CUTTING EDGE

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This issue contains abstracts of studies published in January and February 2025.

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ENGAGEMENT SCIENCE

Patient Partner Engagement in the Publication Process: Challenges and Possible Solutions.
Cooksey KE, Neuman M, Bollini M, Pennington B, de O Campos H, Oberst K, Wurst M, Politi MC.
BMC Med Res Methodol. 2025 Feb 15;25(1):39. doi: 10.1186/s12874-025-02495-4. PMID: 39955495; PMCID: PMC11829384.

Patient engagement in research is gaining traction as an international standard, and often requirement, of many health research funding agencies. Drivers of this increase include patient interest, increased attention to and recognition of the value of patients' voices in research, and more patients leading or partnering in the conduct research. Patient engagement includes collaborating and providing insights into research question and study design, and may extend to the publication process. When patients contribute to publications, they can bring unique perspectives that may enhance the impact, reach, and utility of the research in real-world contexts. Currently, there is limited systematic guidance to support patient partners as they navigate this complex publication process. As a result, it can be difficult for patient partners to understand when and how they should be included as authors, how to collaborate in the writing process, and how to complete mandatory tasks during the submission process. In this paper, we review barriers and facilitators within existing publication practices and offer recommendations to ensure that the scientific publication process is more transparent and accessible for patient partners.

Patient Partner Research has a Compensation Crisis.
Price A, Richards DP.
BMJ. 2025 Feb 27;388:r381. doi: 10.1136/bmj.r381. PMID: 40015731.

No abstract available.

Leveraging Community Engagement to Shape Biomedical Research Priorities.
Suliman S, Agyei L, Afzal SA, Williams S.
Trends Immunol. 2025 Feb;46(2):100-103. doi: 10.1016/j.it.2024.12.004. PMID: 39843309.

Community engagement is essential for shaping equitable biomedical research priorities, but it is often underutilized, especially for marginalized populations. To integrate community feedback from the public into research, herein we describe a collaborative pilot funded by the Chan Zuckerberg Initiative which pairs the University of California San Francisco (UCSF) with the Rafiki Coalition for Health and Wellness. Utilizing focus groups modeled on Research Prioritization by Affected Communities, participants identified themes that included mistrust in healthcare, representation gaps, and the need for culturally responsive research. Priorities such as mental health, chronic disease, and access to black providers were highlighted. The

findings emphasize the need for sustained, grassroots partnerships to drive inclusive research agendas.

A Bibliometric Analysis of Healthcare Intervention-Related Studies Reporting Patient and Public Involvement and Engagement.
Lu W, Li Y, Montayre J, Li M, Ho KY, Li J, Yorke J.
Healthcare (Basel). 2025 Feb 2;13(3):305. doi: 10.3390/healthcare13030305. PMID: 39942494; PMCID: PMC11817042.

Background/Objectives: Patient and public involvement and engagement (PPIE) has gained global recognition as an innovative healthcare research practice. PPIE engages end-users throughout the research process, improving intervention effectiveness, resource efficiency, and user satisfaction. Despite its increasing inclusion in studies, comprehensive bibliometric reviews of healthcare intervention-related studies reporting PPIE are scarce. This study aims to conduct a bibliometric analysis of healthcare intervention-related studies reporting PPIE in recent decades to identify key worldwide bibliometric features, themes, and trends.
Methods: The analysis includes 10,624 relevant English articles published in the Web of Science (WoS) Core Collection up to 26 November 2024. Search terms were selected based on PPIE conceptualization, interventional types, and related healthcare terms. Using WoS descriptive analysis and CiteSpace, we examined bibliometric features and identified major international themes and trends.
Results: There has been a significant increase in the number of healthcare intervention-related studies reporting PPIE over the past five years, especially from the United States and the United Kingdom, with a recent rise in Asia. However, cross-national collaboration remains limited. Key research themes identified include “community participation”, “health equity”, “coronary heart disease”, “web-based patient empowerment”, “mental illness”, and “obesity prevention”, with growing interest in “mobile health” and “digital health”.
Conclusions: This study provides a comprehensive and up-to-date overview of the bibliometric characteristics and evolving trends in healthcare intervention-related studies reporting PPIE. It highlights global regions with limited PPIE implementation, suggests pathways for further development, and identifies key research themes. The study offers researchers and practitioners valuable insights into tracking PPIE trends in healthcare interventions and fostering collaborations on evidence-based PPIE studies with leading scholars and institutions worldwide. Additionally, the findings drive innovations aimed at improving patient and public healthcare outcomes.

