated in the process of pain-related TMD chronification and highlight the relevance of considering disability when defining CP-TMDs.

Tension-Type Headache and Low Back Pain Reconsidered.
Astrup J, Gyntelberg F.
Front Neurol. 2022 Jul 29;13:912348. doi: 10.3389/fneur.2022.912348. PMID: 35968274; PMCID: PMC9372361.

The natural history and clinical course of tension-type headache and non-specific low back pain are reconsidered. By closer examination, these two conditions appear to share several specific clinical features. Both are muscular pain conditions along the spine, they have a preponderance in women, they may occur spontaneously or follow a trivial traumatic incident, and they both have a high risk of chronicity. The affected muscles are tender with tender points. EMG indicates diffuse hyperactivity and abnormal activation pattern, and motor control of the affected muscles and adjacent muscle groups is discoordinated. These shared features suggest analogous pathophysiology involving the neuromotor control of affected and adjacent muscle groups in the cervical and lumbar regions, respectively. As recently suggested for the whiplash disease, we suggest the term spinal dyssynergia for this specific pattern of pathology. This suggestion provides a new perspective for the understanding of these

diseases by placing their cause within the central nervous system and not in the spine or spinal musculature. This perspective warrants further clinical, neurophysiological, and neuropharmacological studies of this 'family' of common yet poorly understood clinical muscular pain conditions along the spine.

A Population-Health Approach to Characterizing Migraine by Comorbidity: Results from the Mindfulness and Migraine Cohort Study.
Sudat SE, Jacobson AS, Avins AL, Lipton RB, Pressman AR.
Cephalalgia. 2022 Oct;42(11-12):1255-1264. doi: 10.1177/03331024221104180. Epub 2022 May 31. PMID: 35642092.

Background: The heterogeneity of migraine has been reported extensively, with identified subgroups usually based on symptoms. Grouping individuals with migraine and similar comorbidity profiles has been suggested, however such segmentation methods have not been tested using real-world clinical data. Objective: To gain insights into natural groupings of patients with migraine using latent class analysis based on electronic health record-determined comorbidities. Methods: Retrospective electronic health record data analysis of primary-care patients at Sutter Health, a large open healthcare system in Northern California, USA. We identified migraine patients over a five-year time period (2015-2019) and extracted 29 comorbidities. We then applied latent class analysis to identify comorbidity-based natural subgroups. Results: We identified 95,563 patients with migraine and found seven latent classes, summarized by their predominant comorbidities and population share: fewest comorbidities (61.8%), psychiatric (18.3%), some comorbidities (10.0%), most comorbidities - no cardiovascular (3.6%), vascular (3.1%), autoimmune/joint/pain (2.2%), and most comorbidities (1.0%). We found minimal demographic differences across classes. Conclusion: Our study found groupings of migraine patients based on comorbidity that have the potential to be used to guide targeted treatment strategies and the development of new therapies.

Clinical Overlap Between Fibromyalgia and Myalgic Encephalomyelitis. A Systematic Review and Meta-Analysis.
Ramírez-Morales R, Bermúdez-Benítez E, Martínez-Martínez LA, Martínez-Lavín M.
Autoimmun Rev. 2022 Aug;21(8):103129. doi: 10.1016/j.autrev.2022.103129. Epub 2022 Jun 9. PMID: 35690247.

Myalgic encephalomyelitis is an illness characterized by profound malaise after mental or physical effort occurring in patients already suffering from constant fatigue. On the other hand, widespread pain and widespread allodynia are the core fibromyalgia clinical features. There is controversy on these two syndromes alikeness. Through the years, different diagnostic and/or classification criteria have been put forward to appraise both fibromyalgia and myalgic encephalomyelitis. The epidemiology of these two illnesses, and their overlap, may vary accordingly to the used definition. The most recent Wolfe et al. 2016 fibromyalgia diagnostic criteria incorporates three myalgic encephalomyelitis features including fatigue, waking unrefreshed and dyscognition. The objective of this meta-analysis was to define the clinical overlap between fibromyalgia and myalgic encephalomyelitis based on a systematic literature review. METHODS: PubMed, Embase, Lilacs, and Cochrane data bases were searched on January 25, 2021 linking the medical subject heading "Fibromyalgia" to the following terms "chronic fatigue syndrome", "myalgic encephalomyelitis" and "systemic exertion intolerance disease". Our review included all original articles in which the clinical overlap between fibromyalgia and myalgic encephalomyelitis could be quantified based on recognized diagnostic or classification criteria. Articles scrutiny and selection followed the PRISMA guidelines. Each study quality was assessed according to GRADE recommendations. The global clinical overlap was calculated using a fixed effect model with inverse variance-weighted average method. RESULTS: Twenty one publications were included in the meta-analysis. Reviewed studies were highly dissimilar in their design, objectives, sample size, diagnostic criteria, and/or outcomes yielding a 98% heterogeneity index. Nevertheless, the clinical overlap between fibromyalgia and myalgic encephalomyelitis was a well defined outcome that could be reliably calculated despite the high heterogeneity value. All reviewed publications had moderate GRADE evidence level. Most evaluated articles used the old 1990 Wolfe et al. fibromyalgia diagnostic criteria. Myalgic encephalomyelitis and fibromyalgia diagnoses overlapped in 47.3% (95% CI: 45.97-48.63) of the reported cases. CONCLUSION: This meta-analysis found prominent clinical overlap between fibromyalgia and myalgic encephalomyelitis. It seems likely that this concordance would be even higher when using the most recent Wolfe et al. 2016 fibromyalgia diagnostic

criteria.

Fibromyalgia, Mood Disorders, Cognitive Test Results, Cognitive Symptoms and Quality of Life in Systemic Lupus Erythematosus.
Raghunath S, Guymer EK, Glikmann-Johnston Y, Golder V, Kandane Rathnayake R, Morand EF, Stout JC, Hoi A.
Rheumatology (Oxford). 2022 Apr 5:keac207. doi: 10.1093/rheumatology/keac207. Epub ahead of print. PMID: 35383358.

OBJECTIVES: Cognitive dysfunction, and comorbidities such as mood disorder and fibromyalgia, are common in systemic lupus erythematosus (SLE). This study aims to explore the associations between fibromyalgia, mood disorders, cognitive symptoms and cognitive dysfunction in SLE patients, and their impact on quality of life. METHODS: We tested cognition in SLE patients and healthy controls (HC), and evaluated cognitive symptoms, mood disorder, fibromyalgia, fatigue and quality of life using patient-reported outcome measures. We examined associations of these comorbidities with both patient-reported cognitive symptoms and cognitive test performance. RESULTS: High fibromyalgia symptom score and history of depression or anxiety were associated with cognitive dysfunction. There were no significant associations between current depression, anxiety symptoms, or fatigue score and objective cognitive dysfunction. In contrast, mood disorder symptoms, history of mood disorder, fibromyalgia symptoms and fatigue all had significant associations with patient-reported cognitive symptoms. There were no significant associations between patient-reported cognitive symptoms and objective cognitive dysfunction. Objective cognitive dysfunction, patient-reported cognitive symptoms, history of mood disorder, and fibromyalgia symptoms all had significant associations with poorer quality of life; fibromyalgia had the biggest impact. CONCLUSIONS: Cognitive symptoms are common in SLE, but there were no associations between cognitive symptoms and objective cognitive dysfunction. Depression, anxiety and fibromyalgia were more consistently associated with patient-reported cognitive symptoms than with objective cognitive dysfunction. These factors all have a significant impact on quality of life. Understanding the discrepancy between patient-reported cognitive symptoms and cognitive test performance is essential to advance care in this area of unmet need.

New Clinical Phenotype of the Post-Covid Syndrome: Fibromyalgia and Joint Hypermobility Condition.
Gavrilova N, Soprun L, Lukashenko M, Ryabkova V, Fedotkina TV, Churilov LP, Shoenfeld Y.
Pathophysiology. 2022 Jan 19;29(1):24-29. doi: 10.3390/pathophysiology29010003. PMID: 35366287; PMCID: PMC8954589.

Fibromyalgia can be defined as a chronic pain condition, affecting the musculoskeletal system, etiology and pathophysiology of which is sufficiently understudied. Despite the fact that many authors consider this entity to be a manifestation of central sensitization, and not an autoimmune disease, the high prevalence of fibromyalgia in patients with post-COVID-19 conditions requires taking a fresh look at the causes of the disease development. During the patient examination, the authors identified a combination of symptoms that occurs so often, that they can be carefully described as a clinical pattern. These manifestations include young age, female gender, joint hypermobility, the onset of pain after COVID-19, physical traumatization of one particular tendon and the development of the fibromyalgia pain syndrome during the next several weeks. As well as an increase in the titer of antinuclear antibodies and some other systemic inflammation factors. It can be assumed with great caution that local damage to the connective tissue in patients with joint hypermobility, having COVID-19 as a trigger factor can lead to the development of fibromyalgia syndrome. This article presents three clinical cases that illustrated this hypothesis.

Beyond Dry Eye: How Co-morbidities Influence Disease Phenotype in Dry Eye Disease.
Lee Y, Kim M, Galor A.
Clin Exp Optom. 2022 Mar;105(2):177-185. doi: 10.1080/08164622.2021.1962210. Epub 2021 Aug 8. PMID: 34369296; PMCID: PMC8821724.

Dry Eye Disease (DED) is a complex and multifactorial disorder of tear homoeostasis that results in pain, visual disturbance, and ocular surface damage. It is highly prevalent around the world and is associated with many co-morbidities that may contribute to or exacerbate symptoms and signs of disease and affect disease phenotype. However, DED is not one disease and can manifest with a variety of symptoms and/or signs. In this review, we discuss relationships between various co-morbidities and DED phenotypes. For example, individuals

with immune mediated diseases, like Sjögren's Syndrome and Graft versus Host Disease, often present with aqueous tear deficiency (ADDE) in the setting of lacrimal gland dysfunction. Individuals with disorders that affect the periocular skin, like rosacea and seborrhoeic dermatitis, often present with evaporative dry eye (EDE) in the setting of eyelid and/or meibomian gland abnormalities. Individuals with pain related disorders, such as chronic pain syndrome and migraine, often present with ocular pain out of proportion to tear film abnormalities, often with accompanying corneal nerve hypersensitivity. Individuals with diabetes mellitus often present with an epitheliopathy in the setting of decreased sensation (neurotrophic keratitis). While not absolute, understanding relationships between co-morbidities and DED phenotypes can help tailor a therapeutic plan to the individual patient.

Stigma Perceived by Patients with Functional Somatic Syndromes and its Effect on Health Outcomes - A Systematic Review.

Ko C, Lucassen P, van der Linden B, Ballering A, Olde Hartman T.
J Psychosom Res. 2022 Mar;154:110715. doi: 10.1016/j.jpsychores.2021.110715. Epub 2022 Jan 6. PMID: 35016138.

BACKGROUND: Patients with functional somatic syndromes (FSS) experience stigma which arguably affects their health. AIM: To determine the presence of perceived stigma and its effects on physical and mental health in patients with FSS compared to patients with comparable explained conditions. METHODS: A comprehensive search of PubMed, Embase, PsycINFO, CINAHL and Cochrane Library was performed to select studies focusing on stigma perceived by patients with irritable bowel syndrome (IBS), fibromyalgia (FM) or chronic fatigue syndrome (CFS), comparing these patients to patients with comparable but explained conditions. RESULTS: We identified 1931 studies after duplicate removal. After screening we included eight studies: one study about all three FSS, one about IBS, five about FM and one about CFS. We found that patients with IBS did not consistently experience higher levels of stigma than those with a comparable explained condition. Patients with CFS and FM experienced higher levels of stigma compared to patients with comparable explained conditions. All studies showed a correlation between stigma and negative health outcomes. DISCUSSION: Patients with FSS experience stigma and negative health outcomes. However, experiencing stigma is not restricted to patients with FSS, as many patients with explained health conditions also experience stigma. Whether stigma has more negative health consequences in patients with FSS compared to patients with explained health conditions remains unclear and should be assessed in future research.

