



# CUTTING EDGE

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This e-newsletter - published by 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 October 2022 and March 2023.

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## **Pathophysiology Studies**

### **Artificial Neural Networks Coupled with MALDI-TOF MS Serum Fingerprinting to Classify and Diagnose Pathological Pain Subtypes in Preclinical Models.**

Deulofeu M, Peña-Méndez EM, Vaňhara P, Havel J, Morán L, Pečinka L, Bagó-Mas A, Verdú E, Salvadó V, Boadas-Vaello P.

ACS Chem Neurosci. 2023 Jan 18;14(2):300-311. doi: 10.1021/acchemneuro.2c00665.

Epub 2022 Dec 30. PMID: 36584284; PMCID: PMC9853500.

Pathological pain subtypes can be classified as either neuropathic pain, caused by a somatosensory nervous system lesion or disease, or nociplastic pain, which develops without evidence of somatosensory system damage. Since there is no gold standard for the diagnosis of pathological pain subtypes, the proper classification of individual patients is currently an unmet challenge for clinicians. While the determination of specific biomarkers for each condition by current biochemical techniques is a complex task, the use of multimolecular techniques, such as matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS), combined with artificial intelligence allows specific fingerprints for pathological pain-subtypes to be obtained, which may be useful for diagnosis. We analyzed whether the information provided by the mass spectra of serum samples of four experimental models of neuropathic and nociplastic pain combined with their functional pain outcomes could enable pathological pain subtype classification by artificial neural networks. As a result, a simple and innovative clinical decision support method has been developed that combines MALDI-TOF MS serum spectra and pain evaluation with its subsequent data analysis by artificial neural networks and allows the identification and classification of pathological pain subtypes in experimental models with a high level of specificity.

Circulating Polyunsaturated Fatty Acids and Pain Intensity in Five Chronic Pain Conditions.  
Sanders AE, Weatherspoon ED, Ehrmann BM, Soma PS, Shaikh SR, Preisser JS, Ohrbach R, Fillingim RB, Slade GD.

J Pain. 2022 Oct 20:S1526-5900(22)00434-5. doi: 10.1016/j.jpain.2022.10.008. Epub ahead of print. PMID: 36273777.

Pain intensity is well-known to be influenced by a wide range of biobehavioral variables. Nutritional factors, however, have not been generally considered for their potential importance. This cross-sectional study examined associations between erythrocyte omega-6 (n-6) and omega-3 (n-3) polyunsaturated fatty acids (PUFAs) and pain intensity in 605 adults. Pain intensity was computed on a 0-100 numeric rating scale from questions about five chronic pain conditions: orofacial pain, headache, low back pain, irritable bowel syndrome, and bodily pain. For each pain condition, multiple linear regression tested the hypothesis that a higher ratio of n-6 arachidonic acid to the sum of n-3 eicosapentaenoic acid and docosahexaenoic acid (AA/(EPA+DHA)) was associated with greater pain intensity. In covariate-adjusted analysis, orofacial pain intensity increased 5.7 points (95% CI: 1.4, 9.9) per unit increase in n-6/n-3 PUFA ratio. Likewise, a one unit increase in n-6/n-3 PUFA ratio was associated with significant increases in pain intensity (range 5-8 points) of headache pain, low back pain, and bodily pain, but not abdominal pain. Separate multiple linear regression models investigated the independent strength of association of individual PUFAs to the intensity of each pain condition. Overall, n-3 docosahexaenoic acid was most strongly, and inversely, associated with pain intensity. PERSPECTIVE: Perspective: A higher ratio of n-6/n-3 long-chain polyunsaturated fatty acids was associated greater pain intensity for orofacial pain, headache, low back pain, and bodily pain, but not abdominal pain. The n-6/n-3 PUFA ratio was more consistently associated with pain intensity than any individual constituent of the long-chain PUFA ratio.

Ratio of Omega-6/Omega-3 Polyunsaturated Fatty Acids Associated with Somatic and Depressive Symptoms in People with Painful Temporomandibular Disorder and Irritable Bowel Syndrome.

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

J Pain. 2022 Oct;23(10):1737-1748. doi: 10.1016/j.jpain.2022.04.006. Epub 2022 Apr 25. PMID: 35477107; PMCID: PMC9561958.

Somatic symptom disturbance is among the strongest predictors of painful temporomandibular disorder (TMD). Related psychological constructs, such as anxiety and depression, respond therapeutically to omega-3 polyunsaturated fatty acids (PUFAs) in clinical trials. This cross-sectional study investigated associations between the omega-6/omega-3 PUFA ratio and somatic symptom disturbance and depressive symptoms in a community-based sample of 501 adults and determined whether these associations differed between adults with and without TMD or irritable bowel syndrome (IBS). Liquid chromatography tandem mass spectrometry quantified PUFAs in circulating erythrocytes. Somatic symptoms and depression were quantified using Symptom Checklist-90-Revised subscales. Presence or absence of TMD and IBS, respectively, were determined by clinical examination and Rome III screening questions. The standardized beta coefficient for the omega-6/omega-3 long-chain PUFA ratio was 0.26 (95% confidence limits (CL): 0.08, 0.43) in a multivariable linear regression model in which somatic symptom disturbance was the dependent variable. When modelling depressive symptoms as the dependent variable, the standardized beta coefficient was 0.17 (95% CL:0.01, 0.34). Both associations were stronger among TMD cases and IBS cases than among non-cases. Future randomized control trials that lower the omega-6/omega-3 PUFA ratio could consider somatic or depressive symptoms as a therapeutic target for TMD or IBS pain. PERSPECTIVE: In people with TMD or IBS, a high n-6/n-3 PUFA ratio was positively associated with somatic symptom disturbance and depressive symptoms. Both measures of psychological distress were elevated in people with painful TMD and IBS. Future randomized clinical trials will determine whether lowering the n-6/n-3 ratio is therapeutic for pain.

The Genetic Basis of Endometriosis and Comorbidity with Other Pain and Inflammatory Conditions.

Rahmioglu N, Mortlock S, et al.

Nat Genet. 2023 Mar;55(3):423-436. doi: 10.1038/s41588-023-01323-z. Epub 2023 Mar 13. PMID: 36914876.

Endometriosis is a common condition associated with debilitating pelvic pain and infertility. A genome-wide association study meta-analysis, including 60,674 cases and 701,926 controls of European and East Asian descent, identified 42 genome-wide significant loci comprising 49 distinct association signals. Effect sizes were largest for stage 3/4 disease, driven by ovarian endometriosis. Identified signals explained up to 5.01% of disease variance and regulated expression or methylation of genes in endometrium and blood, many of which were associated with pain perception/maintenance (SRP14/BMF, GDAP1, MLLT10, BSN and NGF). We observed significant genetic correlations between endometriosis and 11 pain conditions, including migraine, back and multisite chronic pain (MCP), as well as inflammatory conditions, including asthma and osteoarthritis. Multitrait genetic analyses identified substantial sharing of variants associated with endometriosis and MCP/migraine. Targeted investigations of genetically regulated mechanisms shared between endometriosis and other pain conditions are needed to aid the development of new treatments and facilitate early symptomatic intervention.

Are Central Sensitization Symptoms and Psychosocial Alterations Interfering in the Association Between Painful TMD, Migraine, and Headache Attributed to TMD?

Vale Braido GVD, Svensson P, Dos Santos Proença J, Mercante FG, Fernandes G, de Godoi Gonçalves DA.

Clin Oral Investig. 2022 Nov 16. doi: 10.1007/s00784-022-04783-5. Epub ahead of print. PMID: 36383296.

**Objective:** To determine if somatosensory function and symptoms related to central sensitization (CS) differed in individuals with painful temporomandibular disorders (TMD) according to the presence of migraine (MIG) or MIG + headache attributed to TMD (HAT). **Materials and methods:** This study evaluated 92 adults (20-65 years), presenting painful TMD. Standard diagnostic criteria were applied to classification of painful TMD, MIG, and HAT. CS was assessed through the central sensitization inventory (CSI), wind-up ratio (WUR), pressure pain thresholds (PPT), and the conditioned pain modulation test (CPM). Psychosocial factors were evaluated by validated instruments. **Results:** There was a significant difference regarding gender, with more women in the group TMD + MIG + HAT ( $p = 0.028$ ). TMD + MIG and TMD + MIG + HAT had significantly lower PPTs than the TMD group. No group differences were found for the WUR, CPM, or CSI. TMD + MIG + HAT had higher chronic pain intensity ( $p = 0.001$ ), disability points ( $p = 0.045$ ), graded chronic pain scale ( $p = 0.007$ ), and higher somatization (NSPS) scores ( $p = 0.012$ ), compared to the other groups. **Conclusion:** Mechanical hyperalgesia was more pronounced in the group with the highest pain and somatization scores, while CPM and WUR did not differ between groups. Altered somatosensory function and CS may partially underlie the pathophysiology of overlapping TMD pain conditions, pointing towards additive effects of comorbid head pains. **Clinical relevance:** Our results demonstrate the importance of considering the association of primary and secondary headaches during TMD assessment and its implications for maintaining the signs and symptoms of CS. This can influence the conduct of treatment, which must be multidisciplinary, and must include management of mechanisms related to CS.

Alterations of Pain Pathways by Experimental Sleep Disturbances in Humans: Central Pain-inhibitory, Cyclooxygenase, and Endocannabinoid Pathways.

Haack M, Engert LC, Besedovsky L, Goldstein MR, Devine JK, Dang R, Olia K, Molina V, Bertisch SM, Sethna N, Simpson N.

Sleep. 2023 Mar 7:zsad061. doi: 10.1093/sleep/zsad061. Epub ahead of print. PMID: 36881901.

**Study objectives:** There is strong evidence that sleep disturbances are an independent risk factor for the development of chronic pain conditions. The mechanisms underlying this association, however, are still not well understood. We examined the effect of experimental sleep disturbances on three pathways involved in pain initiation/resolution: (1) the central pain-inhibitory pathway, (2) the cyclooxygenase (COX) pathway, and (3) the endocannabinoid (eCB) pathway. **Methods:** Twenty-four healthy participants (50% females) underwent two 19-day long in-laboratory protocols in randomized order: (a) an experimental sleep disturbance protocol consisting of repeated nights of short and disrupted sleep with intermittent recovery sleep; and (b) a sleep control protocol consisting of nights with an 8-hour sleep opportunity. Pain inhibition (conditioned pain modulation, habituation to repeated pain), COX-2 expression at monocyte level (LPS-stimulated and spontaneous), and eCBs (AEA, 2-AG, DHEA, EPEA, DTEA) were measured every other day throughout the protocol. **Results:** The central pain-

inhibitory pathway was compromised by sleep disturbances in females, but not in males ( $p < 0.05$  condition\*sex effect). The COX-2 pathway (LPS-stimulated) was activated by sleep disturbances ( $p < 0.05$  condition effect), and this effect was exclusively driven by males ( $p < 0.05$  condition\*sex effect). With respect to the eCB pathway, DHEA was higher ( $p < 0.05$  condition effect) in the sleep disturbance compared to the control condition, without sex-differential effects on any eCBs. Conclusions: These findings suggest that central pain-inhibitory COX mechanisms through which sleep disturbances may contribute to chronic pain risk are sex specific, implicating the need for sex-differential therapeutic targets to effectively reduce chronic pain associated with sleep disturbances in both sexes.

Patients with Neuropathic Pain from Lumbosacral Radiculopathy Demonstrate Similar Pressure Pain Thresholds and Conditioned Pain Modulation to those with Fibromyalgia.