Evaluating Process and Outcomes of Public Involvement in Applied Health and Social Care Research: A Rapid Systematic Review.
Wearn A, Brennan-Tovey K, Adams EA, Alderson H, Baariu J, Cheetham M, Bartle V, Palfreyman L, Rook V, Shenton F, Ramsay SE, Kaner E.
Health Expect. 2025 Feb;28(1):e70160. doi: 10.1111/hex.70160. PMID: 39840654; PMCID: PMC11751718.

Objective: Public Involvement (PI) in applied health and social care research has grown exponentially in the UK. This review aims to synthesise published UK evidence that evaluates the process and/or outcome(s) of PI in applied health and social care research to identify key contextual factors, effective strategies, outcomes and public partner experiences underpinning meaningful PI in research.
Methods: Following a pre-registered protocol, we systematically searched four databases and two key journals for studies conducted within the UK between January 2006 and July 2024. A team of public partners and researchers carried out independent dual screening and data extraction. Included studies were narratively synthesised via Framework Synthesis.
Results: Nineteen studies evaluated the PI process with a range of populations including National Health Service (NHS) users, carers, and low-income communities. No specific outcome evaluations were identified. Through their experience, public partners described important components of meaningful PI such as mutual respect and seeing and contributing to change, as well as some unintended harms of involvement. Harms related to 'experiencing negative attitudes', 'emotional burden of involvement', 'frustration and disappointment' and 'further marginalisation'. Meaningful PI was underpinned by structural, organisational, interpersonal and individual factors; as well as practical and principle-based strategies of involvement. Both public partners and researchers reflected on a range of outcomes of meaningful PI including changes to the research process and longer term impacts on organisations, researchers and public partners.
Conclusions: PI in research must be facilitated at multiple levels to reduce unintended harm and encourage meaningful and impactful outcomes. Findings are summarised within a model which gives an overview of priorities for individual researchers, organisations and funders to ensure best practice is achievable. From a methodological perspective, researchers should prioritise robust, transparent and co-produced approaches to evaluating PI to increase knowledge in the field.
Patient and public involvement: A regional public advisory network provided insight on the relevance and acceptability of the review concept. Our core research team included three public partners. Public partners contributed to the development of the initial review protocol, abstract and full-text screening, reviewing findings and their interpretation and writing the final report.

Embracing Dissensus in Lived Experience Research: The Power of Conflicting Experiential Knowledge.
Speyer H, Ustrup M.
Lancet Psychiatry. 2025 Feb 26:S2215-0366(25)00003-3. doi: 10.1016/S2215-0366(25)00003-3. Epub ahead of print. PMID: 40023171.

Lived experience is a crucial component in the development of innovative interventions and services in mental health care. To unlock the full potential of this valuable source of knowledge, it is essential to actively cultivate and understand it. A common concern, however, is the variability of perspectives, as individuals with lived experience might express opposing views on some issues. Building on our own journey as researchers with a combination of academic training and lived experience, we have developed an approach that treats dissensus not necessarily as a challenge to be resolved through consensus, but rather as a source of innovation. Our approach involves a two-step model. First, we identify the genuine points of disagreement or true negations between us. Next, we clarify the epistemic goal of the inquiry at hand. Based on this process, we determine whether the dissensus-often a rich, complex expression of variation-offers deeper insights, or if a more generalised, consensus-based message would be the most effective way to answer the inquiry. With this Personal View, we hope to inspire collaborators, both with and without lived experience, to engage rigorously and enthusiastically with dissensus, recognising its potential as a driver of innovation.

PATHOPHYSIOLOGY STUDIES

Chronic Overlapping Pain Conditions and Nociplastic Pain.
Johnston KJA, Signer R, Huckins LM.
HGG Adv. 2025 Jan 9;6(1):100381. doi: 10.1016/j.xhgg.2024.100381. Epub 2024 Nov 4. PMID: 39497418; PMCID: PMC11617767.