Hormonal Treatments for Endometriosis: The Endocrine Background.

Vannuccini S, Clemenza S, Rossi M, Petraglia F.
Rev Endocr Metab Disord. 2022 Jun;23(3):333-355. doi: 10.1007/s11154-021-09666-w. Epub 2021 Aug 17. PMID: 34405378; PMCID: PMC9156507.

Endometriosis is a benign uterine disorder characterized by menstrual pain and infertility, deeply affecting women's health. It is a chronic disease and requires a long term management. Hormonal drugs are currently the most used for the medical treatment and are based on the endocrine pathogenetic aspects. Estrogen-dependency and progesterone-resistance are the key events which cause the ectopic implantation of endometrial cells, decreasing apoptosis and increasing oxidative stress, inflammation and neuroangiogenesis. Endometriotic cells express AMH, TGF-related growth factors (inhibin, activin, follistatin) CRH and stress related peptides. Endocrine and inflammatory changes explain pain and infertility, and the systemic comorbidities described in these patients, such as autoimmune (thyroiditis, arthritis, allergies), inflammatory (gastrointestinal/urinary diseases) and mental health disorders. The hormonal treatment of endometriosis aims to block of menstruation through an inhibition of hypothalamus-pituitary-ovary axis or by causing a pseudodecidualization with consequent amenorrhea, impairing the progression of endometriotic implants. GnRH agonists and antagonists are effective on endometriosis by acting on pituitary-ovarian function. Progestins are mostly used for long term treatments (dienogest, NETA, MPA) and act on multiple sites of action. Combined oral contraceptives are also used for reducing endometriosis symptoms by inhibiting ovarian function. Clinical trials are currently going on selective progesterone receptor modulators, selective estrogen receptor modulators and aromatase inhibitors. Nowadays, all these hormonal drugs are considered the first-line treatment for women with endometriosis to improve their symptoms, to postpone surgery or to prevent post-surgical disease recurrence. This review aims to provide a comprehensive state-of-the-art on the current and future hormonal treatments for endometriosis, exploring the endocrine background of the disease.

Living with Endometriosis: Comorbid Pain Disorders, Characteristics of Pain and Relevance for Daily Life.

Leuenberger J, Kohl Schwartz AS, Geraedts K, Haeberlin F, Eberhard M, von Orellie S, Imesch P, Leeners B.

Eur J Pain. 2022 May;26(5):1021-1038. doi: 10.1002/ejp.1926. Epub 2022 Feb 27. PMID: 35184363; PMCID: PMC9306988.

BACKGROUND: Pain plays a central role in endometriosis. The complex relationship among pain characteristics, comorbid pain disorders and daily life represents a challenge for medical support. This multicentre cross-sectional case-control study analysed the association between endometriosis-related chronic pain and functions of daily life in 510 women with endometriosis, 265 (52%) who experienced chronic pain, either from endometriosis alone (N = 134, 26.3%) or in association with additional pain disorders (N = 131, 25.7%). METHODS: Self-administered questionnaires from the Brief Pain Inventory and the Pain Disability Index were used to investigate associations between pain characteristics (frequency, duration, intensity) and daily life. Also, associations between different endometriosis characteristics (rASRM stage, presence of adhesions, localisation of lesions) and pain were evaluated. RESULTS: Chronic pain is negatively associated with almost all (12/14) aspects of daily life investigated, including standing, walking, sitting, defaecation, sleep, sports activities, family and domestic responsibilities, sexuality, social functioning, professional life, mood, and joy of life. Altogether, 33.7% of women with chronic pain reported moderate and 27.5% severe limitations. Comorbid pain disorders resulted in significantly more limitations. The length of pain episodes showed a particularly important influence, especially for family/domestic responsibilities (OR 22.94, $p < 0.001$), professional life (OR 16.56, $p < 0.001$) and social functioning (OR 41.03, $p < 0.001$). CONCLUSIONS: Our data confirm that despite treatment, about 50% of women experience pain. Pain was associated with at least moderate negative effects on almost all areas of daily life; additional pain comorbidities increased limitations. Improving pain management is essential for improving quality of life in women with endometriosis. SIGNIFICANCE: The study provides an accurate overview of the impact of endometriosis-associated pain on daily life. This is important because pain plays a central role in women living with endometriosis, and despite modern therapies, many women continue to suffer from chronic pain. The detailed analysis of its impact with a comprehensive survey of all aspects of daily life in a very large study population is unique. We expect an improved understanding of consequences of pain to significantly advance medical support in these patients.

Multimorbidity and Co-occurring Musculoskeletal Pain do not Modify the Effect of the SELFBACK App on Low Back Pain-Related Disability.

Øverås CK, Nilsen TIL, Nicholl BI, Rughani G, Wood K, Søgaard K, Mair FS, Hartvigsen J.

BMC Med. 2022 Feb 8;20(1):53. doi: 10.1186/s12916-022-02237-z. PMID: 35130898; PMCID: PMC8822859.

BACKGROUND: SELFBACK, an artificial intelligence (AI)-based app delivering evidence-based tailored self-management support to people with low back pain (LBP), has been shown to reduce LBP-related disability when added to usual care. LBP commonly co-occurs with multimorbidity (≥ 2 long-term conditions) or pain at other musculoskeletal sites, so this study explores if these factors modify the effect of the SELFBACK app or influence outcome trajectories over time. METHODS: Secondary analysis of a randomized controlled trial with 9-month follow-up. Primary outcome is as follows: LBP-related disability (Roland Morris Disability Questionnaire, RMDQ). Secondary outcomes are as follows: stress/depression/illness perception/self-efficacy/general health/quality of life/physical activity/global perceived effect. We used linear mixed models for continuous outcomes and logistic generalized estimating equation for binary outcomes. Analyses were stratified to assess effect modification, whereas control (n = 229) and intervention (n = 232) groups were pooled in analyses of outcome trajectories. RESULTS: Baseline multimorbidity and co-occurring musculoskeletal pain sites did not modify the effect of the SELFBACK app. The effect was somewhat stronger in people with multimorbidity than among those with LBP only (difference in RMDQ due to interaction, - 0.9[95 % CI - 2.5 to 0.6]). Participants with a greater number of long-term conditions and more co-occurring musculoskeletal pain had higher levels of baseline disability (RMDQ 11.3 for ≥ 2 long-term conditions vs 9.5 for LBP only; 11.3 for ≥ 4 musculoskeletal pain sites vs 10.2 for ≤ 1 additional musculoskeletal pain site); along with higher baseline scores for stress/depression/illness perception and poorer pain self-efficacy/general health ratings. In the pooled sample, LBP-related disability improved slightly less over time for people with ≥ 2 long-term conditions additional to LBP compared to no

multimorbidity and for those with ≥4 co-occurring musculoskeletal pain sites compared to ≤ 1 additional musculoskeletal pain site (difference in mean change at 9 months = 1.5 and 2.2, respectively). All groups reported little improvement in secondary outcomes over time. CONCLUSIONS: Multimorbidity or co-occurring musculoskeletal pain does not modify the effect of the selfBACK app on LBP-related disability or other secondary outcomes. Although people with these health problems have worse scores both at baseline and 9 months, the AI-based selfBACK app appears to be helpful for those with multimorbidity or co-occurring musculoskeletal pain.

The Potential Impact of Nutritional Intake on Symptoms Severity in Patients with Comorbid Migraine and Irritable Bowel Syndrome.
Magdy R, Eid RA, Hassan M, Abdelghaffar M, El Sayed AF, Mohammed Z, Hussein M.
BMC Neurol. 2022 May 30;22(1):199. doi: 10.1186/s12883-022-02723-0. PMID: 35637446; PMCID: PMC9150376.

BACKGROUND: Specific dietary recommendations for migraine patients with comorbid irritable bowel syndrome (IBS) re lacking. This work aimed to study the severity scores of such two common pain-related disorders in relation to various macronutrients and micronutrients intake. METHODS: A cross-sectional study was conducted on patients with concomitant migraine and IBS. The frequency and intensity of migraine attacks and the severity of IBS were evaluated. Data on dietary intake were collected using food frequency questionnaires and 24-hour dietary recall. RESULTS: One-hundred patients with a median age of 36 years participated. The severity scores for migraine and IBS were positively correlated with fat and copper and negatively correlated with fiber and zinc intake. Copper intake was an independent predictor of the severity of both migraine and IBS (P 0.033, < 0.001). Patients with episodic migraine (n = 69) had a significantly higher frequency of cooked, fresh vegetables, and wheat bran bread intake (P 0.009, 0.004, 0.021) and lower frequency of hydrogenated oils intake (P 0.046), in comparison to patients with chronic migraine (n = 31). Patients with moderate intensity of migraine (n = 37) had a significantly higher frequency of herbal drinks intake (P 0.014) than patients with a severe intensity of migraine (n = 63). Patients with mild (n = 13) and moderate IBS (n = 41) had a significantly higher frequency of wheat bran bread and sen bread intake (P 0.003, 0.022) than patients with severe IBS (n = 46). CONCLUSION: Patients with comorbid migraine and IBS are advised to adhere to a diet low in fat and copper and rich in fiber and zinc.

The Psychological Features of Distinct Somatic Syndromes: A Cluster Analysis According to Population-Based Somatic Symptom Profiles in Taiwan.
Huang WL, Chang SS, Liao SC.
J Formos Med Assoc. 2022 Sep;121(9):1813-1822. doi: 10.1016/j.jfma.2022.03.009. Epub 2022 Mar 30. PMID: 35367114.

BACKGROUND: Functional somatic syndromes (such as chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome) are often comorbid. Whether these syndromes are distinct constructs and whether they have different psychological features are interesting questions. We perform a cluster analysis based on a nationwide survey in Taiwan to answer these questions. METHODS: A score of at least 5 on the Patient Health Questionnaire-15 (PHQ-15, measuring somatic symptoms) indicated somatic syndromes and the data of 550 subjects were included. According to the gastrointestinal, pain-fatigue and cardiovascular subdimension scores of the PHQ-15, we performed a two-step cluster analysis. The demographic data and the cluster scores of the Health Anxiety Questionnaire and the Patient Health Questionnaire-4 (measuring depression and anxiety) were compared. Multinomial logistic and multiple linear regression analyses were used to clarify the associations between clusters/somatic symptoms and demographics/psychological features. RESULTS: Four clusters were generated and named according to their somatic features: "high gastrointestinal symptoms", "high pain-fatigue and comorbid somatic symptoms", "middle to high pain-fatigue symptoms" and "high cardiovascular symptoms". The high pain-fatigue and comorbid somatic symptom cluster had the highest levels of extent to which symptoms interfere with a person's life, depression and anxiety. The high cardiovascular symptom cluster was featured by high excessive worry over health and illness and low educational level. The high gastrointestinal symptom cluster had relatively low psychopathologies. CONCLUSION: The results of this population-based analysis supported the existence of distinct somatic syndromes that are not parts of a single whole somatic syndrome and have different psychological features.

Effects of onabotulinumtoxinA in Patients Concurrently Diagnosed with Chronic Migraine Encephalalgia and Temporomandibular Disorders: A Retrospective Case Series.

Gross AJ, Hudson JW, Matias C, Jones BJ.
Cranio. 2022 Mar 14:1-11. doi: 10.1080/08869634.2022.2045114. Epub ahead of print. PMID: 35285422.