Knezevic A, Kovacevic M, Jeremic-Knezevic M, Nikolasevic Z, Tomasevic-Todorovic S, Zivanovic Z, Spasojevic T, Garipi E, Vojnovic L, Popovic D, Neblett R. *Neurophysiol Clin.* 2023 Jan 28;53(4):102841. doi: 10.1016/j.neucli.2022.102841. Epub ahead of print. PMID: 36716611.

**Objective:** The purpose of the study was to evaluate pain thresholds, impairment of the endogenous pain modulatory system, and self-reported cognitive-emotional and central sensitization-related symptoms among three subject groups: a rarely studied patient cohort with neuropathic pain from lumbosacral radiculopathy (NPLSR), patients with fibromyalgia (FM) and healthy controls (HC). **Methods:** Patient-reported pain-related symptomology was evaluated with psychometrically validated questionnaires. Pressure pain threshold (PPT), heat pain threshold (HPT), and cold pain threshold (CPT) were assessed in the low back and contralateral forearm. Conditioned pain modulation (CPM) was evaluated with a recently introduced methodology that accounts for a standard error of measurement. **Results:** Compared to the HC subjects, the FM and NPLSR subjects had significantly lower pain thresholds and more CPM impairment. No significant differences in PPT and CPM were observed between the FM and NPLSR groups. Significant group differences were found in self-reported symptoms of depression, anxiety, stress, and central sensitization. Self-reported symptom severity increased in a stair-step fashion, with the HC group scoring lowest and FM group scoring highest. **Conclusion:** The NPLSR group manifested CPM dysfunction and pressure hyperalgesia at similar levels to the FM group, indicating that these two chronic pain syndromes, likely based on different pathophysiological mechanisms, in fact share some common pain processing features. However, though both patient groups demonstrated similarities in pain processing, self-reported cognitive-emotional and central sensitization-related symptom severity was significantly higher in the FM cohort, which distinguished them from the chronic NPLSR cohort.

The Impact of Micro RNA-320a Serum Level on Severity of Symptoms and Cerebral Processing of Pain in Patients with Fibromyalgia.

Hussein M, Fathy W, Abdelaleem EA, Nasser M, Yehia A, Elanwar R. *Pain Med.* 2022 Dec 1;23(12):2061-2072. doi: 10.1093/pm/pnac076. PMID: 35587745.

**Objectives:** The aim of this work was to explore the expression of miR-320a level in fibromyalgia patients in comparison to healthy controls, and to clarify its impact on the severity of symptoms and the cerebral processing of pain assessed by middle latency somatosensory evoked potentials (SSEPs). **Design:** Case-control study. **Setting:** Rheumatology and Neurology outpatient clinics. **Subjects:** Seventy-four fibromyalgia patients and seventy-four normal healthy controls. **Methods:** The included patients were subjected to detailed history taking, assessment of severity of fibromyalgia symptoms using the Fibromyalgia Impact Questionnaire Revised (FIQR), assessment of pain intensity using the Neuropathic Pain Symptom Inventory (NPSI), measurement of the serum level of miR-320a in addition to of measurement peak latencies and amplitudes of middle latency SSEPs. **Results:** Fibromyalgia patients had significantly higher micro-RNA-320a levels ( $0.907 \pm 0.022$ ) in comparison to controls ( $0.874 \pm 0.015$ ) ( $P$ -value  $< .001$ ). The mean values of micro-RNA-320a levels were significantly higher in fibromyalgia patients with insomnia, chronic fatigue syndrome, persistent depressive disorder, and primary headache disorder than those without ( $P$ -value = .024,  $< .001$ , .006, .036 respectively). There were statistically significant positive correlations between micro-RNA-320a levels, and disease duration, FIQR, and NPSI total scores ( $P$ -value  $< 0.001$ , 0.003, 0.002 respectively). There were no statistically significant correlations between micro-RNA-320a levels and middle latency SSEPs. **Discussion:** Micro-RNA-320a level is significantly upregulated in fibromyalgia patient. It has a crucial impact on the severity of symptoms but not related to the cerebral processing of pain.

The Link Between Empty Sella Syndrome, Fibromyalgia, and Chronic Fatigue Syndrome: The Role of Increased Cerebrospinal Fluid Pressure.

Hulens M, Dankaerts W, Rasschaert R, Bruyninckx F, De Mulder P, Bervoets C.

J Pain Res. 2023 Jan 25;16:205-219. doi: 10.2147/JPR.S394321. PMID: 36721849; PMCID: PMC9884441.

The etiopathogenesis of fibromyalgia (FM) and chronic fatigue syndrome (CFS) is not yet elucidated. Hypothalamo-pituitary-adrenal (HPA) axis dysfunction is reflected in the hormonal disturbances found in FM and CFS. Some study groups have introduced a novel hypothesis that moderate or intermittent intracranial hypertension may be involved in the etiopathogenesis of FM and CFS. In these conditions, hormonal disturbances may be caused by the mechanical effect of increased cerebrospinal fluid pressure, which hampers blood flow in the pituitary gland. Severe intracranial pressure may compress the pituitary gland, resulting in primary empty sella (ES), potentially leading to pituitary hormone deficiencies. The aim of this narrative review was to explore whether similar hormonal changes and symptoms exist between primary ES and FM or CFS and to link them to cerebrospinal fluid pressure dysregulation. A thorough search of the PubMed and Web of Science databases and the reference lists of the included studies revealed that several clinical characteristics were more prevalent in primary ES, FM or CFS patients than in controls, including increased cerebrospinal fluid pressure, obesity, female sex, headaches and migraine, fatigue, visual disturbances (visual acuity and eye motility abnormalities), vestibulocochlear disturbances (vertigo and neurosensorial hearing loss), and bodily pain (radicular pain and small-fiber neuropathy). Furthermore, challenge tests of the pituitary gland showed similar abnormalities in all three conditions: blunted adrenocorticotrophic hormone, cortisol, growth hormone, luteinizing hormone, and thyroid stimulating hormone responses and an increased prolactin response. The findings of this narrative review provide further support for the hypothesis that moderately or intermittently increased cerebrospinal fluid pressure is involved in the pathogenesis of FM and CFS and should stimulate further research into the etiopathogenesis of these conditions.

Small-Fiber Polyneuropathy Is Prevalent in Patients with Interstitial Cystitis/Bladder Pain Syndrome.

Wolff DT, Xu R, Overholt T, Bassett EH, Ahn C, Simon T, Lee P, Badlani G, Matthews CA, Evans RJ, Walker SJ.

Urogynecology (Hagerstown). 2022 Nov 1;28(11):786-792. doi: 10.1097/SPV.0000000000001240. Epub 2022 Sep 24. PMID: 36288118.

Importance: The pathophysiology of interstitial cystitis/bladder pain syndrome (IC/BPS) is imperfectly understood. Recent studies reported that small-fiber polyneuropathy (SFPN) is common in fibromyalgia, a condition commonly comorbid with IC/BPS. Objective: The objective of this study was to determine the prevalence of SFPN in a large cohort of IC/BPS patients. Methods: Adults diagnosed with IC/BPS scheduled to undergo either therapeutic hydrodistention (n = 97) or cystectomy with urinary diversion (n = 3) were prospectively recruited to this study. A skin biopsy obtained from the lower leg was used for intraepidermal nerve fiber density measurement. Small-fiber polyneuropathy (+/-) status was determined by comparing linear intraepidermal nerve fiber density (fibers/mm<sup>2</sup>) with normative reference values. Demographic information, medical history, and diagnoses for 14 conditions (both urologic and nonurologic) known to co-occur with IC/BPS were documented from self-report and electronic medical record. Results: In this large cohort of patients with IC/BPS, 31% (31/100) were positive for SFPN. Intraepidermal nerve fiber density was below the median for age and sex in 81% (81/100) of patients. Approximately one-third (31%) of SFPN+ patients reported co-occurring chronic fatigue syndrome, compared with 10.6% of the SFPN- group (P = 0.034). Small-fiber polyneuropathy-positive patients reported significantly fewer allergies than SFPN- patients (37.9% vs 60.6%; P = 0.047). There were no significant differences in bladder capacity or Hunner lesion status between the SFPN+ and SFPN- subgroups. Conclusions: Small-fiber polyneuropathy is a common finding in patients with IC/BPS, and SFPN status is significantly correlated with co-occurring chronic fatigue syndrome and negatively correlated with the presence of allergies in this population.

Genetic and Epigenetic Regulation of Catechol-O-Methyltransferase in Relation to Inflammation in Chronic Fatigue Syndrome and Fibromyalgia.

Polli A, Hendrix J, Ickmans K, Bakusic J, Ghosh M, Monteyne D, Velkeniers B, Bekaert B, Nijs J, Godderis L.

**Background:** Catechol-O-methyltransferase (COMT) has been shown to influence clinical pain, descending modulation, and exercise-induced symptom worsening. COMT regulates nociceptive processing and inflammation, key pathophysiological features of Chronic Fatigue Syndrome and Fibromyalgia (CFS/FM). We aimed to determine the interactions between genetic and epigenetic mechanisms regulating COMT and its influence on inflammatory markers and symptoms in patients with CFS/FM. **Methods:** A case-control study with repeated-measures design was used to reduce the chance of false positive and increase the power of our findings. Fifty-four participants (28 patients with CFS/FM and 26 controls) were assessed twice within 4 days. The assessment included clinical questionnaires, neurophysiological assessment (pain thresholds, temporal summation, and conditioned pain modulation), and blood withdrawal in order to assess rs4818, rs4633, and rs4680 COMT polymorphisms and perform haplotype estimation, DNA methylation in the COMT gene (both MB-COMT and S-COMT promoters), and cytokine expression (TNF- $\alpha$ , IFN- $\gamma$ , IL-6, and TGF- $\beta$ ). **Results:** COMT haplotypes were associated with DNA methylation in the S-COMT promoter, TGF- $\beta$  expression, and symptoms. However, this was not specific for one condition. Significant between-group differences were found for increased DNA methylation in the MB-COMT promoter and decreased IFN- $\gamma$  expression in patients. **Discussion:** Our results are consistent with basic and clinical research, providing interesting insights into genetic-epigenetic regulatory mechanisms. MB-COMT DNA methylation might be an independent factor contributing to the pathophysiology of CFS/FM. Further research on DNA methylation in complex conditions such as CFS/FM is warranted. We recommend future research to employ a repeated-measure design to control for biomarkers variability and within-subject changes.

Circulating microRNA Expression Signatures Accurately Discriminate Myalgic Encephalomyelitis from Fibromyalgia and Comorbid Conditions.

Nepotchatykh E, Caraus I, Elremaly W, Leveau C, Elbakry M, Godbout C, Rostami-Afshari B, Petre D, Khatami N, Franco A, Moreau A.

Sci Rep. 2023 Feb 2;13(1):1896. doi: 10.1038/s41598-023-28955-9. PMID: 36732593; PMCID: PMC9894933.