Chronic overlapping pain conditions (COPCs) are a subset of chronic pain conditions commonly comorbid with one another and more prevalent in women and individuals assigned female at birth (AFAB). Pain experience in these conditions may better fit with a new mechanistic pain descriptor, nociplastic pain, and nociplastic pain may represent a shared underlying factor among COPCs. We applied GenomicSEM common-factor genome-wide association study (GWAS) and multivariate transcriptome-wide association (TWAS) analyses to existing GWAS output for six COPCs in order to find genetic variation associated with nociplastic pain, followed by genetic correlation (linkage disequilibrium score regression), gene set, and tissue enrichment analyses. We found 24 independent single nucleotide polymorphisms (SNPs), and 127 unique genes significantly associated with nociplastic pain, and showed nociplastic pain to be a polygenic trait with significant SNP heritability. We found significant genetic overlap between multisite chronic pain and nociplastic pain, and to a smaller extent with rheumatoid arthritis and a neuropathic pain phenotype. Tissue enrichment analyses highlighted cardiac and thyroid tissue, and gene set enrichment analyses emphasized potential shared mechanisms in cognitive, personality, and metabolic traits and nociplastic pain along with distinct pathology in migraine and headache. We used a well-powered network approach to investigate nociplastic pain using existing COPC GWAS output, and show nociplastic pain to be a complex, heritable trait, in addition to contributing to understanding of potential mechanisms in development of nociplastic pain.

What Has Brain Diffusion Magnetic Resonance Imaging Taught us About Chronic Primary Pain: A Narrative Review.
Bautin P, Fortier MA, Sean M, Little G, Martel M, Descoteaux M, Léonard G, Tétreault P.
Pain. 2025 Feb 1;166(2):243-261. doi: 10.1097/j.pain.0000000000003345. Epub 2024 Aug 21. PMID: 39793098; PMCID: PMC11726505.

Chronic pain is a pervasive and debilitating condition with increasing implications for public health, affecting millions of individuals worldwide. Despite its high prevalence, the underlying neural mechanisms and pathophysiology remain only partly understood. Since its introduction 35 years ago, brain diffusion magnetic resonance imaging (MRI) has emerged as a powerful tool to investigate changes in white matter microstructure and connectivity associated with chronic pain. This review synthesizes findings from 58 articles that constitute the current research landscape, covering methods and key discoveries. We discuss the evidence supporting the role of altered white matter microstructure and connectivity in chronic primary pain conditions, highlighting the importance of studying multiple chronic pain syndromes to identify common neurobiological pathways. We also explore the prospective clinical utility of diffusion MRI, such as its role in identifying diagnostic, prognostic, and therapeutic biomarkers. Furthermore, we address shortcomings and challenges associated with brain diffusion MRI in chronic primary pain studies, emphasizing the need for the harmonization of data acquisition and analysis methods. We conclude by highlighting emerging approaches and prospective avenues in the field that may provide new insights into the pathophysiology of chronic pain and potential new therapeutic targets. Because of the limited current body of research and unidentified targeted therapeutic strategies, we are forced to conclude that further research is required. However, we believe that brain diffusion MRI presents a promising opportunity for enhancing our understanding of chronic pain and improving clinical outcomes.

Similarities and Differences in Resting-State Brain Activity Changes of Distinct Chronic Pain Types.
Chen X, Tang R, Jin Y, Wu L, Liang Y, Xu K, He P, Guo Y, Li J.
Oral Dis. 2025 Feb 4. doi: 10.1111/odi.15271. Epub ahead of print. PMID: 39901770.

Objectives: To explore neural similarities and differences between visceral and somatic pain by comparing spontaneous brain activity in patients with chronic temporomandibular disorder (TMD) and irritable bowel

syndrome (IBS).
Methods: Twenty eight IBS patients, 21 TMD patients, and 28 healthy controls (HC) underwent resting-state fMRI and behavioral assessments. The correlations between fMRI metrics such as the amplitude of low-frequency fluctuations (ALFF), regional homogeneity (ReHo), functional connectivity (FC), and clinical manifestations were further analyzed.
Results: Compared with HC, both patient groups demonstrated increased ALFF in right parahippocampal gyrus (PHG), insula, medial superior frontal gyrus (SFGmed), precentral gyrus (PreCG), and increased ReHo in right SFGmed and left supplementary motor area (SMA). Compared with IBS patients, TMD patients exhibited reduced ALFF in right SFGmed and insula, increased ALFF in right PHG and PreCG, decreased ReHo in right SFGmed and left lingual gyrus, and increased ReHo in left SMA. Both patient groups exhibited enhanced right PHG-related FC in left precuneus and right cingulate gyrus, and right insula-related FC in left superior temporal gyrus and right paracentral lobule. Specifically, IBS patients showed higher FC between right PHG and orbitofrontal cortex than TMD patients, which was negatively correlated with mood and gastrointestinal symptoms. Mediation analysis revealed that pain in TMD and gastrointestinal symptoms in IBS mediated these relationships.
Conclusion: Visceral and somatic pain share abnormal activity in multiple brain networks. Abnormalities in affective region present potential neuroimaging markers for pain disorders, with depression in somatic pain linked to pain intensity and in visceral pain to gastrointestinal symptoms.