OBJECTIVE: Chronic migraine encephalalgia (CME) with concomitant temporomandibular disorder (TMD) is a serious illness with limited effective treatment options. This study explores the effectiveness of onabotulinumtoxinA (BtxA) as an adjunct therapeutic to TMJ arthroscopy in the relief of CME. METHODS: A retrospective cohort study of patients receiving TMJ arthroscopy, with or without BtxA injections for CME, was conducted. Variables assessed include pain using a visual analog scale (VAS), maximal incisal opening (MIO), muscle soreness, and headache frequency and duration. RESULTS: Sixty patients (44 BtxA, 16 Control), consisting of 56 (93.3%) females, met inclusion criteria. A significant reduction in pain is reported with patients receiving BtxA ($p < 0.0001$) on VAS as compared to Control group. BtxA treatment also significantly reduced headache frequency and duration ($p < 0.05$). CONCLUSION: These results support the use of adjunctive BtxA treatment with arthroscopy for the treatment of CME in the context of TMD.

An Observational Study of Centrally Facilitated Pain in Individuals with Chronic Low Back Pain.
Georgopoulos V, Akin-Akinyosoye K, Smith S, McWilliams DF, Hendrick P, Walsh DA.
Pain Rep. 2022 Apr 13;7(3):e1003. doi: 10.1097/PR9.0000000000001003. PMID: 35441119; PMCID: PMC9012603.

INTRODUCTION: Central pain facilitation can hinder recovery in people with chronic low back pain (CLBP). OBJECTIVES: The objective of this observational study was to investigate whether indices of centrally facilitated pain are associated with pain outcomes in a hospital-based cohort of individuals with CLBP undertaking a pain management programme. METHODS: Participants provided self-report and pain sensitivity data at baseline (n = 97) and again 3 months (n = 87) after a cognitive behavioural therapy-based group intervention including physiotherapy. Indices of centrally facilitated pain were pressure pain detection threshold, temporal summation and conditioned pain modulation at the forearm, Widespread Pain Index (WPI) classified using a body manikin, and a Central Mechanisms Trait (CMT) factor derived from 8 self-reported characteristics of anxiety, depression, neuropathic pain, fatigue, cognitive dysfunction, pain distribution, catastrophizing, and sleep. Pain severity was a composite factor derived from Numerical Rating Scales. Cross-sectional and longitudinal regression models were adjusted for age and sex. RESULTS: Baseline CMT and WPI each was associated with higher pain severity (CMT: $r = 0.50$, $P < 0.001$; WPI: $r = 0.21$, $P = 0.04$) at baseline and at 3 months (CMT: $r = 0.38$, $P < 0.001$; WPI: $r = 0.24$, $P = 0.02$). High baseline CMT remained significantly associated with pain at 3 months after additional adjustment for baseline pain ($\beta = 2.45$, $P = 0.04$, $R 2 = 0.25$, $P < 0.0001$). Quantitative sensory testing indices of pain hypersensitivity were not significantly associated with pain outcomes at baseline or at 3 months. CONCLUSION: Central mechanisms beyond those captured by quantitative sensory testing are associated with poor CLBP outcome and might be targets for improved therapy.

Localized and Widespread Pressure Pain Hypersensitivity in Patients with Episodic or Chronic Migraine: A Systematic Review and Meta-Analysis.
Fernández-de-Las-Peñas C, Navarro-Santana MJ, Curiel-Montero F, Plaza-Manzano G, Alburquerque-Sendín F, Rodrigues-de-Souza DP.
Cephalalgia. 2022 Aug;42(9):966-980. doi: 10.1177/03331024221084217. Epub 2022 Mar 25. PMID: 35332797.

OBJECTIVE: This meta-analysis compared pressure pain sensitivity in trigeminal, cervical spine and remote pain-free areas between migraine patients and headache-free controls considering diagnosis (episodic versus chronic) and sex. Databases and data treatment: Electronic databases were searched for cross-sectional or prospective case-control studies comparing pressure pain thresholds between migraine and headache-free controls. Data were extracted by two reviewers. The risk of bias and methodological quality was assessed by Newcastle-Ottawa Quality Assessment Scale. Meta-analyses of trigeminal, extra-trigeminal (cervical spine) and remote pain-free areas were compared. Frequency of migraine and sex were taken into account. Mean differences (MD) and random effects were calculated. RESULTS: Eighteen studies were included. Patients with migraine showed lower pressure pain thresholds than headache-free controls: trigeminal (MD -71.33 kPa, 95%CI -92.14 to -50.53), cervical spine (MD -68.50 kPa, 95%CI -84.67 to -52.33), and remote pain-free (MD -62.49 kPa, 95%CI -99.52 to -25.45) areas. Differences were consistently significant for

episodic migraine in all locations, but only significant in the trigeminal area for chronic migraine (MD -67.36 kOPa, 95% CI -101.31 to -33.42). Overall, women had lower pressure pain thresholds than men. The methodological quality of most studies (66.7%) was good. The results showed a high heterogeneity. CONCLUSION: This meta-analysis found low to high quality evidence showing lower pressure pain thresholds in trigeminal, extra-trigeminal, and remote pain-free areas in migraine sufferers when compared with headache-free controls. Hypersensitivity to pressure pain locally and widespread was consistently observed in episodic migraine, but locally in chronic migraine as compared to headache-free controls.

Epidemiology Studies

Association between Physical Multimorbidity and Sleep Problems in 46 Low- and Middle-Income Countries.
Smith L, Shin JI, Jacob L, Schuch F, Oh H, Tully MA, López Sánchez GF, Veronese N, Soysal P, Yang L, Butler L, Barnett Y, Koyanagi A. Maturitas. 2022 Jun;160:23-31. doi: 10.1016/j.maturitas.2022.01.007. Epub 2022 Jan 21. PMID: 35550705.

BACKGROUND: Little is known about the association between multimorbidity (i.e., two or more chronic conditions) and sleep problems in the general adult populations of low- and middle-income countries (LMICs). Thus, we aimed to assess this association among adults from 46 LMICs, and to quantify the extent to which anxiety, depression, stress, and pain explain this association. METHODS: Cross-sectional, predominantly nationally representative, community-based data from the World Health Survey were analyzed. Nine chronic physical conditions (angina, arthritis, asthma, chronic back pain, diabetes, edentulism, hearing problems, tuberculosis, visual impairment) were assessed. To be included in the analysis, sleep problems had to have been experienced in the past 30 days and to have been severe or extreme; they included difficulties falling asleep, waking up frequently during the night or waking up too early in the morning. Multivariable logistic regression and mediation analyses were conducted to explore the associations. RESULTS: Data on 237,023 individuals aged ≥18 years [mean (SD) age 38.4 (16.0) years; 49.2% men] were analyzed. Compared with no chronic conditions, having 1, 2, 3, and ≥4 conditions was associated with 2.39 (95%CI=2.14, 2.66), 4.13 (95%CI=3.62, 4.71), 5.70 (95%CI=4.86, 6.69), and 9.99 (95%CI=8.18, 12.19) times higher odds for sleep problems. Pain (24.0%) explained the largest proportion of the association between multimorbidity and sleep problems, followed by anxiety (21.0%), depression (11.2%), and stress (10.4%). CONCLUSIONS: Multimorbidity was associated with a substantially increased odds for sleep problems in adults from 46 LMICs. Future studies should assess whether addressing factors such as pain, anxiety, depression, and stress in people with multimorbidity can lead to improvement in sleep in this population.

Frequency, Demographics, Comorbidities, and Health Care Utilization by Veterans with Migraine: A VA Nationwide Cohort Study.
Seng EK, Fenton BT, Wang K, Lipton RB, Ney J, Damush T, Grinberg AS, Skanderson M, Sico JJ.
Neurology. 2022 Sep 13:10.1212/WNL.0000000000200888. doi: 10.1212/WNL.0000000000200888. Epub ahead of print. PMID: 36100439.

Objective: To describe the relative frequency, demographics, comorbidities, and healthcare utilization of veterans who receive migraine care at the Veteran's Health Administration (VHA) and to evaluate differences by gender. Methods: This study extracted data from VHA administrative sources. Veterans diagnosed with migraine by a healthcare provider between fiscal year 2008-2019 were included. Demographics and military exposures were extracted at cohort entry. Comorbidities were extracted within 18 months of the first migraine diagnosis. Health care utilization and headache comorbidities were extracted across the study period. Differences between men and women were evaluated using chi-square tests and student t-tests. Results: More than half a million (n = 567,121) veterans were diagnosed with migraine during the 12-year study period, accounting for 5.3% of the 10.8 million veterans served in the VHA; in the most recent year of the study period (2019), the annual incidence and one-year period prevalence of medically diagnosed migraine was 2.7% and 13.0% for women, and 0.7% and 2.5% for men. In the total cohort diagnosed with migraine, 27.8% were women and 72.2% men. Among those with diagnosed migraine, a higher proportion of men vs. women also had a TBI diagnosis (3.9% vs. 1.1%; $p < 0.001$). A higher proportion of women vs. men reported military sexual trauma (35.5% vs. 3.5%; $p < 0.001$). Participants with

diagnosed migraine had an average of 1.44 (SD 1.73) annual encounters for headache. Primary care was the most common headache care setting (88.1%); almost one-fifth of veterans with diagnosed migraine sought care in the ED at least once during the study period. Common comorbidities were overweight/obesity (80.3%), non-headache pain disorders (61.7%), and mental health disorders (48.8%). Conclusions: Migraine is commonly treated in the VHA setting, but likely under ascertained. Most people treated for migraine in the VHA are men. Pain comorbidities and psychiatric disorders are common. Future research should identify methods to improve diagnosis and treatment and to reduce use of the emergency department.

Associations of Unspecified Pain, Idiopathic Pain and COVID-19 in South Korea: A Nationwide Cohort Study.
Kim N, Kim J, Yang BR, Hahm BJ.
Korean J Pain. 2022 Oct 1;35(4):458-467. doi: 10.3344/kjp.2022.35.4.458. PMID: 36175345; PMCID: PMC9530679.

Background: Few studies have investigated unspecified or idiopathic pain associated with COIVD-19. This study aimed to provide the incidence rates of unspecified pain and idiopathic pain in patients with COVID-19 for 90 days after COVID-19 diagnosis. Methods: A propensity score matched cohort was used, including all patients with COVID-19 in South Korea, and analyzed their electronic medical records. The control group consisted of those who had not had tests for COVID-19 at all. Unspecified pain diagnoses consisted of diagnoses related to pain included in the ICD-10 Chapter XVIII. Idiopathic pain disorders included fibromyalgia, temporomandibular joint disorders, headaches, chronic prostatitis, complex regional pain syndrome, atypical facial pain, irritable bowel syndrome, and interstitial cystitis. Results: After matching, the number of participants in each group was 7,911. For most unspecified pain, the incidences were higher in the COVID-19 group (11.7%; 95% confidence interval [CI], 11.0-12.5) than in the control group (6.5%; 95% CI, 6.0-7.1). For idiopathic pain, only the headaches had a significantly higher incidence in the COVID-19 group (6.6%; 95% CI, 6.1-7.2) than in the control group (3.7%; 95% CI, 3.3-4.1). However, using a different control group that included only patients who visited a hospital at least once for any reasons, the incidences of most unspecified and idiopathic pain were higher in the control group than in the COVID-19 group. Conclusions: Patients with COVID-19 might be at a higher risk of experiencing unspecified pain in the acute phase or after recovery compared with individuals who had not had tests for COVID-19.

Functional Somatic Syndromes are Associated with Suboptimal Outcomes and High Cost after Shoulder Arthroplasty.
Moverman MA, Puzzitiello RN, Pagani NR, Moon AS, Hart PA, Kirsch JM, Jawa A, Menendez ME.
J Shoulder Elbow Surg. 2022 Jan;31(1):48-55. doi: 10.1016/j.jse.2021.05.015. Epub 2021 Jun 9. PMID: 34116194.