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), and fibromyalgia (FM) are two chronic complex diseases with overlapping symptoms affecting multiple systems and organs over time. Due to the absence of validated biomarkers and similarity in symptoms, both disorders are misdiagnosed, and the comorbidity of the two is often unrecognized. Our study aimed to investigate the expression profiles of 11 circulating miRNAs previously associated with ME/CFS pathogenesis in FM patients and individuals with a comorbid diagnosis of FM associated with ME/CFS (ME/CFS + FM), and matched sedentary healthy controls. Whether these 11 circulating miRNAs expression can differentiate between the two disorders was also examined. Our results highlight differential circulating miRNAs expression signatures between ME/CFS, FM and ME/CFS + FM, which also correlate to symptom severity between ME/CFS and ME/CFS + FM groups. We provided a prediction model, by using a machine-learning approach based on 11 circulating miRNAs levels, which can be used to discriminate between patients suffering from ME/CFS, FM and ME/CFS + FM. These 11 miRNAs are proposed as potential biomarkers for discriminating ME/CFS from FM. The results of this study demonstrate that ME/CFS and FM are two distinct illnesses, and we highlight the comorbidity between the two conditions. Proper diagnosis of patients suffering from ME/CFS, FM or ME/CFS + FM is crucial to elucidate the pathophysiology of both diseases, determine preventive measures, and establish more effective treatments.

Stimulated Whole Blood Cytokine/Chemokine Responses are Associated with Interstitial Cystitis/Bladder Pain Syndrome Phenotypes and Features of Nociceptive Pain: a MAPP Research Network Study.

Schrepf A, Kaplan C, Harris RE, Williams DA, Clauw DJ, As-Sanie S, Till S, Clemens JQ, Rodriguez LV, Van Bokhoven A, Landis R, Gallop R, Bradley C, Naliboff B, Pontari M, O'Donnell M, Luo Y, Kreder K, Lutgendorf SK, Harte SE; See MAPP masthead. Pain. 2022 Oct 19. doi: 10.1097/j.pain.0000000000002813. Epub ahead of print. PMID: 36279178.

Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) is a common and debilitating disease with poor treatment outcomes. Studies from the Multidisciplinary Approach to the study of chronic Pelvic Pain (MAPP) research network established that IC/BPS patients with chronic

overlapping pain conditions (COPCs) experience poorer quality of life and more severe symptoms, yet the neurobiological correlates of this subtype are largely unknown. We previously showed that ex-vivo Toll-Like Receptor 4 (TLR4) cytokine/chemokine release is associated with the presence of COPCs, as well as widespread pain and experimental pain sensitivity women with IC/BPS. Here we attempt to confirm these findings in the multisite MAPP Symptom Patterns Study using TLR4 stimulated whole blood (female IC/BPS patients with COPC n =99; without n=36). Samples were collected in tubes preloaded with TLR4 agonist, incubated for 24 hours, and resulting supernatant assayed for seven cytokines/chemokines. These were subject to a principal components analysis and the resulting components used as dependent variables in general linear models. Controlling for patient age, body mass index, and site of collection, we found that greater ex-vivo TLR4 stimulated cytokine/chemokine release was associated with the presence of COPCs ( $p < 0.01$ ), extent of widespread pain ( $p < 0.05$ ), but not experimental pain sensitivity ( $p > 0.05$ ). However, a second component of anti-inflammatory, regulatory, and chemotactic activity was associated with reduced pain sensitivity ( $p < 0.01$ ). These results confirm that the IC/BPS + COPCs subtype show higher levels of ex-vivo TLR4 cytokine/chemokine release and support a link between immune priming and nociplastic pain in IC/BPS.

Plasma and Interstitial Levels of Endocannabinoids and N-acylethanolamines in Patients with Chronic Widespread Pain and Fibromyalgia: A Systematic Review and Meta-analysis.

Kurlyandchik I, Lauche R, Tiralongo E, Warne LN, Schloss J.

Pain Rep. 2022 Nov 7;7(6):e1045. doi: 10.1097/PR9.0000000000001045. PMID: 36381652; PMCID: PMC9646668.

The endocannabinoid system (ECS) is an essential endogenous signaling system that may be involved in the pathophysiology of chronic widespread pain (CWP) and fibromyalgia syndrome (FMS). Further research is required to understand the role of ECS in the development and maintenance of CWP and FMS. We provided the first systematic review and meta-analysis exploring the clinical relevance of ECS alterations in patients with CWP and FMS by comparing plasma and interstitial levels of endocannabinoids and N-acylethanolamines in patients and healthy controls. A systematic search was conducted to identify studies that measured plasma and/or interstitial levels of endocannabinoids and N-acylethanolamines in patients with CWP or FMS and healthy controls. A total of 8 studies were included for qualitative review, and 7 studies were included for meta-analysis. The findings identified increased plasma levels of oleoylethanolamide and stearoylethanolamide in patients with FMS compared with those in controls ( $P = 0.005$  and  $P < 0.0001$ , respectively) and increased plasma levels of palmitoylethanolamide and interstitial levels of stearoylethanolamide in patients with CWP compared with those in controls ( $P = 0.05$  and  $P = 0.001$ , respectively). There were no significant differences in other ECS parameters. Most studies did not account for variables that may influence ECS function, including cannabis use, concomitant medication, comorbidities, physical activity, stress levels, circadian rhythm, sleep quality, and dietary factors, suggesting that future studies should explore the correlation between these variables and endocannabinoid activity. We highlight the importance of investigating endocannabinoid activity in CWP and FMS because it will underpin future translational research in the area.

Exploring the Sex Differences in Conditioned Pain Modulation and its Biobehavioral Determinants in Healthy Adults.

Umeda M, Okifuji A.

Musculoskelet Sci Pract. 2022 Dec 19:102710. doi: 10.1016/j.msksp.2022.102710. Epub ahead of print. PMID: 36566112.

Background: Females are at greater risk of chronic pain, and exhibit higher pain sensitivity compared to males. However, sex differences in conditioned pain modulation (CPM), a neurophysiological risk factor of chronic pain, are unclear. CPM is influenced by many factors, some of which are sex-dependent. This study explored the sex differences in CPM and its biobehavioral determinants, such as blood pressure responses, physical activity levels, pain catastrophizing scores, and conditioning stimulus intensity, in young, healthy, physically active males and females. Methods: Twenty-six males and 24 females completed the CPM test using an electrical pain stimulus and a cold pain stimulus induced via 2 min of cold pressor test. Blood pressure was assessed at baseline and during cold pressor test, whereas cold pain ratings were obtained during cold pressor test to monitor the conditioning stimulus intensity. Physical activity was evaluated via questionnaires and accelerometer, whereas pain catastrophizing was evaluated via a questionnaire. Results: Both males and



females exhibited CPM, without sex differences in the magnitude of CPM. The males showed higher resting blood pressure, higher physical activity levels, and lower pain catastrophizing scores than the females, without sex differences observed in cold pain ratings and proportion of those who met the physical activity guidelines. No correlations were observed between CPM and its determinants. Conclusions: The results suggest the complexity of mechanisms underlying the sex differences in CPM. The sex differences in CPM, along with its determinants, may need to be examined in individuals with some risk factors for chronic pain.

#### Spinal GABAergic Disinhibition Allows Microglial Activation Mediating the Development of Nociceptive Pain in Male Mice.

McDonough KE, Hammond R, Wang J, Tierney J, Hankerd K, Chung JM, La JH. *Brain Behav Immun.* 2022 Oct 21;107:215-224. doi: 10.1016/j.bbi.2022.10.013. Epub ahead of print. PMID: 36273650.

Previously we developed a murine model in which postinjury stimulation of an injured area triggers a transition to a nociceptive pain state manifesting as persistent mechanical hypersensitivity outside of the previously injured area. This hypersensitivity was maintained by sex-specific mechanisms; specifically, activated spinal microglia maintained the hypersensitivity only in males. Here we investigated whether spinal microglia drive the transition from acute injury-induced pain to nociceptive pain in males, and if so, how they are activated by normally innocuous stimulation after peripheral injury. Using intraplantar capsaicin injection as an acute peripheral injury and vibration of the injured paw as postinjury stimulation, we found that inhibition of spinal microglia prevents the vibration-induced transition to a nociceptive pain state. The transition was mediated by the ATP-P2X4 pathway, but not BDNF-TrkB signaling. Intrathecal injection of GABA receptor agonists after intraplantar capsaicin injection prevented the vibration-induced transition to a nociceptive pain state. Conversely, in the absence of intraplantar capsaicin injection, intrathecal injection of GABA receptor antagonists allowed the vibration stimulation of a normal paw to trigger the transition to a spinal microglia-mediated nociceptive pain state only in males. At the spinal level, TNF- $\alpha$ , IL-1 $\beta$ , and IL-6, but not prostaglandins, contributed to the maintenance of the nociceptive pain state in males. These results demonstrate that in males, the transition from acute injury-induced pain to nociceptive pain is driven by spinal microglia causing neuroinflammation and that peripheral injury-induced spinal GABAergic disinhibition is pivotal for normally innocuous stimulation to activate spinal microglia.

#### Kinins and their B1 and B2 Receptors as Potential Therapeutic Targets for Pain Relief.

Brusco I, Fialho MFP, Becker G, da Silva Brum E, da Silva AF, Marchezin LP, Serafini PT, Oliveira SM. *Life Sci.* 2022 Dec 16:121302. doi: 10.1016/j.lfs.2022.121302. Epub ahead of print. PMID: 36535404.

Kinins are endogenous peptides that belong to the kallikrein-kinin system, extensively studied for over a century. Their essential role in multiple physiological and pathological processes is demonstrated by activating two transmembrane G-protein-coupled receptors, the kinin B1 and B2 receptors. Attention is mainly given to the pathological role of kinins in pain transduction mechanisms. In the past years, a wide range of preclinical studies has amounted to the literature reinforcing the need for an updated review about the participation of kinins and their receptors in pain disorders. Here, we performed an extensive literature search since 2004, describing the historical progress and the current understanding of the kinin receptors' participation and its potential therapeutic in several acute and chronic painful conditions. These include inflammatory (mainly arthritis), neuropathic (caused by different aetiologies, such as cancer, multiple sclerosis, antineoplastic toxicity and diabetes) and nociceptive (mainly fibromyalgia) pain. Moreover, we highlighted the pharmacological actions and possible clinical applications of the kinin B1 and B2 receptor antagonists, kallikrein inhibitors or kallikrein-kinin system signalling pathways-target molecules in these different painful conditions. Notably, recent findings sought to elucidate mechanisms for guiding new and better drug design targeting kinin B1 and B2 receptors to treat a disease diversity. Since the kinin B2 receptor antagonist, Icatibant, is clinically used and well-tolerated by patients with hereditary angioedema gives us hope kinin receptors antagonists could be more robustly tested for a possible clinical application in the treatment of pathological pains, which present limited pharmacology management.



## Clinical Studies

### Generalized Sensory Sensitivity is Associated with Comorbid Pain Symptoms: A Replication Study in Women with Dysmenorrhea.

Schrepf A, Hellman KM, Bohnert AM, Williams DA, Tu FF.

Pain. 2023 Jan 1;164(1):142-148. doi: 10.1097/j.pain.0000000000002676. Epub 2022 May 10. PMID: 35543649; PMCID: PMC9704354.