Predicting Individual Pain Sensitivity Using a Novel Cortical Biomarker Signature.
Chowdhury NS, Bi C, Furman AJ, Chiang AKI, Skippen P, Si E, Millard SK, Margeaplan krison SM, Spies D, Keaser ML, Da Silva JT, Chen S, Schabrun SM, Seminowicz DA.
JAMA Neurol. 2025 Jan 27:e244857. doi: 10.1001/jamaneurol.2024.4857. Epub ahead of print. PMID: 39869323; PMCID: PMC11773403.

Importance: Biomarkers would greatly assist decision-making in the diagnosis, prevention, and treatment of chronic pain.
Objective: To undertake analytical validation of a sensorimotor cortical biomarker signature for pain consisting of 2 measures: sensorimotor peak alpha frequency (PAF) and corticomotor excitability (CME).
Design, setting, and participants: This cohort study at a single center (Neuroscience Research Australia) recruited participants from November 2020 to October 2022 through notices placed online and at universities across Australia. Participants were healthy adults aged 18 to 44 years with no history of chronic pain or a neurological or psychiatric condition. Participants experienced a model of prolonged temporomandibular pain with outcomes collected over 30 days. Electroencephalography to assess PAF and transcranial magnetic stimulation (TMS) to assess CME were recorded on days 0, 2, and 5. Pain was assessed twice daily from days 1 through 30.
Exposure: Participants received an injection of nerve growth factor (NGF) to the right masseter muscle on days 0 and 2 to induce prolonged temporomandibular pain lasting up to 4 weeks.
Main outcomes and measures: The predictive accuracy of the PAF/CME biomarker signature was determined using a nested control-test scheme: machine learning models were run on a training set (n = 100), where PAF and CME were predictors and pain sensitivity was the outcome. The winning classifier was assessed on a test set (n = 50) comparing the predicted pain labels against the true labels.
Results: Among the final sample of 150 participants, 66 were female and 84 were male; the mean (SD) age was 25.1 (6.2) years. The winning classifier was logistic regression, with an outstanding area under the curve (AUC = 1.00). The locked model assessed on the test set had excellent performance (AUC = 0.88; 95% CI, 0.78-0.99). Results were reproduced across a range of methodological parameters. Moreover, inclusion of sex and pain catastrophizing as covariates did not improve model performance, suggesting the model including biomarkers only was more robust. PAF and CME biomarkers showed good to excellent test-retest reliability.
Conclusions and relevance: This study provides evidence for a sensorimotor cortical biomarker signature for pain sensitivity. The combination of accuracy, reproducibility, and reliability suggests the PAF/CME biomarker signature has substantial potential for clinical translation, including predicting the transition from acute to chronic pain.

Differences in Plasma BDNF Levels Between Chronic Primary Musculoskeletal Pain, Fibromyalgia Syndrome, and Asymptomatic Subjects: A Cross-Sectional Study.
Silvia DB, Francisco GÁ, Álvaro RV, Kevin PB, Miguel MÁ, Josué FC, Raúl FP.
Biol Res Nurs. 2025 Jan 9:10998004251313741. doi: 10.1177/10998004251313741. Epub ahead of print. PMID: 39789935.

This cross-sectional study compared plasma brain-derived neurotrophic factor (BDNF) levels among chronic primary musculoskeletal pain patients, chronic widespread pain patients, and asymptomatic controls. The study included 126 participants aged 18-65, divided into three groups of 42 each. Pain intensity was assessed using a Numeric Rating Scale (NRS), and plasma BDNF levels were measured via ELISA. Differences between groups were evaluated using ANOVA with 2000 bootstrap resamples and a bias-corrected and accelerated method. Results showed significantly higher plasma B0DNF levels in chronic widespread pain patients (mean difference [MD] = 0.44; 95% CI = 0.28, 0.62; $p < .001$) compared to controls, and higher than in chronic primary musculoskeletal pain patients (MD = 0.83; 95% CI = 0.64, 1.02; $p < .001$). Chronic primary musculoskeletal pain patients had lower plasma BDNF levels compared to controls (MD = -0.39; 95% CI = -0.54, -0.24; $p < .001$). No significant correlations were observed between plasma BDNF levels and clinical variables. These findings suggest the potential of BDNF as a biomarker to differentiate chronic primary pain conditions.