BACKGROUND: The presence of functional somatic syndromes (chronic physical symptoms with no identifiable organic cause) in patients undergoing elective joint arthroplasty may affect the recovery experience. We explored the prevalence of functional somatic syndromes among shoulder arthroplasty patients, as well as their association with postoperative outcomes and costs. METHODS: We identified 480 patients undergoing elective total shoulder arthroplasty (anatomic or reverse) between 2015 and 2018 in our institutional registry with minimum 2-year follow-up. Medical records were queried for the presence of 4 well-recognized functional somatic syndromes: fibromyalgia, irritable bowel syndrome, chronic headaches, and chronic low-back pain. Multivariable linear regression modeling was used to determine the independent association of these diagnoses with hospitalization time-driven activity-based costs and 2-year postoperative American Shoulder and Elbow Surgeons (ASES), Single Assessment Numeric Evaluation (SANE), and pain scores. RESULTS: Nearly 1 in 5 patients (17%) reported at least 1 functional somatic syndrome. These patients were more likely to be women, to be chronic opioid users, to report more allergies, to have a diagnosis of anxiety, and to have shoulder pathology other than degenerative joint disease (all $P \leq .001$). After multivariable adjustment, the presence of at least 1 functional somatic syndrome was independently predictive of lower 2-year ASES (-9.75 points) and SANE (-7.63 points) scores and greater residual pain (+1.13 points) (all $P \leq .001$). When considered cumulatively, each additional functional disorder was linked to a stepwise decrease in ASES and SANE scores and an increase in residual pain ($P < .001$). These patients also incurred higher hospitalization costs, with a stepwise rise in costs with an increasing number of

disorders (P < .001). CONCLUSIONS: Functional somatic syndromes are common in patients undergoing shoulder arthroplasty and correlate with suboptimal outcomes and greater resource utilization. Efforts to address the biopsychosocial determinants of health that affect the value proposition of shoulder arthroplasty should be prioritized in the redesign of care pathways and bundling initiatives.

The Prevalence of Chronic Pain in Young Adults: A Systematic Review and Meta-Analysis.
Murray CB, de la Vega R, Murphy LK, Kashikar-Zuck S, Palermo TM.
Pain. 2022 Sep 1;163(9):e972-e984. doi: 10.1097/j.pain.0000000000002541. Epub 2021 Nov 22. PMID: 34817439.

Previous systematic reviews have summarized the prevalence and impact of chronic pain in "average" pediatric (ie, school-age children) and adult (ie, middle-aged individuals) age groups. To the best of our knowledge, this is the first study to describe the prevalence of chronic pain in the subgroup of individuals who fall in between established boundaries of "childhood" and "adulthood"-known as young adulthood. The goal of this research was to meta-analyze prevalence data on pain in young adults based on available data published between 2008 and 2020. Searches were identified with MEDLINE, Embase, and PsycINFO. We included general population and university-based studies presenting prevalence estimates of chronic pain (pain lasting ≥3 months) in young adults. We identified 43 articles providing prevalence estimates across a combined population of 97,437 young adult respondents (age range: 15-34 years), with studies undertaken in 22 countries. Available data allowed for stratification of prevalence according to pain condition. The overall pooled random-effect prevalence rate of chronic pain in young adults was 11.6%, suggesting that 1 in every 9 young adults experience chronic pain worldwide. Prevalence rates varied considerably according to pain condition. Estimates did not vary according to sex, geographic location, and several study methodological characteristics (ie, population type, sampling area, sampling year, investigation period, and assessment method). Overall, young adult chronic pain is common and should be recognized as a major public health concern. Considering the difficulties young adults face accessing adult health care, greater attention is needed to develop transition programs and evidence-based treatments tailored to the unique needs of this age group.

The Association between Age at Menarche and Chronic Pain Outcomes in Women: the Tromsø Study, 2007 to 2016.
Lund CI, Engdahl B, Rosseland LA, Stubhaug A, Grimnes G, Furberg AS, Steingrímsdóttir ÓA, Nielsen CS.
Pain. 2022 Sep 1;163(9):1790-1799. doi: 10.1097/j.pain.0000000000002579. Epub 2022 Mar 1. PMID: 35239542; PMCID: PMC9393800.

Sex differences in chronic pain are well established with documented predominance in women. This study assessed relationships between age at menarche and chronic pain, site-specific chronic pain, pain characteristics, and chronic widespread pain (CWP). We used data from the Tromsø Study conducted in 2007 to 2008 and 2015 to 2016 (Tromsø 6 and Tromsø 7 waves) including participants aged 30 to 99 years. The associations between age at menarche and chronic pain were examined in Tromsø 6 (n = 6449), Tromsø 7 (n = 5681), and the combination of Tromsø 6 and Tromsø 7 (n = 12,130). Tromsø 7 data were used further to examine the associations between age at menarche and site-specific chronic pain, 4 pain characteristics (pain duration, pain intensity, episode duration, and episode frequency), and CWP. All analyses were adjusted for body mass index, age, and economic status of the household in childhood. Lower age at menarche was associated with an increased risk of chronic pain in all 3 samples (risk ratio for each year delay in menarche 0.98, 95% CI [0.97 to 0.99] across samples). Risk differences were -0.014, CI 95% (-0.02 to -0.005) in Tromsø 6, -0.011, CI 95% (-0.02 to -0.02) in Tromsø 7, and -0.012, CI 95% (-0.02 to -0.01) in the combined sample. Age at menarche was significantly associated with chronic pain in the neck, abdomen, and both arms, and CWP. Of the 4 pain characteristics, pain duration was statistically significant. We conclude that early menarche is an independent risk factor for pain across a broad spectrum of pain outcomes.

The Problem of Pain in Rheumatology: Clinical Profiles Associated with Concomitant Diagnoses with Chronic Overlapping Pain Conditions.
Falasinnu T, Nguyen T, Jiang TE, Chaichian Y, Rector A, Darnall BD, Mackey S, Simard JF.
ACR Open Rheumatol. 2022 Oct;4(10):890-896. doi: 10.1002/acr2.11488. Epub 2022 Jul 25. PMID: 35872631.

Objective: The chronification of pain is heterogeneous in rheumatology. Chronic overlapping pain conditions (COPCs) such as fibromyalgia, endometriosis, migraine, and back pain may co-occur with one another and in rheumatic diseases. We describe the sociodemographic and clinical profiles associated with concomitant COPCs among patients with rheumatic diseases. Methods: We retrospectively identified patients visiting rheumatology clinics at a single institution from 2010 to 2020 for five common rheumatic conditions: psoriatic arthritis (PsA), rheumatoid arthritis (RA), Sjögren syndrome (SjS), systemic lupus erythematosus (SLE), and systemic sclerosis (SSc). We compared sociodemographic, clinical, and lifestyle factors by rheumatic condition and by COPC status. We also report sex-stratified diagnosis of COPCs. The primary outcome was diagnostic validation of one or more COPCs. Results: We identified 5992 rheumatology patients: 846 with PsA, 2605 with RA, 956 with SjS, 975 with SLE, and 610 with SSc. Approximately 36-62% of patients had a concomitant COPC diagnosis. Patients with SjS had the highest prevalence (62%). Diagnosis of one or more COPCs was highest among Black patients and lowest among Asian patients. Patients using public insurance had a higher prevalence of one or more COPCs compared with those with private insurance. Patients with one or more COPCs had more depression and anxiety and more frequent emergency department visits, surgeries, and hospitalizations. Conclusion: Our findings suggest that COPCs are strikingly common among patients with rheumatic disease and are associated with lower quality of life and greater health care needs. Future research may elucidate drivers of chronic pain and how to best address the unique analgesic needs of this multimorbid population.

Prevalence and Severity of Temporomandibular Disorders in Rheumatoid Arthritis Patients.
Mustafa MA, Al-Attas BA, Badr FF, Jadu FM, Wali SO, Bawazir YM.
Cureus. 2022 Jan 15;14(1):e21276. doi: 10.7759/cureus.21276. PMID: 35070578; PMCID: PMC8761059.

Introduction: The temporomandibular joint (TMJ) is an important joint that plays major functions, including dental occlusion, mastication, and facial expressions. Different diseases can affect the TMJ, including chronic inflammatory arthritis. Rheumatoid arthritis (RA) is the most common inflammatory arthritis worldwide associated with TMJ dysfunction. In this study, we assess the prevalence of TMJ among RA patients based on the Fonseca Anamnestic Index. Methods: Eighty-one patients with rheumatoid arthritis were interviewed by a trained physician to fulfill the Fonseca Anamnestic Index questionnaire. All participants underwent a medical file review to collect their sociodemographic data, RA duration, co-existing comorbidities, and different lab results. Result: According to the Fonseca score, 29.6% had no temporomandibular disorder (TMD) among RA patients, while 39.5% had mild TMD. Only 6% had severe TMD. The female sex and increased body weight were associated with TMJ disease. Conclusion: The majority of rheumatoid arthritis patients (70%) suffer from some degree of temporomandibular joint disorder.

Endometriosis and Irritable Bowel Syndrome: A Systematic Review and Meta-Analyses.
Nabi MY, Nauhria S, Reel M, Londono S, Vasireddi A, Elmiry M, Ramdass PVAK.
Front Med (Lausanne). 2022 Jul 25;9:914356. doi: 10.3389/fmed.2022.914356. PMID: 35957857; PMCID: PMC9357916.

Objective: To estimate the pooled odds ratio of endometriosis and irritable bowel syndrome, and to estimate the pooled prevalence of irritable bowel syndrome in patients with endometriosis. Data sources: Using Cochrane Library, MEDLINE, Science Direct, ClinicalTrials.gov, Web of Science, and CINAHL, we conducted a systematic literature search through October 2021, using the key terms "endometriosis" and "irritable bowel syndrome." Articles had to be published in English or Spanish. No restriction on geographical location was applied. Methods of study selection: The following eligibility criteria were applied: full-text original articles; human studies; studies that investigated the association between endometriosis and irritable bowel syndrome. Two investigators screened and reviewed the studies. A total of 1,776 studies were identified in 6 separate databases. After screening and applying the eligibility criteria, a total of 17 studies were included for analyses. The meta-analysis of association between endometriosis and irritable bowel syndrome included 11 studies, and the meta-analysis on the prevalence of irritable bowel syndrome in endometriosis included 6 studies. Tabulation integration and results: Overall 96,119 subjects were included in the main meta-analysis (11 studies) for endometriosis and irritable bowel syndrome, with 18,887 endometriosis patients and 77,171 controls. The odds of irritable bowel syndrome were approximately 3 times higher among patients with endometriosis compared with healthy

controls (odds ratio 2.97; 95% confidence interval, 2.17 - 4.06). Similar results were obtained after subgroup analyses by endometriosis diagnosis, irritable bowel syndrome diagnostic criteria, and Newcastle-Ottawa Scale scores. Six studies reported prevalence rates of irritable bowel syndrome in women with endometriosis, ranging from 10.6 to 52%. The pooled prevalence of irritable bowel syndrome in women with endometriosis was 23.4% (95% confidence interval, 9.7 - 37.2). Conclusion: Patients with endometriosis have an approximately threefold increased risk of developing irritable bowel syndrome. Development and recent update of Rome criteria has evolved the diagnosis of IBS, potential bias should still be considered as there are no specific tests available for diagnosis.

Bidirectional Association between Fibromyalgia and Migraine among Probands and Unaffected Non-Twin Siblings: A Nationwide Population-Based Study.
Lin PC, Tsai SJ, Chen TJ, Bai YM, Chen MH, Liang CS.
Pain Pract. 2022 Aug 30. doi: 10.1111/papr.13160. Epub ahead of print. PMID: 36054795.