Dysmenorrhea is characterized by high rates of transition to chronic pain. In a previous study using structural equation modeling, we demonstrated that several symptom domains associated with the emerging concept of nociplastic pain can be described using 2 symptom groups: generalized sensory sensitivity (GSS; composed of widespread pain, interceptive sensitivity, and environmental sensitivity) and SPACE (composed of unrefreshing sleep, pain, affective disturbances, cognitive issues, and reduced energy). Here, we perform a secondary cross-sectional analysis examining the same symptom groups in a cohort of patients with dysmenorrhea without a diagnosis of chronic pain. Our purpose is to determine if the same symptom patterns are apparent and if they are associated with the presence and severity of comorbid pain. Participants were 201 women with dysmenorrhea. We replicated the hypothesized 2-factor structure in this cohort (comparative fit index = 0.971 and root mean square error of approximation = 0.055; 90% CI: 0.000-0.097). Generalized sensory sensitivity was associated with the severity of bladder, bowel, and overall pain in multivariable models including SPACE, patient age, and BMI (all  $\beta > 0.32$ , all  $P < 0.05$ ). Sleep, pain, affective disturbances, cognitive issues, and reduced energy were associated with menstrual pain during nonsteroidal anti-inflammatory drug use, whereas GSS was associated with the same in the absence of nonsteroidal anti-inflammatory drug use (both  $P < 0.05$ ). This 2-factor model of symptoms seems to be replicable and valid in a cohort of women at risk for developing chronic pain conditions. These symptom groups are promising potential markers of future pain chronification and may point to patients in need of earlier or more aggressive intervention.

### Association Between Nociplastic Pain and Pain Severity and Impact in Women with Chronic Pelvic Pain.

Till SR, Schrepf A, Clauw DJ, Harte SE, Williams DA, As-Sanie S.

J Pain. 2023 Mar 21:S1526-5900(23)00369-3. doi: 10.1016/j.jpain.2023.03.004. Epub ahead of print. PMID: 36958459.

Exploring the relationship between nociplastic pain and the severity and impact of pelvic pain symptoms could lend insight into the heterogeneous symptom presentation and treatment response that complicates management of chronic pelvic pain. In this prospective cross-sectional study, we sought to evaluate relationships between degree of nociplastic pain, measured by the Fibromyalgia (FM) Survey Score, and multiple aspects of the chronic pelvic pain (CPP) experience, including severity, frequency, tenderness during pelvic myofascial exam, interference with daily life, and high-impact pain. The study included 303 women who presented to a tertiary referral clinic for chronic pelvic pain and endometriosis. Multiple measures of pelvic pain, including pain severity, frequency, interference, pelvic myofascial pain, and high-impact pain were examined in General Linear Models with FM Survey Score as the primary predictor of interest in models controlling for endometriosis, surgical history, use of opioids, body mass index, and patient age. Higher level of nociplastic pain was associated with greater pelvic pain severity, frequency, interference, and pelvic myofascial pain (all  $p < .05$ ). For all models, degree of nociplastic pain was more strongly associated with pain outcomes than the presence of endometriosis, and use of opioids was the only stronger predictor of worse pain outcomes. The likelihood of high impact pain increased 7% for each additional point on the FM Survey Score. Degree of nociplastic pain was robustly associated with severity, frequency, and impact of pelvic pain, and was independent of the presence of endometriosis, history of surgical procedures for pelvic pain, age, and BMI. Trial registration: not applicable Perspective: This article evaluates the impact of nociplastic pain on symptoms and functional status in chronic pelvic pain. These findings raise the possibility that a simple screening tool for nociplastic pain might provide clinically actionable information without the need for deep neurobiological phenotyping and may inform development of personalized management strategies.

### Pain Management and Rehabilitation for Central Sensitization in Temporomandibular Disorders: A Comprehensive Review.

Ferrillo M, Giudice A, Marotta N, Fortunato F, Di Venere D, Ammendolia A, Fiore P, de Sire A.

Temporomandibular disorders (TMD) are a group of musculoskeletal diseases affecting masticatory muscles and temporomandibular joints (TMJ). In this context, the chronic TMD could be considered as a condition with chronic primary orofacial pain, presenting as myofascial TMD pain or TMJ arthralgia. In this context, myogenous TMD may present overlapping features with other disorders, such as fibromyalgia and primary headaches, characterized by chronic primary pain related to dysfunction of the central nervous system (CNS), probably through the central sensitization. This phenomenon could be defined as an amplified response of the CNS to sensory stimuli and peripheral nociceptive, characterized by hyperexcitability in the dorsal horn neurons in the spinal cord, which ascend through the spinothalamic tract. The main objectives of the management of TMD patients are: decreasing pain, increasing TMJ function, and reducing the reflex masticatory muscle spasm/pain. The first-line treatments are physical therapy, pharmacological drugs, occlusal splints, laser therapy, extracorporeal shockwave therapy, transcutaneous electrical nerve stimulation, and oxygen-ozone therapy. Although all these therapeutic approaches were shown to have a positive impact on the central sensitization of TMD pain, there is still no agreement on this topic in the scientific literature. Thus, in this comprehensive review, we aimed at evaluating the evidence on pain management and rehabilitation for the central sensitization in TMD patients.

#### Pain Widespreadness, and Not Primary Pain Location, is Associated with Comorbid Symptoms in Children With Chronic Pain.

Foxen-Craft E, Bouchtein E, Kaplan C, Clauw DJ, Scott E.

Clin J Pain. 2023 Jan 1;39(1):1-7. doi: 10.1097/AJP.0000000000001083. PMID: 36524767.

Objectives: Pediatric chronic pain represents heterogeneous diagnoses; often, primary pain location informs research classifications and treatment. In contrast, recent research has highlighted the role of widespread pain and this perspective has been adopted in assessments in specialty pediatric pain clinics. The lack of direct comparison between these 2 methods of categorizing pediatric chronic pain may hinder the adoption of evidence-based practices across the spectrum of care. Therefore, this study aimed to compare whether primary pain location or pain widespreadness is more informative for pain-related symptoms in pediatric chronic pain. Methods: Youth (n=223) between the ages of 8 to 23 years (M=15.93, SD=2.11, 83% female) completed surveys upon intake at the pediatric chronic pain clinic. Free-text entries of primary pain location were coded into categories: headache, abdominal pain, and musculoskeletal pain. Additional domains assessed included widespread pain, pain interference, kinesiophobia, catastrophizing, anxiety, depression, sleep, and fatigue. Results: Differences based on primary pain location only emerged for kinesiophobia,  $F(2,150)=8.20$ ,  $P<0.001$ , with the highest scores among those with musculoskeletal pain. In contrast, controlling for sex, age, and pain intensity, pain widespreadness was associated with pain interference, pain catastrophizing, fatigue, anxiety, and depression ( $P<0.05$ ). Discussion: Pain widespreadness was more consistently associated with pain-related outcomes among pediatric chronic pain patients than primary pain location, and body maps may be useful in determining a nociplastic pain mechanism to inform treatment. Improved assessment of pediatric pain mechanisms may help advance more precise treatment delivery.

#### Sleep Quality in Individuals with Chronic Low Back Pain and Central Sensitization.

Aoyagi K, He J, Clauw DJ, Sharma NK.

Physiother Res Int. 2022 Oct;27(4):e1968. doi: 10.1002/pri.1968. Epub 2022 Aug 7. PMID: 35933729.

Background and purpose: Sleep problems are common in individuals with chronic low back pain (CLBP). Central sensitization (CS) is present in a subgroup of individuals with CLBP. However, our knowledge about whether sleep quality varies between the subgroups of CLBP is limited. Therefore, we sought to examine whether the subgroup of CLBP with CS has poorer sleep quality than the subgroup without CS. Methods: 2011 Fibromyalgia Survey (2011 FM survey) was used as a surrogate measure of CS to divide the CLBP participants into two subgroups: CLBP with CS and CLBP without CS. We also created a CS index comprising a set of quantitative sensory testing measures (i.e., pressure pain thresholds, conditioned pain modulation) to evaluate pain sensitivity. Sleep quality was assessed with Pittsburgh Sleep Quality Index (PSQI). Group differences about PSQI and CS index and associations between

sleep quality and CS across the groups were analyzed. Results: We included 60 participants with CLBP and 23 healthy controls (HCs). Overall, 80% of the participants with CLBP presented with poor sleep quality. Participants with CLBP with CS showed significantly higher PSQI scores (poorer sleep) than participants with CLBP without CS and HCs ( $p < 0.05$ ). Both the 2011 FM survey and CS index were significantly correlated with sleep quality ( $r = 0.5870$ ,  $p < 0.001$  and  $r = -0.264$ ,  $p = 0.04$ ). Logistic regression models revealed that the FM status (odds ratio (OR) = 6.00,  $p = 0.02$  [95% confidence interval: 1.31-42.1]), but not the CS index (OR = 1.11,  $p = 0.79$  [95% CI: 0.48-2.71]) was associated with PSQI. After adjusting covariates, the results remained similar but became non-significant for the FM status. Discussion: We found that sleep problems were more common and severe in those who exhibited signs of CS. Thus, clinicians may consider using 2011 FM survey to identify those with CS and co-existing sleep problems.

Rationale and Design of a Multicenter Randomized Clinical Trial of Vestibulodynia: Understanding Pathophysiology and Determining Appropriate Treatments (vestibulodynia: UPDATE).

Carey ET, Geller EJ, Rapkin A, Farb D, Cutting H, Akaninwor J, Stirling C, Bortsov A, McNulty S, Merrill P, Zakrotsky P, DeLaRosa J, Luo S, Nackley AG. *Ann Med.* 2022 Dec;54(1):2885-2897. doi: 10.1080/07853890.2022.2132531. PMID: 36269028; PMCID: PMC9624211.

Background: Limited data are available to establish evidence-based management protocols for vestibulodynia (VBD), a chronic vulvar pain condition that affects approximately 14 million women in the U.S. For the purposes of the study, our group subdivided VBD subtypes that may benefit from different types of treatment: 1) VBD peripheral (VBD-p), characterized by pain localized to the vulvar vestibule and 2) VBD central (VBD-c), characterized by VBD alongside one or more other chronic overlapping pain conditions (e.g. irritable bowel syndrome, temporomandibular disorder, and fibromyalgia syndrome) that affect remote body regions. Here, we describe the rationale and design of an NIH-funded multicenter clinical trial comparing the effectiveness of topical and/or systemic medication for alleviating pain and normalizing pain-relevant biomarkers among women with VBD-p and VBD-c. Methods: Participants will be randomly assigned to one of four parallel arms: peripheral treatment with 5% lidocaine + 0.5 mg/ml 0.02% oestradiol compound cream + oral placebo pill, 2) central treatment with the tricyclic antidepressant nortriptyline + placebo cream, 3) combined peripheral cream and central pill treatments, or 4) placebo cream and placebo pill. The treatment phase will last 16 weeks, with outcome measures and biomarkers assessed at 4 time points (0, 8, 16, and 24 weeks). First, we will compare the efficacy of treatments in alleviating pain using standardized tampon insertion with a numeric rating scale and self-reported pain on the short form McGill Pain Questionnaire. Next, we will compare the efficacy of treatments in improving perceived physical, mental, and sexual health using standardized questionnaires. Finally, we will measure cytokines and microRNAs in local vaginal and circulating blood samples using multiplex assays and RNA sequencing, and determine the ability of these biomarkers to predict treatment response. Conclusion: This is the first multicenter randomized controlled trial to evaluate the efficacy of peripherally and centrally acting medications currently used in clinical practice for treating unique VBD subtypes based on distinct clinical and biological signatures.

Phenotyping Post-COVID Pain as a Nociceptive, Neuropathic, or Nociplastic Pain Condition.

Fernández-de-Las-Peñas C, Nijs J, Neblett R, Polli A, Moens M, Goudman L, Shekhar Patil M, Knaggs RD, Pickering G, Arendt-Nielsen L. *Biomedicines.* 2022 Oct 13;10(10):2562. doi: 10.3390/biomedicines10102562. PMID: 36289827; PMCID: PMC9599440.

Pain after an acute Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection and coronavirus disease 2019 (COVID-19) condition (post-COVID pain) is becoming a new healthcare emergency. Precision medicine refers to an evidence-based method of grouping patients based on their diagnostic/symptom presentation and then tailoring specific treatments accordingly. Evidence suggests that post-COVID pain can be categorized as nociceptive (i.e., pain attributable to the activation of the peripheral receptive terminals of primary afferent neurons in response to noxious chemical, mechanical, or thermal stimuli), neuropathic (i.e., pain associated with a lesion or disease of the somatosensory nervous system and limited to a "neuroanatomically plausible" distribution of the system), nociplastic (i.e., pain arising from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or

lesion of the somatosensory system causing the pain), or mixed type (when two pain phenotypes co-exist). Each of these pain phenotypes may require a different treatment approach to maximize treatment effectiveness. Accordingly, the ability to classify post-COVID pain patients into one of these phenotypes would likely be critical for producing successful treatment outcomes. The 2021 International Association for the Study of Pain (IASP) clinical criteria and grading system provide a framework for classifying pain within a precision pain medicine approach. Here we present data supporting the possibility of grouping patients with post-COVID pain into pain phenotypes, using the 2021 IASP classification criteria, with a specific focus on nociplastic pain, which is probably the primary mechanism involved in post-COVID pain. Nociplastic pain, which is usually associated with comorbid symptomology (e.g., poor sleep quality, fatigue, cognitive-emotional disturbances, etc.) and is considered to be more difficult to treat than other pain types, may require a more nuanced multimodal treatment approach to achieve better treatment outcomes.

#### How Negative and Positive Constructs and Comorbid Conditions Contribute to Disability in Chronic Orofacial Pain.

Thomas S, Wang Y, Cundiff-O'Sullivan R, Massalee R, Colloca L.

Eur J Pain. 2022 Oct 6. doi: 10.1002/ejp.2042. Epub ahead of print. PMID: 36203350.

**Background:** Temporomandibular disorders (TMD) symptoms develop into chronic pain for some patients, but the reasons for this are unclear. Psychosocial factors and chronic overlapping pain conditions are believed to contribute to the development of pain-related disability. We examined the role of jaw function, negative and positive psychological factors and chronic overlapping pain conditions (COPCs) on pain-related disability whilst controlling for demographic variables. **Methods:** We collected demographics, medical and psychosocial history and the Graded Chronic Pain Scale, a measure of pain intensity and pain interference from 400 participants with chronic TMD. Structural equation modelling was used to assess a model of COPCs and the latent variables of psychological unease (pain catastrophizing, somatic symptoms and negative affect), positive valence factors (optimism and positive affect), jaw function (chewing, opening and expression limitation) and pain-related disability (pain intensity and pain interference) whilst controlling for demographic variables. **Results:** We achieved good fit of a parsimonious model (root-mean-square error of approximation = 0.063 [90% CI] [0.051-0.075]), comparative fit index = 0.942, standard root-mean-square residual = 0.067. Jaw function was the strongest latent variable predictor, followed by psychological unease and COPCs suggesting resources focused on improving joint function, psychosocial support and management of COPCs will improve pain-related disability in TMDs. **Conclusions:** These findings not only increase the body of knowledge related to TMD clinical phenotypes but also, have a translational impact in further supporting the potential value of targeting physical therapy such as jaw exercise along with psychological interventions as multidisciplinary nonpharmacological therapeutic solutions.

#### Diseases of the Musculoskeletal System and Connective Tissue in Relation to Temporomandibular Disorders-A SWEREG-TMD Nationwide Case-Control Study.

Salinas Fredricson A, Naimi-Akbar A, Adami J, Lund B, Rosén A, Hedenberg-Magnusson B, Fredriksson L, Krüger Weiner C.

PLoS One. 2022 Oct 12;17(10):e0275930. doi: 10.1371/journal.pone.0275930. PMID: 36223372; PMCID: PMC9555668.

**Introduction:** Temporomandibular disorders (TMD) are comprised by a heterogenous group of diagnoses with multifaceted and complex etiologies. Although diseases of the musculoskeletal system and connective tissue (MSD) have been reported as risk factors for developing TMD, no nationwide population-based registry studies have been conducted to investigate this possible link. The aim of this study was to investigate the association between MSD and TMD in a population-based sample using Swedish registry data, and to further investigate the difference in such association between patients diagnosed with TMD in a hospital setting and patients surgically treated for the condition. **Materials and methods:** Population based case-control study using Swedish nationwide registry data. Data was collected between 1998 and 2016 from 33 315 incident cases and 333 122 controls aged  $\geq 18$ , matched for sex, age, and living area. Cases were stratified into non-surgical (NS), surgically treated once (ST1) and surgically treated twice or more (ST2). Information on MSD exposure (ICD-10 M00-M99) was collected between 1964 and 2016. Odds ratios were calculated using conditional logistic regression, adjusted for country of birth, educational level, living area, and mental health comorbidity. **Results:** A significant association between MSD and the development of TMD was found for all diagnostic categories: arthropathies (OR 2.0, CI 1.9–

2.0); systemic connective tissue disorders (OR 2.3, CI 2.1–2.4); dorsopathies (OR 2.2, CI 2.1–2.2); soft tissue disorders (OR 2.2, CI 2.2–2.3); osteopathies and chondropathies (OR 1.7, CI 1.6–1.8); and other disorders of the musculoskeletal system and connective tissue (OR 1.9, CI 1.8–2.1). The associations were generally much stronger for TMD requiring surgical treatment. The diagnostic group with the strongest association was inflammatory polyarthropathies, M05-M14 (OR 11.7, CI 8.6–15.9), which was seen in the ST2 group. Conclusions: Patients with MSD diagnoses have a higher probability of being diagnosed with TMD, in comparison to individuals without MSD. This association is even stronger for TMD that requires surgery. The results are in line with earlier findings, but present new population-based evidence of a possible causal relationship between MSD and TMD, even after adjusting for known confounders. Both dentists and physicians should be aware of this association and be wary of early signs of painful TMD among patients with MSD, to make early referral and timely conservative treatment possible.

Migraine in the Context of Chronic Primary Pain, Chronic Overlapping Pain Disorders, and Functional Somatic Disorders: A Narrative Review.

Henningesen P, Hausteiner-Wiehle C, Häuser W.

Headache. 2022 Nov 14. doi: 10.1111/head.14419. Epub ahead of print. PMID: 36373821.

Objective: To contextualize migraine as the most common primary headache disorder in relation to other chronic primary pain and non-pain functional somatic and mental conditions. Background: Migraine is increasingly understood as a sensory processing disorder within a broader spectrum of symptom disorders. This has implications for diagnosis and treatment. Method: Narrative review based on a search of the literature of the last 15 years on the overlap of migraine with other symptom disorders. Results: Migraine as the prototypical primary headache disorder not only comprises many non-headache symptoms in itself, it also shows high comorbidity with other chronic pain and non-pain conditions (e.g., fibromyalgia syndrome, irritable bowel syndrome, functional non-epileptic seizures, depression, anxiety, and posttraumatic stress disorder). Such "symptom disorders" share several etiological factors (e.g., female preponderance, psychological vulnerability) and psychophysiological mechanisms (e.g., altered sensory processing, pain expectancy). These facts are acknowledged by several recent integrative conceptualizations such as chronic primary pain, chronic overlapping pain conditions, or functional somatic disorders. Accordingly, migraine management increasingly addresses the total symptom burden and individual contributors to symptom experience, and thus incorporates centrally acting pharmacological and non-pharmacological, that is, psychological and behavioral, treatment approaches. Conclusions: Migraine and also other primary headache disorders should be seen as particular phenotypes within a broader spectrum of symptom perception and processing disorders that require integrative diagnostics and treatment. A harmonization of classifications and better interdisciplinary collaboration are desirable.

Patients With Functional Somatic Syndromes-Fibromyalgia, Irritable Bowel Syndrome, Chronic Headaches, and Chronic Low Back Pain-Have Lower Outcomes and Higher Opioid Usage and Cost After Shoulder and Elbow Surgery.

Masood R, Mandalia K, Moverman MA, Puzitiello RN, Pagani NR, Menendez ME, Salzler MJ.

Arthroscopy. 2022 Dec 30:S0749-8063(22)00867-2. doi: 10.1016/j.arthro.2022.12.028. Epub ahead of print. PMID: 36592697.

Purpose: To perform a systematic review assessing the relationship between functional somatic syndromes (FSSs) and patient-reported outcome measures (PROMs), postoperative opioid consumption, and hospitalization costs after shoulder and elbow surgery. Methods: A systematic review of the PubMed and Web of Science databases was conducted according to Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines to identify all studies evaluating the effect of having at least 1 FSS (fibromyalgia, irritable bowel syndrome, chronic headaches, chronic low back pain) on outcomes after shoulder and elbow surgeries. Outcomes of interest included postoperative analgesic use, PROMs, and hospitalization costs. Results: The review identified a total of 320 studies, of which 8 studies met the inclusion criteria. The total number of participants in our 8 included studies was 57,389. Three studies (n = 620) reported PROMs. These studies demonstrated that the presence of at least 1 FSS is predictive of significantly greater pain scores and lower quality of recovery, Disability Arm Shoulder and Hand, American Shoulder and Elbow Surgeons Shoulder Score, and Single Assessment Numeric Evaluation scores postoperatively. Although scores were inferior in among patients with FSS, 2 of the 3 studies showed

improvement in PROMs in this group of patients. Seven studies (n = 56,909) reported postoperative opioid use. Of these, 5 reported that a diagnosis of at least 1 FSS was a strong risk factor for long-term opioid use after surgery. One study (n = 480) found that time-driven activity-based costs were significantly greater in patients with FSSs. Conclusions: Patients with functional somatic syndromes have less-favorable PROMs postoperatively, consume more opioids postoperatively, and have greater health care costs after elective shoulder and elbow procedures. Although PROMs among patients with FSSs are inferior compared with those without FSSs, PROMs still improved compared with baseline. Level of evidence: Level III, systematic review of Level II-III studies.

#### Determinants of Health-Related Quality of Life Across the Spectrum of Connective Tissue Diseases Using Latent Profile Analysis: Results from the LEAP cohort.

Dyball S, Reynolds JA, Herrick AL, Haque S, Chinoy H, Bruce E, Naz S, Parker B, Bruce IN. *Rheumatology* (Oxford). 2022 Dec 19;keac680. doi: 10.1093/rheumatology/keac680. Epub ahead of print. PMID: 36534822.

Objectives: Poor health-related quality of life (HR-QoL) is well recognised in patients with connective tissue diseases (CTD). We hypothesised that subgroups of patients across the spectrum of CTD experience different HR-QoL patterns, and aimed to determine patient-level characteristics associated with these different subgroups. Methods: Using the eight continuous domains of the Medical Outcomes Study Short-Form 36 (SF-36) questionnaire we performed data-driven clustering to derive latent profiles (LP) of patients with distinct HR-QoL patterns. Multivariable ordinal logistic regression was used to determine patient-level characteristics associated with each HR-QoL subgroup identified. Results: 309 CTD patients completed the SF-36 questionnaire. The most impaired SF-36 domains in each disease group were vitality, general health and bodily pain. The physical component of the SF-36 was consistently more impaired compared with the mental component, with similar scores across disease groups. Three latent profiles were identified with poor (n = 89; 29%), average (n = 190; 61.4%) and excellent (n = 30; 9.7%) HR-QoL. LP were not associated with diagnostic grouping or autoantibody profiles. Black background (OR 0.22 [95% CI 0.08-0.63]), Indo-Asian background (0.39 [0.19-0.78]), concomitant fibromyalgia (0.40 [0.20-0.78]), sicca symptoms (0.56 [0.32-0.98]) and multi-morbidity (Charlson Comorbidity Index, 0.81 [0.67-0.97]) were associated with the 'poor' HR-QoL LP. Conclusion: Distinct HR-QoL subgroups exist that are not primarily driven by the specific diagnosis or autoantibody profiles. We identified a number of key demographic and clinical factors associated with poor HR-QoL. These factors need to be addressed across the whole CTD spectrum as part of a holistic management approach aimed at improving overall patient outcomes.