Objective: This study explored the bidirectional relationship between fibromyalgia and migraine among probands with either of the two disorders and their unaffected siblings. Background: Evidence suggests a bidirectional association between fibromyalgia and migraine in individuals and in twins. However, whether a bidirectional association between fibromyalgia and migraine also occurs among siblings remains unknown. Methods: Using the Taiwan National Health Insurance Research Database, we examined the data of 2677 probands with fibromyalgia, 2780 unaffected siblings, and 11,120 matched controls to assess the risk of migraine. In contrast, 1830 probands with migraine, 1936 unaffected siblings, and 7744 matched controls to assess the risk of fibromyalgia. Results: Logistic regression analyses demonstrated that patients with fibromyalgia (odds ratio [OR]: 3.69; 95% confidence interval [CI]: 2.87-4.74) and unaffected siblings (OR: 1.51; 95% CI: 1.08-2.10) were more likely to develop migraine than the controls during the follow-up period. Moreover, patients with migraine and unaffected siblings had a 4.86-fold (95% CI: 3.86-6.09) and 1.59-fold (95% CI: 1.18-2.12) increased risk of fibromyalgia than the controls. Conclusion: The bidirectional association between fibromyalgia and migraine among probands and unaffected siblings suggests a familial coaggregation of these two conditions. Additional studies are required to investigate the genetic and environmental etiologies for this coaggregation.

Central Sensitisation in Pelvic Pain: A Cohort Study.
Ryan A, Healey M, Cheng C, Dior U, Reddington C.
Aust N Z J Obstet Gynaecol. 2022 Aug 11. doi: 10.1111/ajo.13596. Epub ahead of print. PMID: 35950448.

Background: Central sensitisation (CS) leads to pain amplification and impacts on the management of pelvic pain (PP). Identification of CS in patients with PP may provide additional treatment pathways and improve patient outcomes. Aims: The aims are to quantify the prevalence of questionnaire-predicted CS (QPCS) in patients presenting with PP and investigate associations between QPCS and clinical variables. Materials and methods: This was an observational, cross-sectional study. Subjects with PP completed a questionnaire comprising four validated tools: the Central Sensitisation Inventory (CSI) for QPCS, Pain Catastrophising Scale for Catastrophising Trait, Bladder Pain/Interstitial Cystitis Symptom Score for bladder pain syndrome (BPS) and the Rome IV criteria for irritable bowel syndrome (IBS). Results: One hundred and eleven women were enrolled in the study; 74.8% (n = 83) had a CSI score of >40, indicating the presence of QPCS. Subjects with QPCS were more likely to screen positive for catastrophising trait (odds ratio (OR) 3.57, 95% CI 1.19-10.76, P = 0.02), BPS (OR 11.77, 95% CI 2.13-64.89, P = 0.005) and IBS (OR 2.6, 95% CI 1.05-6.43, P = 0.04). They were more likely to experience pain for more than two years (OR 4.98, 95% CI 1.94-12.82, P = 0.001) and other pain symptoms involving bladder (OR 9.87, 95% CI 2.52-38.67, P = 0.001), bowel (OR 3.13, 95% CI 1.31-7.48, P = 0.01), back (OR 4.17, 95% CI 1.66-10.51, P = 0.002) and vulva (OR 3.61, 95% CI 1.21-10.82, P = 0.02). They also had higher previous diagnoses of mental health disorder (OR 3.5, 95% CI 1.5-8.4, P = 0.005) or IBS (OR 8.9, 95% CI 1.6-49.1, P = 0.01). Conclusions: QPCS occurs frequently in patients with PP, and subjects with QPCS experience more prolonged and complex pain.

Sex Differences in Comorbidities Associated with Sjögren's Disease.
Bruno KA, Morales-Lara AC, Bittencourt EB, Siddiqui H, Bommarito G, Patel J, Sousou JM, Salomon GR, Paloka R, Watford ST, Hodge DO, Lieberman SM, Rozen TD, Atwal PS, Dorsher PT, Seim LA, Fairweather D.
Front Med (Lausanne). 2022 Aug 4;9:958670. doi: 10.3389/fmed.2022.958670. PMID:

35991633; PMCID: PMC9387724.

Background: Little is known about the association of comorbidities with sex and age at diagnosis in Sjögren's disease. We tested the hypothesis that sex differences occur in comorbidities in patients with Sjögren's disease. Methods: Patients with Sjögren's disease were identified from 11/1974 to 7/2018 in the Mayo Clinic electronic medical record and assessed for 22 comorbidities according to sex and age at diagnosis. Results: Of the 13,849 patients identified with Sjögren's disease, 11,969 (86%) were women and 1,880 (14%) men, primarily white (88%) with a sex ratio of 6.4:1 women to men. The mean age at diagnosis was 57 years for women and 59.7 years for men, and 5.6% had a diagnosis of fibromyalgia at Sjögren's diagnosis. Men with Sjögren's disease were more likely than women to be a current or past smoker. The average time to diagnosis of comorbidities after diagnosis of Sjögren's disease was 2.6 years. The top comorbidities in patients with Sjögren's disease were fibromyalgia (25%), depression (21.2%) and pain (16.4%). Comorbidities that occurred more often in women were hypermobile syndromes (31:1), CREST (29:1), migraine (23:1), Ehlers-Danlos syndrome (EDS) (22:1), Raynaud's syndrome (15:1), SLE (13:1), systemic sclerosis (SSc) (13:1), and fibromyalgia (12:1). Women with Sjögren's disease were at increased risk of developing hypermobile syndromes (RR 7.27, CI 1.00-52.71, $p = 0.05$), EDS (RR 4.43, CI 1.08-18.14, $p = 0.039$), CREST (RR 4.24, CI 1.56-11.50, $p = 0.005$), migraine (RR 3.67, CI 2.39-5.62, $p < 0.001$), fibromyalgia (RR 2.26, CI 1.92-2.66, $p < 0.001$), Raynaud's syndrome (RR 2.29, CI 1.77-2.96, $p < 0.001$), SLE (RR 2.13, CI 1.64-2.76, $p < 0.001$), and SSc (RR 2.05 CI 1.44-2.92; $p < 0.001$). In contrast, men with Sjögren's were at increased risk for developing myocardial infarction (RR 0.44, CI 0.35-0.55, $p < 0.001$), atherosclerosis/CAD (RR 0.44, CI 0.39-0.49, $p < 0.001$), cardiomyopathy (RR 0.63, CI 0.46-0.86, $p = 0.003$), stroke (RR 0.66 CI 0.51-0.85, $p = 0.001$), and congestive heart failure (RR 0.70, CI 0.57-0.85, $p < 0.001$). Conclusions: The top comorbidities in Sjögren's disease were fibromyalgia, depression, and pain. Women with Sjögren's disease had a higher relative risk of developing fibromyalgia, depression, pain, migraine, hypermobile syndrome, EDS and other rheumatic autoimmune diseases. Men with Sjögren's disease had higher risk of developing cardiovascular diseases.

Psychosocial Variables and Healthcare Resources in Patients with Fibromyalgia, Migraine and Comorbid Fibromyalgia and Migraine: A Cross-Sectional Study.
Calandre EP, García-Leiva JM, Ordoñez-Carrasco JL.
Int J Environ Res Public Health. 2022 Jul 23;19(15):8964. doi: 10.3390/ijerph19158964. PMID: 35897335; PMCID: PMC9331095.

Fibromyalgia and migraine frequently coexist. We aimed to compare the burden caused by fibromyalgia (FM), migraine (M) and comorbid fibromyalgia and migraine (FM + M) by assessing psychosocial variables and the use of healthcare resources. A survey was posted to the websites of different patients' associations. It included sociodemographic data, the Patient Health Questionnaire-9, the Insomnia Severity Index, the EuroQOL-5D-5L and a questionnaire evaluating the use of healthcare resources during the past six months. In total, 139 FM patients, 169 M patients and 148 FM + M patients participated in the survey. Mean depression and insomnia scores were clinically relevant in every group and significantly higher in FM + M (16.3 ± 5.4 for depression, 18.5 ± 5.6 for insomnia) than in FM (14.3 ± 5.7 for depression, 16.8 ± 5.5 for insomnia) or M (11.7 ± 5.4 for depression, 13.1 ± 5.9 for depression), where p < 0.001 in both cases. Suicidal ideation was frequent in every group, but significantly more frequent in FM + M (63% vs. 45% in FM and 35% in M; p < 0.001). EQ-5D-5L (0.656 ± 0.1 in FM + M, 0.674 ± 0.1 in FM, 0.827 ± 0.1 in M, p < 0.001) and EQ-5D-5L VAS scores (38.2 ± 21.9 in FM + M, 45.6 ± 21.8 in FM, 63.5 ± 23.7 in M, p < 0.00) were lower than the reported mean population values and the lowest in FM + M. FM and FM + M used more healthcare resources than M. It is concluded that the psychosocial burden was high in the three samples. FM and FM + M had a more relevant impact on patients' wellbeing and required more medical attention than M. The burden caused by FM + M was higher than in both individual diseases.

Irritable Bowel Syndrome is Strongly Associated with the Primary and Idiopathic Mast Cell Disorders.
Kurin M, Elangovan A, Alikhan MM, Al Dulaijan B, Silver E, Kaelber DC, Cooper G.
Neurogastroenterol Motil. 2022 May;34(5):e14265. doi: 10.1111/nmo.14265. Epub 2021 Sep 17. PMID: 34535952; PMCID: PMC9191257.

BACKGROUND: Mounting evidence supports a mechanistic association between irritable

bowel syndrome (IBS) symptoms and mast cell hyperactivity. Yet, association between IBS and mast cell disorders (MCDs) has not been studied. We examined this association using two large databases and verified with manual chart review. METHODS: The IBM Watson Health Explorys database (Somers, NY), an aggregate of electronic health record (EHR) data from over two dozen US healthcare systems, and Epic's SlicerDicer tool, a self-service tool containing de-identified data from the Epic EHR, were used to identify patients with IBS and MCDs. Patients with organic gastrointestinal disease or diseases associated with secondary mast cell hyperproliferation were excluded. Results were verified with manual chart review from two academic centers. KEY RESULTS: Up to 4% of IBS patients had a comorbid MCD. IBS was strongly associated with all MCDs. The strongest association was between IBS and mast cell activation syndrome (OR 16.3; 95% CI 13.1-20.3). Odds ratios for IBS+urticaria, IBS+idiopathic urticaria, IBS+non-malignant mastocytosis, and IBS+mast cell malignancy ranged from 4.5 to 9.9. Patients from each of these overlap cohorts were predominantly female, and the overlap occurred with all IBS subtypes. Thorough endoscopic evaluation and comorbid mood disorders and migraines are more common in the overlap cohorts than in IBS alone. CONCLUSIONS/INFERENCES: In a large US database encompassing >53 million patients over >20 years, patients with IBS are at least 4 times more likely to have a MCD than the general population. Further study of mast cell involvement in the pathogenesis of IBS is warranted.

Endometriosis and Irritable Bowel Syndrome: Similarities and Differences in the Spectrum of Comorbidities.

Peters M, Mikeltadze I, Karro H, Saare M; Estonian Biobank Research Team, Salumets A, Mägi R, Laisk T.

Hum Reprod. 2022 Aug 25;37(9):2186-2196. doi: 10.1093/humrep/deac140. PMID: 35713579.