#### Patient-Reported Disease Impact of Systemic Lupus Erythematosus with Active Joint Symptoms: Results from the Systemic Lupus Erythematosus-Update Survey.

Kamen DL, Birt JA, Hadi MA, Gibbons E, Bushnell DM, Yu R, Delbecque LA, Griffing K, Askanase A.

*Lupus*. 2022 Dec 21;9612033221147479. doi: 10.1177/09612033221147479. Epub ahead of print. PMID: 36541633.

Background: Many people with systemic lupus erythematosus (SLE) experience joint pain, swelling, and stiffness. These joint symptoms are associated with problems in physical functioning and work disability. We used survey data from adults with SLE to explore the burden and impact of joint symptoms. Methods: SLE-UPDATE was a 2019 cross-sectional US survey of adults with SLE. We compared respondents with "currently active" joint symptoms' and those "without currently active" joint symptoms. The active joint cohort comprised survey respondents who self-reported current "stiffness in joints" or "pain/swelling in joints" and who had moderate to severe joint pain (Worst Joint Pain Numeric Rating Scale [NRS] score  $\geq 4$ ). Respondents not fulfilling these criteria were included in the non-active joint cohort. Outcomes included frequency and severity of pain, patient-reported outcomes (LupusPRO™ and Work Productivity and Activity Impairment: Lupus [WPAI-Lupus]), satisfaction with current treatments, and importance of different treatment goals. Results: More respondents in the active joint cohort (N = 285) than in the non-active joint cohort (N = 215) reported pain most or all the time over the preceding 7 days (77.5% vs. 32.1%,  $p < .0001$ ), fibromyalgia (45% vs. 12%,  $p < .0001$ ), and higher (worse) mean scores on the Worst Pain NRS (6.5 vs. 4.8,  $p < .0001$ ) and Worst Joint Pain NRS (6.7 vs. 4.5,  $p < .0001$ ). Mean Lupus PRO health-related quality of life (HRQoL) total score was lower (worse) in the active joint cohort (48.9 vs. 64.1,  $p < .0001$ ). WPAI-Lupus scores indicated greater work productivity losses and activity impairment in the active joint cohort. More respondents in the active joint

cohort than in the non-active joint cohort were neutral or not satisfied with current treatments and rated reducing pain as a "very important" treatment goal (26.7% vs. 18.1%). Conclusions: Respondents with SLE and active joint manifestations in addition to having more pain report lower HRQoL and were less satisfied with their current treatments. Comorbid fibromyalgia may play a role in joint symptoms in patient with SLE joint manifestations. There is an unmet need for new therapeutic options to reduce joint symptom burden among patients with SLE.

#### Understanding the Female Physical Examination in Patients with Chronic Pelvic and Perineal Pain.

Pereira A, Fuentes L, Almoguera B, Chaves P, Vaquero G, Perez-Medina T.

J Clin Med. 2022 Dec 17;11(24):7490. doi: 10.3390/jcm11247490. PMID: 36556104; PMCID: PMC9783077.

(1) Background: The objective was to compare the exploration of chronic pelvic pain syndrome (CPPS) patients in different locations and establish the role of physical examination in CPPS patients. (2) Methods: We reviewed clinical data from 107 female patients with CPPS unresponsive to conventional therapies at Puerta de Hierro University Hospital Madrid, Spain, from May 2018 to June 2022. Patients were classified into three groups: (a) pelvic pain; (b) anorectal pain; or (c) vulvar/perineal pain. (3) Results: Although the demographics of patients with CPPS were different, their physical examinations were strikingly similar. Our study observed a comorbidity rate of 36% and 79% of central sensitization of pain. Seventy-one percent of patients had vulvar allodynia/hyperalgesia. Pain on examination was identified in any pelvic floor muscle, in any pelvic girdle structure, and neuropathic pain in 98%, 96%, and 89%, respectively. Patients with vulvar and perineal pain were more different from the other groups; these patients were younger and had fewer comorbidities and less central sensitization, less anorectal pain, more pain during intercourse, and greater nulliparity ( $p = 0.022$ ;  $p = 0.040$ ;  $p = 0.048$ ;  $p = 0.000$ ;  $p = 0.006$ ;  $p = 0.005$ ). (4) Conclusions: The findings of this study are related to the understanding of the pathophysiology of CPPS. The physical examination confirms the central sensitization of female patients with CPPS, helps us to determine the therapeutic management of the patient, and can be considered as a prognostic factor of the disease.

#### Impact of Treating Depression on Associated Comorbidities: A Systematic Literature Review.

Arnaud AM, Brister TS, Duckworth K, Foxworth P, Fulwider T, Suthoff ED, Werneburg B, Aleksanderek I, Reinhart ML.

Prim Care Companion CNS Disord. 2023 Jan 3;25(1):22r03330. doi: 10.4088/PCC.22r03330. PMID: 36638539.

Objective: To identify and summarize data that describe the impact of effectively treating major depressive disorder (MDD) on the severity or risk of serious comorbidities. Data Sources: MEDLINE, Embase, PsycINFO, Cochrane Database of Systematic Reviews, and several congresses were searched. Searches included terms related to MDD, randomized controlled trials (RCTs), and physical comorbidities and were restricted to English-language publications. Searches were conducted in November 2019 for the previous 2 years for conference proceedings; no date restriction was applied to the database searches. Study Selection: Included studies were RCTs or meta-analyses that assessed depression therapies. Studies were required to report a statistically significant improvement in depression scores as well as the concurrent impact on comorbidities. A total of 1,997 articles were initially identified for screening. Data Extraction: Two investigators extracted data and assessed study quality. Results: A total of 30 studies, including 24 RCTs ( $N = 6,333$ ) and 6 meta/pooled analyses of RCTs, were included. Findings in several comorbidity categories were mixed; for example, in half (4 of 8) of the identified studies in people with cardiovascular disease and depression, individuals who received treatment leading to reduced depressive symptoms compared with a control arm also had a significantly decreased incidence of cardiovascular events or significantly improved cardiac disease symptom/severity scores compared with controls. Significant improvements in comorbid disease severity observed alongside improvements in depressive symptoms were also noted in studies of comorbid Parkinson's disease, multiple sclerosis, chronic pain and fibromyalgia, and chronic obstructive pulmonary disease. Conclusions: Effective treatment of MDD may lead to a reduction in the severity of certain serious comorbidities. These results highlight the importance of appropriate and timely treatment of MDD.

#### Endometriosis-associated Chronic Pelvic Pain.

Karp BI, Stratton P.



Endometriosis is a heterogeneous disease where neurogenic sensitization can lead to chronic pain within and beyond the pelvis. Coincident pain and comorbidities merit specific attention. We discuss the causes, comorbidities, and management of endometriosis-associated chronic pelvic pain, advocating for a multidisciplinary approach to develop more effective treatments.

### The Cognitive and Emotional Aspect in Fibromyalgia: The Importance of the Orofacial Sphere.

Bordoni B, Escher AR, Cannadoro G, Tobbi F.

Cureus. 2023 Mar 19;15(3):e36380. doi: 10.7759/cureus.36380. PMID: 36945233; PMCID: PMC10025772.

Fibromyalgia syndrome (FMS) is a systemic and multifactorial disease of unknown etiology. There are many co-morbidities that the patient presents, making the clinical picture not immediate. Cognitive decline and emotional alteration (anxiety and depression) are found in fibromyalgic patients, as well as temporomandibular joint arthrokinematic disorders, dental malocclusion, and periodontitis. There seems to be a biunivocal relationship between oral and psychiatric dysfunctions in fibromyalgia. The article reviews the information regarding oral health alterations with respect to the patient's cognitive and emotional response, as the most recent information we have raises new hypotheses about the diagnosis of FMS.

### Endometriosis Features in Women with and without Migraine.

Neumeier MS, Pohl H, Dietrich H, Knobel C, Portmann L, Metzler J, Imesch P, Merki-Feld GS.

J Womens Health (Larchmt). 2023 Mar 10. doi: 10.1089/jwh.2022.0359. Epub ahead of print. PMID: 36897310.

**Background:** This study examines endometriosis (EM) features in women with EM and migraines (MG) (EM-MG) and women with EM alone (EM-O). The comorbidity of MG and EM is well known. However, knowledge about differences in symptoms, clinical manifestations, and severity of EM between EM-MG and EM-O is scarce. **Materials and Methods:** We conducted a cross-sectional observational study of premenopausal patients with biopsy-confirmed EM treated in our department from 2015 to 2021. All patients underwent surgical treatment for EM. Information about infiltration depth and localization of EM was available. We interviewed patients using a structured questionnaire that includes questions about clinical characteristics, symptoms, and treatment history. We reported categorical variables as frequencies and continuous variables as means with standard deviations. We compared subgroups (EM-MG vs. EM-O) using an independent sample t-test, the Wilcoxon-Mann-Whitney test, chi-square test, and Fisher's exact test. The significance level was 0.05. **Results:** We included 344 participants: 250 with EM-O and 94 with EM-MG. EM-MG had less severe revised American Society of Reproductive Medicine scores ( $p = 0.023$ ), more deliveries ( $p = 0.009$ ), more and higher scores of dysmenorrhea at menarche ( $p = 0.044$ ;  $p = 0.036$ ), prolonged heavy menstrual bleeding ( $p = 0.009$ ), more and prolonged pain during menstrual bleeding ( $p = 0.011$ ,  $p = 0.039$ ), and more dyschezia ( $p < 0.001$ ) compared with EM-O. **Conclusion:** Migraineurs experienced more intense EM symptoms at lower EM stages. This discrepancy strongly indicates pain sensitizations and a lower pain threshold in patients with EM-MG. Knowledge about EM features allows early diagnosis and treatment of women with potential EM-MG, both highly disabling conditions. Clinical Trials.gov ([NCT04816357](https://clinicaltrials.gov/ct2/show/study/NCT04816357)).

## **Epidemiology Studies**

### Identifying and Visualising Multimorbidity and Comorbidity Patterns in Patients in the English National Health Service: A Population-Based Study.

Kuan V, Denaxas S, Patalay P, Nitsch D, Mathur R, Gonzalez-Izquierdo A, Sofat R, Partridge L, Roberts A, Wong ICK, Hingorani M, Chaturvedi N, Hemingway H, Hingorani AD; Multimorbidity Mechanism and Therapeutic Research Collaborative (MMTRC).

Lancet Digit Health. 2023 Jan;5(1):e16-e27. doi: 10.1016/S2589-7500(22)00187-X. Epub 2022 Nov 29. PMID: 36460578.

Background: Globally, there is a paucity of multimorbidity and comorbidity data, especially for minority ethnic groups and younger people. We estimated the frequency of common disease combinations and identified non-random disease associations for all ages in a multiethnic population. Methods: In this population-based study, we examined multimorbidity and comorbidity patterns stratified by ethnicity or race, sex, and age for 308 health conditions using electronic health records from individuals included on the Clinical Practice Research Datalink linked with the Hospital Episode Statistics admitted patient care dataset in England. We included individuals who were older than 1 year and who had been registered for at least 1 year in a participating general practice during the study period (between April 1, 2010, and March 31, 2015). We identified the most common combinations of conditions and comorbidities for index conditions. We defined comorbidity as the accumulation of additional conditions to an index condition over an individual's lifetime. We used network analysis to identify conditions that co-occurred more often than expected by chance. We developed online interactive tools to explore multimorbidity and comorbidity patterns overall and by subgroup based on ethnicity, sex, and age. Findings: We collected data for 3 872 451 eligible patients, of whom 1 955 700 (50.5%) were women and girls, 1 916 751 (49.5%) were men and boys, 2 666 234 (68.9%) were White, 155 435 (4.0%) were south Asian, and 98 815 (2.6%) were Black. We found that a higher proportion of boys aged 1-9 years (132 506 [47.8%] of 277 158) had two or more diagnosed conditions than did girls in the same age group (106 982 [40.3%] of 265 179), but more women and girls were diagnosed with multimorbidity than were boys aged 10 years and older and men (1 361 232 [80.5%] of 1 690 521 vs 1 161 308 [70.8%] of 1 639 593). White individuals (2 097 536 [78.7%] of 2 666 234) were more likely to be diagnosed with two or more conditions than were Black (59 339 [60.1%] of 98 815) or south Asian individuals (93 617 [60.2%] of 155 435). Depression commonly co-occurred with anxiety, migraine, obesity, atopic conditions, deafness, soft-tissue disorders, and gastrointestinal disorders across all subgroups. Heart failure often co-occurred with hypertension, atrial fibrillation, osteoarthritis, stable angina, myocardial infarction, chronic kidney disease, type 2 diabetes, and chronic obstructive pulmonary disease. Spinal fractures were most strongly non-randomly associated with malignancy in Black individuals, but with osteoporosis in White individuals. Hypertension was most strongly associated with kidney disorders in those aged 20-29 years, but with dyslipidaemia, obesity, and type 2 diabetes in individuals aged 40 years and older. Breast cancer was associated with different comorbidities in individuals from different ethnic groups. Asthma was associated with different comorbidities between males and females. Bipolar disorder was associated with different comorbidities in younger age groups compared with older age groups. Interpretation: Our findings and interactive online tools are a resource for: patients and their clinicians, to prevent and detect comorbid conditions; research funders and policy makers, to redesign service provision, training priorities, and guideline development; and biomedical researchers and manufacturers of medicines, to provide leads for research into common or sequential pathways of disease and inform the design of clinical trials.

#### Overlaps with Bladder Pain Syndrome and Irritable Bowel Syndrome are Associated with Higher Symptom Burden and Reduced Quality of Life in Functional Dyspepsia.

Wuestenberghs F, Baron M, Melchior C, Desprez C, Cornu JN, Leroi AM, Gourcerol G. *Neurogastroenterol Motil.* 2022 Nov;34(11):e14414. doi: 10.1111/nmo.14414. Epub 2022 May 24. PMID: 35608061.

Background: Functional dyspepsia and bladder pain syndrome are well-known to overlap with irritable bowel syndrome. Whether functional dyspepsia overlaps with bladder pain syndrome remains unknown. Our aim was to evaluate the presence of bladder pain syndrome in functional dyspepsia patients and its impact. Methods: All consecutive patients with investigated dyspeptic symptoms in our tertiary care center between March 2015 and November 2018 were studied. Functional dyspepsia and irritable bowel syndrome were diagnosed according to Rome III and IV criteria while bladder pain syndrome was diagnosed using ESSIC criteria. Validated questionnaires were filled to assess quality of life (GIQLI), anxiety and depression (HADS), sleep (PSQI), and insomnia (ISI). Dyspeptic symptoms severity was assessed individually for eight dyspeptic complaints. Key results: Among 1453 patients with dyspeptic symptoms, 61.4% fulfilled Rome criteria for functional dyspepsia. Bladder pain syndrome was present in 16.0% of the patients not fulfilling diagnostic criteria for functional dyspepsia, 22.2% of patients with functional dyspepsia alone, and 36.4% of patients with overlapping functional dyspepsia and irritable bowel syndrome (p-values <0.0001). In patients with bladder pain syndrome overlapping with functional dyspepsia, dyspeptic symptoms severity, anxiety, depression, and insomnia levels were higher while quality of life and sleep quality were reduced (p-values <0.0001). These results were even

more pronounced in case of overlap with irritable bowel syndrome (p-values <0.0001).  
Conclusions and inferences: Bladder pain syndrome is present in 26.9% of functional dyspepsia patients and is associated with higher gastrointestinal, psychological distresses, and sleep symptom burdens, and with reduced quality of life.

#### Multisensory Sensitivity Differentiates Between Multiple Chronic Pain Conditions and Pain-free Individuals.

Wang D, Frey-Law LA.

Pain. 2023 Feb 1;164(2):e91-e102. doi: 10.1097/j.pain.0000000000002696. Epub 2022 May 19. PMID: 35588150.

Multisensory sensitivity (MSS) to nonpainful stimuli has been identified as a risk factor for the presence of coexisting chronic pain conditions. 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 comorbidities assessed. MSS was highest in FM, followed by migraine, then LBP, and lowest in pain-free individuals (adjusted between condition Cohen  $d = 0.32-1.2$ ,  $P \leq 0.0007$ ). However, when secondly grouping patients by the total number of pain comorbidities reported, those with a single pain condition (but not FM) did not have significantly elevated MSS vs 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 ( $P \leq 0.0001$ ). Furthermore, those with low MSS levels were 55% to 87% less likely to have  $\geq 2$  pain comorbidities with or without FM (OR 0.45 [0.22, 0.88]-0.13 [0.05, 0.39];  $P \leq 0.0001$ ). Our findings support that MSS can differentiate between pain phenotypes with different degrees of expected central mechanism involvement and also serve as a risk and resilience marker for total coexisting chronic pain conditions. 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.

#### Fibromyalgia: Epidemiology and Risk Factors. a Population-Based Case-Control Study in Damascus, Syria.

Alzabibi MA, Shibani M, Alsuliman T, Ismail H, Alasaad S, Torbey A, Altorkmani A, Sawaf B, Ayoub R, Khalayli N, Kudsi M.

BMC Rheumatol. 2022 Oct 31;6(1):62. doi: 10.1186/s41927-022-00294-8. PMID: 36310163; PMCID: PMC9618353.

Background: Fibromyalgia is a chronic disease with a high burden. We aim to be the first to investigate the prevalence of fibromyalgia (FM) in Syria and assess its risk factors. Methods: A self-reported questionnaire was distributed to the public to identify fibromyalgia patients using the American College of Rheumatology (ACR) 2010 modified criteria. Identified cases were matched using age with controls free from rheumatic disorders that were randomly sampled from the same population. Results: Out of 2966 participants, 350 (11.8%) satisfied the diagnostic criteria. Of these, only 29 (8.2%) were previously diagnosed by a physician, 239 (68.3%) were females, and 69 (19.71%) were diagnosed with depression. Female sex (OR = 1.31), diagnosis of major depressive disorder (OR = 2.62), irritable bowel syndrome (OR = 1.8), and Restless legs syndrome (OR = 1.72) were associated with a higher likelihood of fibromyalgia. Conclusion: Our study revealed one of the highest prevalence rates of fibromyalgia ever reported in the general population. Efforts must be intensified to increase awareness about this disease in Syrian society as well as among healthcare providers.

#### Design and Validation of a Predictive Model for Determining the Risk of Developing Fibromyalgia.

Benachi Sandoval N, Fernández Solà J, Guaita Mateo A, Navarrete Durán MP, Meneses Urrea LA, Torres Belmonte S, Mañes López E, López Poyato M.

Clin Exp Rheumatol. 2023 Jan 2. doi: 10.55563/clinexprheumatol/r23r95. Epub ahead of print. PMID: 36622095.

Objectives: Fibromyalgia is a prevalent disease of unknown aetiology and is difficult to diagnose. Despite the availability of the American College of Rheumatology criteria for diagnosis, it continues to be a challenge in the field of primary health care in terms of identifying individuals with susceptibility to developing the disease. The aim of this study is to design and validate a predictive model of fibromyalgia in subjects with a history of chronic pain. Methods: This multicentre observational retrospective cohort study was performed on

patients aged >18 years, who visited four primary health centres between 2017 and 2020, with a diagnosis of fibromyalgia or arthritis. The Bootstrapping resampling method was used for the validation of the model. Results: A total of 198 subjects with fibromyalgia (93 with osteoarthritis, 20 with other types of arthritis, 4 with rheumatoid arthritis) and 120 without fibromyalgia (116 with osteoarthritis, 23 with other types of arthritis, 7 with rheumatoid arthritis) participated in the study. The predictive factors of the final model were self-reported age at onset of symptoms, first-line family history of neurological diseases, exposure to levels of stress, history of post-traumatic acute emotional stress, and personal history of chronic widespread pain prior to diagnosis, comorbidity, and pharmacological prescription during the year of diagnostic confirmation. The predictive capacity adjusted by Bootstrapping was 0.972 (95% CI: 0.955-0.986). Conclusions: The proposed model showed an excellent predictive capacity. The risk calculator designed from the predictive model allows health professionals to have a useful tool to identify subjects at risk of developing fibromyalgia.

#### Chronic Low Back Pain Comorbidity Count and its Impact on Exacerbating Opioid and Non-Opioid Prescribing Behavior.

Moses-Hampton MK, Povieng B, Ghorayeb JH, Zhang Y, Wu H.

Pain Pract. 2022 Nov 29. doi: 10.1111/papr.13185. Epub ahead of print. PMID: 36447402.

Research objectives: To determine the characteristics of chronic low back pain (CLBP) comorbidity and its impact on opioid and non-opioid treatments among Chicagoland patients with CLBP. Design: A retrospective cross-sectional study comparing differences in comorbidity and treatment patterns among Chicagoland patients with CLBP against a matched control arm without chronic low back pain (NCLBP). Setting: Academic hospital system outpatient services. Participants: Using the International Classification of Diseases, 10th Revision codes (ICD 10) 9,589 patients were identified with CLBP with a median age of 57 years old and 62.32% female distribution. The NCLBP group comprised 9,589 age-, sex-, race-, and region-matched patients. Results: An increased prevalence across all 17 studied comorbidities was found in CLBP patients as compared to NCLBP patients. CLBP patients carried an average of 3.5 comorbidities compared to 2.4 comorbidities in NCLBP patients. Rheumatoid arthritis (RA), joint arthritis and obesity had the strongest relationship with CLBP. Additionally, we found that the most prescribed treatment for CLBP were opioids, which ranked above NSAIDs and physical therapy. 56% of CLBP patients were prescribed opioids as compared to 36% of NCLBP patients (Odds Ratio = 2.28, 95% CI: 2.16-2.42). Tramadol was the agent with the strongest relationship to CLBP. CLBP patients were more likely to use 2 or more opioids concomitantly. The number of total treatments was positively associated with the number of comorbidities in both CLBP and NCLBP patients (Cochran-Armitage trend test  $p < 0.0001$ ). Conclusions: CLBP patients showed a higher number of comorbidities, than their NCLBP counterparts. Comorbidity count trended positively with higher treatment burden with opioids being the most prescribed treatment, often with poly-opioid use, over conservative modalities such as NSAIDs and physical therapy.