STUDY QUESTION: Do the spectrum and prevalence of comorbidities of endometriosis and irritable bowel syndrome (IBS) overlap? SUMMARY ANSWER: Despite several overlapping symptoms, the most significantly associated comorbidities of endometriosis and IBS are different and are rather related to the organ systems primarily involved in the index diagnosis. WHAT IS KNOWN ALREADY: Endometriosis and IBS both have several similar unspecific symptoms, such as recurrent abdominal pain, cramping and anxiety, and both diseases affect young women and are associated with a number of comorbidities causing a poor quality of life. However, a detailed study, revealing the full spectrum of endometriosis and IBS comorbidities in the same study population, is lacking. STUDY DESIGN, SIZE, DURATION: This article presents a retrospective in silico analysis of the data from a large nationwide biobank-based cohort consisting of 121 773 women. After excluding all first- and second-degree relatives, the data of up to 65 421 women were analyzed. PARTICIPANTS/MATERIALS, SETTING, METHODS: International Classification of Disease-10 diagnosis main codes associated with endometriosis (N80) and IBS (K58) diagnoses were identified from the Estonian Biobank dataset by linking with the Estonian Health Insurance Fund and other relevant registries. The associations between N80 and K58 and other diagnosis codes were tested using logistic regression, adjusting for age at recruitment and 10 genetic principal components to account for potential population stratification. Bonferroni correction was applied to account for multiple testing. MAIN RESULTS AND THE ROLE OF CHANCE: Both women with endometriosis and IBS suffered from more conditions compared to the control group, with 226 and 428 diagnosis codes statistically significantly more frequent in women with respective diagnosis compared to controls. Women suffering from both conditions had 275 significantly associated comorbidities. A remarkable proportion of women with IBS or endometriosis suffered also from endometriosis (9.0%) or IBS (13.6%), respectively. In endometriosis, the most prevalent diagnoses were related to diseases of the genitourinary system (33 N-category codes) and in women with IBS, the most associated diagnoses were related to digestive disorders and gastrointestinal tract (52 codes from K-category). Among the most significant diagnoses in endometriosis were uterine leiomyomas (D25), menstrual disorders (N92) and infertility (N97) ($P < 1 \times 10\text{-}315$ for all), and in IBS, lactose intolerance (E73), gastritis and duodenitis (K29) and functional dyspepsia (K30) were in the top list of most significant comorbidities ($P < 1 \times 10\text{-}315$ for all). LIMITATIONS, REASONS FOR CAUTION: The information about the severity stages of endometriosis and subtypes of IBS was not available for analysis. The findings may not be fully extrapolated to all female populations, because all participants were from one geographic area and had good access to health services. WIDER IMPLICATIONS OF THE FINDINGS: These findings support previous studies that have found a high prevalence of pre-selected comorbidities in women with endometriosis and IBS. However, taking into account the differences in the full

spectrum of comorbidities of endometriosis and IBS may aid in diagnosing these disorders. Women and healthcare providers need to be aware that women with endometriosis are at high risks of complications during pregnancy and should be carefully monitored.

Migraine Is More Prevalent in Advanced-Stage Endometriosis, Especially When Co-Occurring with Adenomoysis.
Wu Y, Wang H, Chen S, Lin Y, Xie X, Zhong G, Zhang Q.
Front Endocrinol (Lausanne). 2022 Jan 24;12:814474. doi: 10.3389/fendo.2021.814474. PMID: 35140688; PMCID: PMC8818695.

BACKGROUND: Emerging data suggest a significant association between migraine and endometriosis, however the relationship between migraine and endometriosis severity or adenomyosis is unclear. Our objectives were to explore the relationship between migraine and endometriosis, according to the endometriosis severity and co-exist with adenomyosis or not. METHODS: This case-control study of 167 endometriosis patients verified by surgery and 190 patients for other benign gynecological conditions (control subjects) was performed from September 2017 and January 2021. There is 49 adenomyosis detected by transvaginal ultrasound or histologic diagnosis among the endometriosis patients. Besides, we also included 41 adenomyosis but without endometriosis patients as a subgroup. All women completed a self-administered headache questionnaire and diagnosed as migraine according to the International Headache Society classification. The severity and stage of endometriosis was evaluated with revised American Society of Reproductive Medicine (rASRM) score. We used logistic regression to estimate the association between the presence of migraine and endometriosis severity while accounting for important confounders, including age, body mass index (BMI) and family history of migraine. We also estimate the risk of adenomyosis alone and adenomyosis with co-occurring endometriosis in migrainous women. RESULTS: Migraine was significantly more prevalent in endometriosis patients compared with controls (29.9% vs. 12.1%, $p<0.05$), but the prevalence was similar between isolated adenomyosis patients and controls (9.8% vs.12.1%, $p>0.05$). For all endometriosis and control participants, migraineurs were 4.6-times (OR=4.6; 95% CI 2.7-8.1) more likely to have severe endometriosis. However, the strength of the association decreased when the analysis examined in moderate stage (OR=3.6, 95% CI 2.1-6.2). The risk of mild and minimal endometriosis was not significant (OR=1.9, 95%CI 0.9-4.0; OR=1.6, 95% CI 0.8-3.4; respectively). When we divided the endometriosis patients according to whether co-occurring with adenomyosis. We found in migrainous women, the risk of endometriosis co-exist with adenomyosis increased, with nearly fivefold greater odds compared with control (OR=5.4;95% CI 3.0-9.5), and nearly two times higher than the risk of endometriosis without co-exist adenomyosis patients (OR=2.2; 95% CI 1.2-3.8). CONCLUSION: Our study supports the strong association between migraine and endometriosis. We found migrainous women suffer more frequently from severe endometriosis, especially endometriosis with co-occurring adenomyosis. It is advisable to heighten suspicion for patients who are presenting with either these conditions in order to optimize therapy.

Increased Prevalence of Irritable Bowel Syndrome in Migraine Patients: A Systematic Review and Meta-Analysis.
Wongtrakul W, Charoenngam N, Ungprasert P.
Eur J Gastroenterol Hepatol. 2022 Jan 1;34(1):56-63. doi: 10.1097/MEG.0000000000002065. PMID: 33470704.

OBJECTIVE: Even though evidence showing increased prevalence of irritable bowel syndrome (IBS) among migraine patients exists, it has not been well-established and the magnitude of association varies substantially across the studies. This study aimed to comprehensively compare the prevalence of IBS among migraineurs versus nonmigraineurs using the systematic review and the meta-analysis technique. METHODS: Two authors independently conducted a literature search in MEDLINE, EMBASE and Google Scholar database up to April 2020. The eligible study must consist of two groups of participants, migraineurs and nonmigraineurs, and report the prevalence of IBS in both groups. Alternatively, an eligible study may report the odds ratio (OR) with a 95% confidence interval (CI) of the association between migraine and IBS. Point estimates and standard errors from each eligible study were combined together using the generic inverse variance method of DerSimonian and Laird. RESULTS: Of the 2531 articles identified from the three databases, 11 studies with a total of 28 336 migraineurs and 1 535 758 nonmigraineurs met the selection criteria and were included into the meta-analysis. The pooled analysis found that migraineurs had a significantly higher prevalence of IBS than nonmigraineurs with the pooled OR of 2.49

(95% CI, 2.22-2.78; I2, 42%). The funnel plot was asymmetric and suggested the presence of publication bias. CONCLUSION: A significantly increased prevalence of IBS among patients with migraine was demonstrated in this study.

Association Between Endometriosis and Subsequent Risk of Sjögren's Syndrome: A Nationwide Population-Based Cohort Study.
Chao YH, Liu CH, Pan YA, Yen FS, Chiou JY, Wei JC. Front Immunol. 2022 May 3;13:845944. doi: 10.3389/fimmu.2022.845944. PMID: 35592328; PMCID: PMC9110644.

OBJECTIVE: The relationship between endometriosis and the ensuing risk of Sjögren's syndrome has remained unclear. This study aims to present epidemiological evidence for this connection. METHODS: This is a retrospective cohort study of endometriosis patients (ICD-9-CM 617.0-617.9 and 621.3) and matched comparison group between 2000 and 2012 in the National Taiwan Insurance Research Database. After age matching, we analyzed the association between endometriosis and Sjögren's syndrome (ICD-9-CM 710.2). We used the Cox proportional hazard model to examine the hazard ratio of incidental Sjögren's syndrome. Subgroup analyses on age, comorbidities, and disease duration were also performed. RESULTS: A total of 73,665 individuals were included in this study. We identified 14733 newly diagnosed endometriosis patients and 58,932 non-endometriosis comparison group. The adjusted hazard ratio (HR) for incidental Sjögren's syndrome was 1.45 (95% confidence interval CI=1.27-1.65) in the endometriosis group, compared to the non-endometriosis comparison group. In subgroup analysis, the adjusted HR was 1.53 (95% CI=1.25-1.88) in the age group of 20-39 and 1.41 (95% CI =1.18-1.68) in the age of 40-64. Time-vary analysis showed that endometriosis who have a follow-up time of fewer than five years (adjusted HR=1.57, 95% CI=1.32-1.87) have a significantly highest risk of having subsequent Sjögren's syndrome. CONCLUSION: This population-based cohort study indicated that having a history of endometriosis puts patients at an increased risk of getting Sjögren's syndrome afterward, especially in the age group of 20-39 and within the first five years after the diagnosis of endometriosis. Clinicians should recognize this possible association in managing endometriosis or Sjögren's syndrome patients.

Characteristics and Comorbidities of Headache in Patients over 50 years of age: A Cross-Sectional Study.
Togha M, Karimitafti MJ, Ghorbani Z, Farham F, Naderi-Behdani F, Nasergivehchi S, Vahabi Z, Ariyanfar S, Jafari E.
BMC Geriatr. 2022 Apr 10;22(1):313. doi: 10.1186/s12877-022-03027-1. PMID: 35399063; PMCID: PMC8994908.

BACKGROUND: Although headache is a common complaint in younger individuals, it is one of the most common complaints among persons over the age of 50 and is a significant cause of morbidity. As there are differences in the causes and types of headache, the diagnosis and management of headache in older adults differ from that in younger individuals. METHODS: In this cross-sectional study, 570 patients ≥ 50 years were recruited at a university affiliated tertiary headache center between 2016 and 2019. Demographic data, headache characteristics, and comorbid medical conditions were recorded. The presence of depression was explored using the Beck Depression Inventory. The patients were evaluated using the STOP-BANG scale to determine the risk of obstructive sleep apnea. RESULTS: The mean age of the patients was 57.7 years. Seventy-three percent of the patients had primary headache disorders, with the most prevalent types being migraine, followed by tension-type headache. Secondary headaches were primarily the result of overuse of medication, cervical spine disease, and hypertension. Patients with medication-overuse headache were significantly more likely to suffer from hypothyroidism and gastrointestinal problems such as bleeding/ulcers. Irritable bowel syndrome was also more common in patients with medication-overuse headaches and migraines. The risk for obstructive sleep apnea was intermediate in 45.2% of the patients with hypertension-induced headache, but was lower in the majority of others. There was a high tendency for moderate-to-severe depression in the participants; however, the Beck Depression Inventory scores were significantly higher in medication-overuse headache patients. CONCLUSION: Proper treatment of headache in middle-aged and older adults requires the recognition of secondary causes, comorbid diseases, and drug induced or medication overuse headaches. Special attention should be paid to depression and obstructive sleep apnea in such patients suffering from headache disorders.

Burden of Endometriosis: Infertility, Comorbidities, and Healthcare Resource Utilization.
Eisenberg VH, Decter DH, Chodick G, Shalev V, Weil C.

J Clin Med. 2022 Feb 21;11(4):1133. doi: 10.3390/jcm11041133. PMID: 35207404; PMCID: PMC8880408.

The goal of our study was to evaluate the burden of endometriosis in the community by comparing healthcare resource utilization, total direct medical costs, infertility, and comorbidity rates of women with and without a diagnosis of endometriosis. A retrospective case-control study was performed using the databases of a 2.1 million-member nationwide healthcare plan. The study population included women aged 15-55 years enrolled in the healthcare plan. Women with a diagnosis (ICD-9) of endometriosis were compared to controls without diagnosed endometriosis. Women were individually matched (1:4) on age and residence area. Patient characteristics were described, including infertility, comorbidities, and annual healthcare resource utilization. Total direct medical costs were analyzed in a generalized linear model adjusting for age. Women with endometriosis (n = 6146, mean age ± SD: 40.4 ± 8.0 y) were significantly more likely than controls (n = 24,572) to have a lower BMI and a higher socioeconomic status. After adjusting for BMI and socioeconomic status, endometriosis was significantly associated with infertility (OR = 3.3; 95% CI 3.1-3.5), chronic comorbidities, higher utilization of healthcare services (hospitalization: OR = 2.3; 95% CI 2.1-2.5), pain medications, and antidepressants. Women aged 15-19 y with endometriosis had substantially higher utilization of primary care visits (57.7% vs. 14.4%) and oral contraceptive use (76.9% vs. 9.6%). Direct medical costs associated with endometriosis were higher than those for controls (OR = 1.75; 95% CI 1.69-1.85). Endometriosis is associated with a high burden of comorbidities, increased healthcare resource utilization, and excess costs, particularly for younger patients whose healthcare needs may differ widely from the older population.