#### Comorbidities in Patients with Migraine in Japan: A Cross-Sectional Study Using Data from National Health and Wellness Survey.

Kikui S, Chen Y, Ikeda K, Hasebe M, Asao K, Takeshima T.

BMJ Open. 2022 Nov 30;12(11):e065787. doi: 10.1136/bmjopen-2022-065787. PMID: 36450434.

Objectives: This study aims to examine the association between migraine and various psychiatric and somatic comorbidities in Japan. Design: Cross-sectional study using existing data of the 2017 Japan National Health and Wellness Survey (NHWS). Setting: Nationally representative sample of persons (in terms of age and gender) living in the general community aged 18 years or older in Japan. Participants: Out of a sample of 30 001 NHWS respondents, 378 respondents were identified as migraine patients and 25 209 were identified as non-migraine patients. After propensity score (PS) matching (1:4), 1512 matched non-migraine respondents were identified. Primary and secondary outcome measures: Prevalence and PS-matched prevalence ORs (PORs) were assessed for each psychiatric and somatic comorbidity among migraine patients and matched non-migraine respondents (including migraine patients with less than 15 monthly headache days (MHDs) and migraine patients with more than 15 MHDs). Results: Migraine patients were predominately female and had significantly higher prevalence than matched non-migraine respondents to have psychiatric and somatic comorbidities. Psychiatric comorbidities with >5% prevalence among migraine patients included depression, post-traumatic stress disorder and anxiety disorders, while gastrointestinal disorders were the most prevalent somatic comorbidity category. Other

somatic comorbidities included allergies, insomnia, premenstrual syndrome and anaemia. Migraine patients with more than 15 MHDs tended to have higher point estimates for POR. Conclusion: Psychiatric and somatic conditions were more prevalent in migraine patients than matched non-migraine respondents, some being novel associations not previously reported in Japan. This study provided insights on comorbidities, which could complicate care, clinical practice and outcomes among migraine patients.

### The Prevalence and Clinical Features of Fibromyalgia in Chinese Hospital Patients with Primary Headache: The Survey of Fibromyalgia Comorbid with Headache.

Dong Z, Liu K, Liu H, Jia Z, Gui W, Dong M, Cheng Y, Lv Y, Qu K, Zhao H, Chen J, Zhang D, Fan Z, Yang X, Hu D, Zhang Y, Xie H, Li M, Wen B, Chen S, Xu P, Rong Q, He Q, Ren Z, Yan F, Zhao H, Chen M, Yu T, Qu H, An X, Guo H, Zhang X, Pan X, Wang X, Qiu S, Zhang L, Zhao H, Pan X, Wan Q, Yan L, Liu J, Yu Z, Zhang M, Ran Y, Han X, Yu S. Headache. 2023 Jan;63(1):62-70. doi: 10.1111/head.14443. Epub 2023 Jan 18. PMID: 36651491.

**Objective:** The aims were to explore the prevalence and clinical features of fibromyalgia in Chinese hospital patients with primary headache. **Background:** Studies done in non-Chinese populations suggest that around one-third of patients with primary headache have fibromyalgia, but data from mainland China are limited. Investigations into the prevalence and clinical features of fibromyalgia in Chinese patients with primary headache would improve our understanding of these two complex disease areas and help guide future clinical practice. **Methods:** This cross-sectional study included adults with primary headache treated at 23 Chinese hospitals from September 2020 to May 2021. Fibromyalgia was diagnosed using the modified 2010 American College of Rheumatology criteria. Mood and insomnia were evaluated employing the Hospital Anxiety and Depression Scale and the Insomnia Severity Index. **Results:** A total of 2782 participants were analyzed. The fibromyalgia prevalence was 6.0% (166/2782; 95% confidence interval: 5.1%, 6.8%). Compared to primary headache patients without combined fibromyalgia, patients with primary headache combined with fibromyalgia were more likely to be older (47.8 vs. 41.7 years), women (83.7% [139/166] vs. 72.8% [1904/2616]), less educated (65.1% [108/166] vs. 45.2% [1183/2616]), and with longer-duration headache (10.0 vs. 8.0 years). Such patients were more likely to exhibit comorbid depression (34.3% [57/166] vs. 9.9% [260/2616]), anxiety (16.3% [27/166] vs. 2.7% [70/2612]), and insomnia (58.4% [97/166] vs. 17.1% [447/2616]). Fibromyalgia was more prevalent in those with chronic (rather than episodic) migraine (11.1% [46/414] vs. 4.4% [72/1653],  $p < 0.001$ ) and chronic (rather than episodic) tension-type headache (11.5% [27/235] vs. 4.6% [19/409],  $p = 0.001$ ). Most fibromyalgia pain was in the shoulders, neck, and upper back. **Conclusions:** The prevalence of fibromyalgia in mainland Chinese patients with primary headache was 6.0%. Fibromyalgia was more common in those with chronic rather than episodic headache. The most common sites of fibromyalgia pain were the neck, shoulders, and back.

### Classification of Patients with Osteoarthritis through Clusters of Comorbidities Using 633,330 Individuals from Spain.

Pineda-Moncusí M, Dernie F, Dell'Isola A, Kamps A, Runhaar J, Swain S, Zhang W, Englund M, Pitsillidou I, Strauss VY, Robinson DE, Prieto-Alhambra D, Khalid S. Rheumatology (Oxford). 2023 Jan 23;kead038. doi: 10.1093/rheumatology/kead038. Epub ahead of print. PMID: 36688706.

**Objectives:** To explore clustering of comorbidities among patients with a new diagnosis of osteoarthritis (OA) and estimate the 10-year mortality risk for each identified cluster. **Methods:** This is a population-based cohort study of individuals with first incident diagnosis of OA of the hip, knee, ankle/foot, wrist/hand, or 'unspecified' site between 2006 and 2020, using SIDIAP (a primary care database representative from Catalonia, Spain). At the time of OA diagnosis, conditions associated with OA in the literature that were found in  $\geq 1\%$  of the individuals ( $n = 35$ ) were fitted into two cluster algorithms, K-means and latent class analysis (LCA). Models were assessed using a range of internal and external criteria evaluation procedures. Mortality risk of the obtained clusters was assessed by survival analysis using Cox proportional hazards. **Results:** We identified 633 330 patients with a diagnosis of OA. Our proposed best solution used LCA to identify four clusters: 'Low-morbidity (relatively low number of comorbidities)', 'Back/neck pain plus mental health', 'Metabolic syndrome' and 'Multimorbidity' (higher prevalence of all study comorbidities). Compared with the 'Low-morbidity', the 'Multimorbidity' cluster had the highest risk of 10-year mortality (adjusted HR: 2.19 [95%CI: 2.15-2.23]), followed by 'Metabolic syndrome' (adjusted HR: 1.24 [95%CI: 1.22-

1.27]] and 'Back/neck pain plus mental health' (adjusted HR: 1.12 [95%CI: 1.09-1.15]). Conclusion: Patients with a new diagnosis of OA can be clustered into groups based on their comorbidity profile, with significant differences in 10-year mortality risk. Further research is required to understand the interplay between OA and particular comorbidity groups, and the clinical significance of such results.

#### Increased Overall Morbidity in Women with Endometriosis: A Population-Based Follow-up Study Until Age 50.

Henna-Riikka R, Outi U, Anna T, Paula P, Sari K, Terhi P.

Fertil Steril. 2022 Dec 7:S0015-0282(22)01782-4. doi: 10.1016/j.fertnstert.2022.09.361. Epub ahead of print. PMID: 36496274.

Objective: To investigate whether there is an association between endometriosis and nongynecological diseases in the general female population by age 50? Design: A prospective cohort study. Setting: Study participants with and without endometriosis were identified from a general population-based birth cohort. The analyzed data, linking to the national hospital discharge registers, spanned up to the age of 50 years. Patient(s): Endometriosis case identification was based on national register data and self-reported diagnoses, producing a study population of 349 women with endometriosis and 3,499 women without endometriosis. Main outcome measure(s): International Classification of Diseases diagnosis codes from 1968 to 2016 were accumulated from the Finnish national Care Register for Health Care, whereas self-reported symptoms and continuous medication usage data were collected from the questionnaires distributed at age 46. The associations between endometriosis and comorbidities were assessed using logistic regression models that included several covariates. The odds ratios and 95% confidence intervals (CIs) were modeled. Endometriosis subtype and temporal analyses were also performed. Results(s): Women with endometriosis were on average twice as likely to have hospital-based nongynecological diagnoses as women without endometriosis (adjusted odds ratio [aOR] 2.32; 95% CI, 1.07-5.02). In more detail, endometriosis was associated with allergies, infectious diseases, pain-causing diseases, and respiratory diseases. Moreover, the affected women presented with nonspecific symptoms and signs (aOR 3.56; 95% CI, 2.73-4.64), especially abdominal and pelvic pain (aOR 4.33; 95% CI, 3.13-4.76) more often compared with nonendometriosis controls. The temporal analysis revealed that diagnoses accumulated at a significantly younger age among women with endometriosis than in nonendometriosis counterparts. Conclusion(s): Women with endometriosis have a high risk for several chronic diseases compared with women without endometriosis, underlying the need for awareness and targeted resources for these women in the health care system. Moreover, endometriosis should be considered in the presence of nonspecific symptoms and abdominal pain, as they may conceal the disease and cause considerable delay in diagnosis and treatment.

#### Occurrence of Comorbidity Following Osteoarthritis Diagnosis: A Cohort Study in the Netherlands.

Kamps A, Runhaar J, de Ridder MAJ, de Wilde M, van der Lei J, Zhang W, Prieto-Alhambra D, Englund M, de Schepper EIT, Bierma-Zeinstra SMA.

Osteoarthritis Cartilage. 2022 Dec 14:S1063-4584(22)00957-8. doi: 10.1016/j.joca.2022.12.003. Epub ahead of print. PMID: 36528309.

Objective: To determine the risk of comorbidity following diagnosis of knee or hip osteoarthritis (OA). Design: A cohort study was conducted using the Integrated Primary Care Information database, containing electronic health records of 2.5 million patients from the Netherlands. Adults at risk for OA were included. Diagnosis of knee or hip OA (=exposure) and 58 long-term comorbidities (=outcome) were defined by diagnostic codes following the International Classification of Primary Care (ICPC) coding system. Time between the start of follow-up and incident diagnosis of OA was defined as unexposed, and between diagnosis of OA and the end of follow-up as exposed. Age and sex adjusted hazard ratios (HRs) comparing comorbidity rates in exposed and unexposed patient time were estimated with 99.9% confidence intervals (CI). Results: The study population consisted of 1,890,712 patients. For 30 of the 58 studied comorbidities, exposure to knee OA showed a HR larger than 1. Largest positive associations (HR with (99.9% CIs)) were found for obesity 2.55 (2.29-2.84) and fibromyalgia 2.06 (1.53-2.77). For two conditions a HR<1 was found, other comorbidities showed no association with exposure to knee OA. For 26 comorbidities, exposure to hip OA showed a HR larger than 1. The largest were found for polymyalgia rheumatica 1.81 (1.41-2.32) and fibromyalgia 1.70 (1.10-2.63). All other comorbidities showed no associations with hip OA. Conclusion: This study showed that many comorbidities were

diagnosed more often in patients with knee or hip OA. This suggests that the management of OA should consider the risk of other long-term-conditions.



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