The Prevalence of Comorbid Chronic Pain Conditions among Patients with Temporomandibular Disorders: A Systematic Review.
Kleykamp BA, Ferguson MC, McNicol E, Bixho I, Arnold LM, Edwards RR, Fillingim R, Grol-Prokopczyk H, Ohrbach R, Turk DC, Dworkin RH.
J Am Dent Assoc. 2022 Mar;153(3):241-250.e10. doi: 10.1016/j.adaj.2021.08.008. Epub 2021 Dec 21. PMID: 34952681.

BACKGROUND: This systematic review was designed to evaluate the presence of comorbid conditions among patients with temporomandibular disorders (TMDs). TYPES OF STUDIES REVIEWED: The authors reviewed studies that reported the prevalence or incidence of chronic pain conditions or psychiatric disorders (anxiety, mood, personality disorders) among patients with any type of TMD. The authors calculated sample size-weighted prevalence estimates when data were reported in 2 or more studies for the same comorbid condition. RESULTS: A total of 9 prevalence studies and no incidence studies were eligible for review; 8 of the studies examined chronic pain comorbidities. Weighted estimates showed high prevalence of pain comorbidities across studies, including current chronic back pain (66%), myofascial syndrome (50%), chronic stomach pain (50%), chronic migraine headache (40%), irritable bowel syndrome (19%), and fibromyalgia (14%). A single study examined psychiatric disorders and found that current depression was the most prevalent disorder identified (17.5%). CONCLUSIONS AND PRACTICAL IMPLICATIONS: There is a high prevalence of comorbid chronic pain conditions among patients with TMDs, with more than 50% of patients reporting chronic back pain, myofascial syndrome, and chronic stomach pain. Psychiatric disorders among patients with different types of TMDs were studied less commonly in this pain population. Knowledge of the distribution of these and other comorbid disease conditions among patients with different types of TMDs can help dentists and other health care providers to identify personalized treatment strategies, including the coordination of care across medical specialties.

Association of Temporomandibular Disorder-Related Pain with Severe Headaches-a Bayesian View.
Ashraf J, Närhi M, Suominen AL, Saxlin T.
Clin Oral Investig. 2022 Jan;26(1):729-738. doi: 10.1007/s00784-021-04051-y. Epub 2021 Jul 5. PMID: 34224000; PMCID: PMC8791898.

OBJECTIVES: Association of temporomandibular disorders (TMD)-related pain with severe headaches (migraine and tension-type headaches [TTH]) was studied over a follow-up period of 11 years. MATERIALS AND METHODS: The data used was from two nationally representative health surveys in Finland-the Health 2000 Survey (baseline) and the Health 2011 Survey (follow-up) (Bioresource Research Impact Factor [BRIF] 8901)-conducted by the Finnish Institute for Health and Welfare (THL). The primary dataset of the current study

included a subset of the population undergoing a clinical oral examination, including TMD examination, at baseline, and answering the questions related to severe headaches, both at baseline and at follow-up (n = 530). From the primary dataset, two datasets were created to study the onset of migraine (dataset 1) and TTH (dataset 2) separately. Dataset 1 included participants healthy of migraine, but not other headaches, at baseline (n = 345), and dataset 2 participants healthy of TTH and other headaches, except migraine, at baseline (n = 464). Bayesian logistic regression models with weakly informative priors were utilized to assess the association of muscle-related TMD pain (mTMD) at baseline and temporomandibular joint-related TMD pain (jTMD) at baseline with the presence of migraine and TTH at follow-up. RESULTS: Neither of the baseline TMD-related pain variables were associated with the presence of migraine at follow-up (posterior effect estimates-0.12, 95% credible interval [CI] -0.49-0.24, and 0.11, 95% CI -0.38-0.59, for mTMD and jTMD, respectively), whereas mTMD at baseline (posterior effect estimate 0.36, 95% CI 0.02-0.69), but not jTMD at baseline (posterior effect estimate -0.32, 95% CI -0.94-0.25), was associated with the presence of TTH at follow-up. Bayesian sensitivity analyses revealed that the estimates of the regression models were stable, demonstrating sufficient validity and consistency of the estimates. CONCLUSION: These results indicate that diverse mechanisms may exist behind the associations of TMD-related painful conditions with different types of severe headaches. CLINICAL RELEVANCE: TMD-related pain is a frequent comorbidity of severe primary headaches. Therapy of severe primary headaches may thus benefit significantly with the incorporation of a multi-disciplinary clinical team.

Prevalence, Incidence, and Factors Associated with Non-Specific Chronic Low Back Pain in Community-Dwelling Older Adults Aged 60 Years and Older: A Systematic Review and Meta-Analysis.
Wong CK, Mak RY, Kwok TS, Tsang JS, Leung MY, Funabashi M, Macedo LG, Dennett L, Wong AY.
J Pain. 2022 Apr;23(4):509-534. doi: 10.1016/j.jpain.2021.07.012. Epub 2021 Aug 24. PMID: 34450274.

Chronic low back pain (CLBP) is common among older adults. This systematic review aimed to summarize: (1) the prevalence and incidence of CLBP in older adults, and (2) demographic, psychological, and clinical factors positively/negatively associated with prevalence/incidence of CLBP among older adults. Four databases were searched to identify relevant publications. Ten studies (31,080 older adults) were included after being screened by 5 independent reviewers using predetermined criteria. The methodological quality of these studies was evaluated by standardized tools. The quality of evidence for all factors were appraised by modified GRADE for cohort studies. Twenty-eight and 1 factors were associated with a higher prevalence and a lower 5-year cumulative incidence of CLBP, respectively. No prognostic factor was identified. There was very limited to limited evidence that females, obesity, anxiety, depression, mental disorders, self-expectation of recovery, self-perceived health status, lifestyle (smoking, daily fluoride consumption), previous falls or lower body injury, retirement/disability due to ill health, family history of body pain, comorbidity (knee osteoarthritis, or chronic obstructive pulmonary disease with/without hypertension), weak abdominal muscles, leg pain, leg pain intensity, widespread pain, pain interference on functioning, use of pain medication, occupational exposure (driving for >20 years, or jobs involving bending/twisting for >10 years), disc space narrowing and severe facet osteoarthritis were significantly related to a higher prevalence of CLBP in older adults. However, very limited evidence suggested that intermediate level of leisure-time physical activity was associated with a lower prevalence of CLBP in older adults. Given the aging population and limited information regarding risk factors for CLBP in older adults, future high-quality prospective studies should identify relevant risk factors to help develop proper preventive and treatment strategies. PERSPECTIVE: Despite the high prevalence of non-specific chronic low back pain among older adults, there is only very limited to limited evidence regarding factors associated with a higher prevalence of chronic low back pain in this population. Given the aging population, high-quality prospective studies are warranted to address this gap.

Association of Migraine and Irritable Bowel Syndrome in Saudi Arabia: A Nationwide Survey.
Bin Abdulrahman KA, Alenazi NS, Albishri SB, Alshehri FF.
Biomed Res Int. 2022 Jan 18;2022:8690562. doi: 10.1155/2022/8690562. PMID: 35087910; PMCID: PMC8789428.

Migraine is a primary headache disorder with a prevalence of 11.6% globally and 27% in Saudi Arabia. Irritable bowel syndrome (IBS) has a prevalence of 9.2% worldwide. The

prevalence of IBS has not been established nationally. However, provincial studies for migraine and IBS have been conducted nationwide. There is a significant link between migraine and IBS globally. Migraineurs had a considerably greater prevalence of IBS than nonmigraineurs (OR = 2.49, 95% CI 2.22-2.78). Patients with IBS have 60% higher odds for migraines. This identifies an association that needs to be investigated in a nationwide manner. The study has two main aims. The first is to measure the prevalence of migraine and irritable bowel syndrome in Saudi Arabia. The second is to observe the association and the relationship between migraine and irritable bowel syndrome in Saudi Arabia. A cross-sectional study was conducted among the general population of Saudi Arabia between March 2021 and June 2021, whose ages are 15 years old or greater. Participants filled an online self-administered survey. The data collection tools included the Migraine Screen Questionnaire (MS-Q) for migraine symptoms, migraine severity (MIGSEV) scale for severity of migraine, and the IBS module of the Rome IV Diagnostic Questionnaire (R4DQ) for IBS symptoms and their subtype. With 2802 participants, the majority of the study samples were males, who constituted 52.5%. Among the study's sample, the prevalence of migraine consisted of 27.4%, and the prevalence of IBS was 16.4%. The odds of having IBS in migraineurs were much higher than in those without migraine (OR 4.127; 95% CI 3.325-5.121), and the association was statistically significant ($p < 0.001$). In conclusion, there is a strong association between migraine and irritable bowel syndrome in Saudi Arabia.

Association between Gastrointestinal Diseases and Migraine.
Kim J, Lee S, Rhew K.
Int J Environ Res Public Health. 2022 Mar 28;19(7):4018. doi: 10.3390/ijerph19074018. PMID: 35409704; PMCID: PMC8997650.

Migraine is a common disease worldwide, and recent studies showed that the incidence of migraine was increased in patients with gastrointestinal (GI) diseases. In addition, preclinical evidence suggested a bidirectional relationship between the GI nervous system and the central nervous system called the gut-brain axis. This study aimed to determine the association between several high-prevalence GI diseases and migraine. Patients diagnosed with migraine or GI diseases were classified as the patient group at least twice a year. We included peptic ulcer disease, dyspepsia, inflammatory bowel disease, irritable bowel syndrome, and gastroesophageal disease as GI diseases. A total of 781,115 patients from the HIRA dataset were included in the study. The prevalence of migraine was about 3.5 times higher in patients with one or more GI diseases after adjusting for age, gender, and insurance type (adjusted odds ratio (ORadj = 3.46, 95% CI: 3.30-3.63, p < 0.001). In addition, the prevalence of migraine was increased as the number of comorbid GI diseases increased. The prevalence of GI disease was also higher in patients with medication for migraine, both preventive and acute treatment, compared to patients with either acute preventive or acute treatment. There was a statistically significant association between the prevalence of GI diseases and migraine, and the higher the number of accompanying GI diseases, the higher the correlation was in patients using both preventive and acute treatment drugs for migraine.

Painful and Non-painful Comorbidities Associated with Short- and Long-term Painful Temporomandibular Disorders: A Cross-sectional Study among Adolescents from Brazil, Canada and France.
Velly AM, Botros J, Bolla MM, Khan K, Teixeira Junior OA, Guimarães AS, Gornitsky M.
J Oral Rehabil. 2022 Mar;49(3):273-282. doi: 10.1111/joor.13280. Epub 2021 Dec 27. PMID: 34731502.

BACKGROUND: Temporomandibular disorder (TMD) pain is common among adolescents. The association between painful TMD and other comorbidities has been demonstrated. However, the difference between short-term (<6 months) and long-term (≥ 6 months) painful TMD is not yet clear. OBJECTIVE: The aim of this study was to assess the association between comorbidities and short- and long-term painful TMD among adolescents. METHODS: In this cross-sectional study, adolescents were recruited from Montreal (Canada), Nice (France) and Arceburgo (Brazil). Self-reported painful TMD, comorbidities, school absence and analgesic intake were assessed using reliable instruments. Multivariable logistic regression analyses were conducted to assess the study aims. RESULTS: The prevalence of short- and long-term painful TMD was estimated at 22.29% and 9.93% respectively. The number of comorbidities was associated with short- (OR = 1.71, 95%CI = 1.53-1.90) and long-term painful TMD (OR = 1.79, 95%CI = 1.55-2.08) compared to controls. Frequent headaches (ORshort-term = 4.39, 95%CI = 3.23-5.98, ORlong-term = 3.69, 95%CI = 2.45-5.57) and back pain (ORshort-term = 1.46, 95%CI = 1.06-

2.03, ORlong-term = 1.69, 95%CI = 1.11-2.59) were associated with both painful TMD groups. Frequent neck pain (OR = 2.23, 95%CI = 1.53-3.26) and allergies were only associated with short-term painful TMD (OR = 1.54, 95%CI = 1.13-2.10). Frequent stomach pain was related to long-term (OR = 2.01, 95%CI = 1.35-3.26), and it was the only comorbidity significantly more frequent among the long than short-term TMD (OR = 1.82, 95%CI: 1.14-2.90). These analyses were adjusted by sex, age and city. CONCLUSION: In this multi-centre study, both short- and long-term painful TMD are associated with frequent headaches and back pain, whereas frequent neck pain and allergies are related to only short-term and frequent stomach pain with long-term painful TMD.

Patients with Ankylosing Spondylitis have High Risk of Irritable Bowel Syndrome: A Long-term Nationwide Population-based Cohort Study.
Feng HY, Chan CH, Chu YC, Qu XM, Wang YH, Wei JC.
Postgrad Med. 2022 Apr;134(3):290-296. doi: 10.1080/00325481.2022.2041338. Epub 2022 Feb 21. PMID: 35139724.

OBJECTIVE: Ankylosing spondylitis (AS) is a chronic inflammatory disease, might carry a high risk of irritable bowel syndrome (IBS) due to abnormal gut microbiota or inflammatory reaction. METHODS: We conducted a 14-year retrospective cohort study based on Taiwan's National Health Insurance Research Database (NHIRD). A total of 4007 patients with newly diagnosed AS (outpatient visits≧3 times, or hospitalization≧1 time) and 988,084 non-AS comparisons were enrolled during 2000-2012. To ensure baseline comparability, the propensity score was matched by age, gender, comorbidities, and other possible confounders. The outcome was the incidence of IBS, followed up to the end of 2013. Cox proportional hazard model calculated adjusted hazard ratio (aHR) and the cumulative incidence of both groups was analyzed by the Kaplan-Meier method. RESULT: After propensity score matching, baseline demographic characteristics were comparable between AS patients and the comparison group. The crude HR for IBS in the AS group was significantly higher 2.41 (95%C.I. = 1.84-3.16) than comparison group. After adjusting for possible confounders, adjusted HR was 2.50 (95%C.I. = 1.91-3.29). The cumulative incidence of IBS in AS was significantly higher than non-AS comparisons during the 14-year follow-up (P < 0.001). CONCLUSION: This nationwide population-based cohort study showed that patients with AS have higher risks of IBS than those of the non-AS comparison group.

Comprehensive Assessment of Multimorbidity Burden in a Population-Based Cohort of Patients with Rheumatoid Arthritis.
Crowson CS, Gunderson TM, Dykhoff HJ, Myasoedova E, Atkinson EJ, Kronzer VL, Coffey CM, Davis Iii JM. RMD Open. 2022 Jan;8(1):e002022. doi: 10.1136/rmdopen-2021-002022. PMID: 35042730; PMCID: PMC8768925.

OBJECTIVE: To comprehensively assess multimorbidity burden in patients with rheumatoid arthritis (RA) in order to unify the multimorbidity definition for RA research and clinical practice. METHODS: In this population-based study, residents of eight Minnesota counties with prevalent RA on 1 January 2015 were identified. Age, sex and county-matched non-RA comparators were selected from the same population. Diagnostic codes were retrieved for 5 years before 1 January 2015. Using two codes ≥30 days apart, 44 previously defined morbidities and 78 non-overlapping chronic disease categories based on Clinical Classification Software were defined. Prevalence of each morbidity in the RA versus non-RA cohorts was compared using false discovery rate to adjust for multiple comparisons. Morbidities more common in RA than non-RA and those with prevalence ≥5% were retained. RESULTS: 1643 patients with RA and 1643 non-RA subjects (72% women; mean age 63.1 years) were studied. Using the 44 morbidities, multimorbidity (defined as 2+ morbidities) was present in 1411 (86%) of RA and 1164 (71%) of non-RA subjects (p<0.001) with 5+ morbidities present in 907 (55%) of RA and 619 (38%) of non-RA (p<0.001). Patients with RA had significantly higher prevalence of 24 of the 44 morbidities compared with non-RA, especially interstitial lung disease, fibromyalgia, osteoarthritis and osteoporosis. Among the additional 78 categories, 7 were significantly higher in RA than non-RA, including organic sleep disorders, vitamin D deficiency and foot ulcers. CONCLUSION: Patients with RA have a higher prevalence of multimorbidity compared with non-RA subjects. These results confirm the list of 44 morbidities and add several other morbidities of interest in RA.

Risk of Burning Mouth Syndrome in Patients with Migraine: A Nationwide Cohort Study.
Kim DK, Lee HJ, Lee IH, Lee JJ.
J Pers Med. 2022 Apr 11;12(4):620. doi: 10.3390/jpm12040620. PMID: 35455736; PMCID:

PMC9029595.

Migraine is a common neurological disease that causes a variety of symptoms, most notably throbbing, which is described as a pulsing headache on one side of the head. Burning mouth syndrome (BMS) is defined as an intra-oral burning sensation. Currently, no medical or dental cause has been identified for BMS. Interestingly, neuropathic pain is a characteristic feature of BMS; however, it remains unclear whether migraine can cause BMS. We aimed to identify the association of migraine with the risk of developing BMS. We used a representative nationwide cohort sample of approximately 1 million patients from 2002 to 2013 to investigate the prospective association between migraine and BMS. A total of 4157 migraine patients (migraine group) and 16,628 patients without migraine (comparison group) were enrolled after 1:4 propensity score matching. The overall incidence of BMS was significantly higher in the migraine group (0.15 per 1000 person-years) than in the comparison group (0.05 per 1000 person-years). The adjusted HR for patients with migraine who reported BMS events during the 10-year follow-up period was 2.96 (95% confidence interval, (1.02-8.56), after adjusting for other covariates. However, in the subgroup analysis, the adjusted HR for BMS events did not show a significant difference between the migraine and comparison group according to sex, age, and comorbidities. This study suggests that migraine is associated with an increased incidence of BMS. Therefore, clinicians should be attentive to detect BMS at an early stage when treating patients with migraine.

Increased Risk of Being Diagnosed with Endometriosis in Patients with Systemic Lupus Erythematosus: A Population-based Cohort Study in Taiwan.
Sun YH, Leong PY, Huang JY, Wei JC.
Sci Rep. 2022 Aug 3;12(1):13336. doi: 10.1038/s41598-022-17343-4. PMID: 35922461; PMCID: PMC9349269.

Epidemiological study shows inconsistent results in the association between endometriosis and Systemic lupus erythematosus (SLE). We conducted a nationwide retrospective cohort study and analyzed data from the Taiwan Longitudinal Health Insurance Research Database 2000 (n = 958,349) over a 13-year follow-up period (2000-2013). After matching 1930 SLE women with 7720 non-SLE women in a 1:4 ratio by age, we used Cox proportional hazard regression to calculate the adjusted hazard ratio (aHR) for endometriosis diagnosed after SLE. We also used a diagnosis of endometriosis with previous gynecologic surgery codes as secondary outcomes and performed sensitivity analyses using a landmark analysis. After adjustment for age, urbanization, income, length of hospital stay, and comorbidities in the age-matched group, women with SLE had a higher risk of endometriosis than women without SLE (aHR 1.32, 95% CI 1.02-1.70). When we defined endometriosis as patients with an ICD-9 endometriosis code after undergoing gynecologic surgery, the increased risk of endometriosis in patients with SLE was not significant. Our findings suggest that the risk of endometriosis was significantly elevated in the cohort of women with SLE compared with the age-matched general cohort of women. The burden of endometriosis in SLE patients requires special attention.

Women with Polycystic Ovary Syndrome are Burdened with Multimorbidity and Medication Use Independent of Body Mass Index at Late Fertile Age: A Population-based Cohort Study.
Kujanpää L, Arffman RK, Pesonen P, Korhonen E, Karjula S, Järvelin MR, Franks S, Tapanainen JS, Morin-Papunen L, Piltonen TT.
Acta Obstet Gynecol Scand. 2022 Jul;101(7):728-736. doi: 10.1111/aogs.14382. Epub 2022 Jun 8. PMID: 35673942.

Introduction: This population-based follow-up study investigated the comorbidities, medication use, and healthcare services among women with polycystic ovary syndrome (PCOS) at age 46 years. Material and methods: The study population derived from the Northern Finland Birth Cohort 1966 and consisted of women reporting oligo/amenorrhea and hirsutism at age 31 years and/or a PCOS diagnosis by age 46 years (n = 246) and controls without PCOS symptoms or diagnosis (n = 1573), referred to as non-PCOS women. The main outcome measures were self-reported data on symptoms, diagnosed diseases, and medication and healthcare service use at the age of 46 years. Results: Overall morbidity risk was increased by 35% (risk ratio [RR] 1.35, 95% confidence interval [CI] 1.16-1.57) and medication use by 27% [RR 1.27, 95% CI 1.08-1.50) compared with non-PCOS women, and the risk remained after adjusting for body mass index. Diagnoses with increased prevalence in women with PCOS were migraine, hypertension, tendinitis, osteoarthritis, fractures, and endometriosis. PCOS was also associated with autoimmune diseases and recurrent upper respiratory tract

infections and symptoms. Interestingly, healthcare service use did not differ between the study groups after adjusting for body mass index. Conclusions: Women with PCOS are burdened with multimorbidity and higher medication use, independent of body mass index.

An Online Survey of Pelvic Congestion Support Group Members Regarding Comorbid Symptoms and Syndromes.
Smith SJ, Sichlau M, Sewall LE, Smith BH, Chen B, Khurana N, Rowe PC.
Phlebology. 2022 Sep;37(8):596-601. doi: 10.1177/02683555221112567. Epub 2022 Jul 13.
PMID: 35831253.

Objectives: Patients with pelvic congestion syndrome (PCS) often report overlapping somatic symptoms and syndromes. The objective of this study was to explore the prevalence of co-existing symptoms and self-reported syndrome diagnoses among women with PCS and to inform future research hypotheses. Methods: A brief online survey was offered to members of a PCS support group website. Responses were assessed for self-reported co-existing symptoms and formal diagnoses, including: chronic fatigue syndrome, fibromyalgia, postural tachycardia syndrome, irritable bowel syndrome, migraines, interstitial cystitis, and temporomandibular joint dysfunction. Results: Of a total of 6000 members, there were 398 respondents; 232 (59%) had not yet been treated for PCS. Among these, the most prevalent co-existing symptoms were as follows: severe fatigue (72%), dizziness (63%), IBS symptoms (61%), brain fog (33%), migraines (49%), polyuria or dysuria (41%), excessive sweating (31%), TMJ pain (31%), and loose skin or lax joints (18%). These are much higher than reported for the general female population. The most commonly self-reported comorbid syndrome diagnoses for the overall group of 398 were: irritable bowel syndrome (29%), fibromyalgia (13%), spinal nerve problems (18%), interstitial cystitis (10%), postural tachycardia syndrome (9%), hypertension (11%), chronic fatigue syndrome (10%), and Ehlers-Danlos syndrome (6%). Other than with hypertension, these rates are variably higher than in the general population. Conclusion: Several self-reported co-existing symptoms and syndromes are more prevalent in members of a PCS support group relative to the reported prevalence in the general population. More formal investigation is warranted to evaluate this finding and to investigate potential etiologic links. Ehlers-Danlos Syndrome appears to be common in self identifying PCS women.