Gut, Vaginal, and Urinary Microbiota as Potential Biomarkers of Sensitization in Women with Chronic Pelvic Pain.

Cardaillac C, Trottier C, Brochard C, Aubert P, Bordron P, Perrouin-Verbe MA, Thubert T, Chaffron S, Levesque A, Ploteau S, Marchix J, Neunlist M.

Am J Obstet Gynecol. 2025 Jan 16:S0002-9378(25)00019-5. doi: 10.1016/j.ajog.2025.01.013. Epub ahead of print. PMID: 39826623.

Background: A subgroup of patients with chronic pelvic pain (CPP) exhibit organ sensitization, whose origin and mechanism remains largely unknown. Changes in microbiota composition in pelvic organs have been found to be associated with various pelvic pathological conditions. Therefore, a comprehensive analysis of the gut and genito-urinary microbiota composition and interactions in women with CPP may be key to understanding their involvement in the sensitization processes.
Objective: To identify pelvic organ microbiota signatures that are associated with organ hypersensitivity in CPP patients.
Study design: This study involved women with high (S-CPP, n=14) and low (NS-CPP, n=14) pelvic sensitization scores according to the Convergences PP criteria. Pelvic organ sensitivity was assessed by rectal barostat, and noninvasive bladder, muscular and vulvar sensory tests. Quality of life, pelvic symptoms and psychological state were assessed. Using 16S rRNA gene sequencing, the gut, vaginal and urinary microbiota diversity and composition were analyzed and compared between S-CPP and NS-CPP women. Differentially abundant bacterial amplicon sequence variants (ASVs) between groups were associated with clinical characteristics and organ sensitivity. System biology approaches using Weighted Gene Correlation Network Analysis (WGCNA) were used to identify bacterial ASV modules associated with functional and clinical parameters.
Results: Pain pressure thresholds were significantly decreased in S-CPP women for the vulva and for the rectum, the bladder and the perineal muscles as compared to NS-CPP. However, pain intensity felt at rectal, muscular and bladder pain thresholds was significantly increased in S-CPP women. After stimulation, S-CPP women presented increased and prolonged pain in perineal muscles and bladder compared to NS-CPP women. Alpha and β-diversities were significantly increased in S-CPP women in vaginal and urinary but not in gut microbiota. Using, differential abundance analysis, we showed that 13 ASVs in the gut, 6 in the vagina and 2 in the bladder were differentially expressed between S-CPP and NS-CPP patients. More specifically, in vaginal microbiota, a significant increase of Streptococcus and Prevotella genera was observed in S-CPP as compared to NS-CPP. A significant increase in Clostridium sensu stricto 1 ASV was observed in urinary microbiota of S-CPP as compared to NS-CPP patients. Next, we found that 4 gut microbiota ASVs (belonging to Akkermansia, Desulfovibrio, Faecalibacterium and CAG-352) were correlated with pain intensity at maximal rectal distension threshold. We also identified an ASV (Blautia) which is increased in NS-CPP as being inversely correlated to several gut sensitization markers. In the vaginal microbiota, the Lactobacillus jensenii ASV was associated with less dysmenorrhea and an increased bladder capacity. Furthermore, we identified two vaginal ASVs belonging to Prevotella which are increased in S-CPP as being associated with dysmenorrhea. Finally, using WGCNA analysis methods, we identified vaginal and urinary tract ASVs modules driven by Peptostreptococcales-Tissierellales Peptoniphilus which were strongly correlated with rectal, muscular and bladder poststimulation pain. We also identified a gut ASVs module driven by Christensenellaceae_R-7 that significantly associated with anxiety, gastro-intestinal symptoms and rectal sensitivity.
Conclusions: This work identified specific bacterial signatures of specific pelvic organs and their association with organ sensitization, which are potential therapeutic targets in CPP women.

Evidence of a Persistent Altered Neural State in People with Fibromyalgia Syndrome during Functional MRI Studies and its Relationship with Pain and Anxiety.

Stroman PW, Staud R, Pukall CF.

PLoS One. 2025 Jan 24;20(1):e0316672. doi: 10.1371/journal.pone.0316672. PMID: 39854440; PMCID: PMC11759356.

Altered neural signaling in fibromyalgia syndrome (FM) was investigated with functional magnetic resonance imaging (fMRI). We employed a novel fMRI network analysis method, Structural and Physiological Modeling (SAPM), which provides more detailed information than previous methods. The study involved brain fMRI data from participants with FM (N = 22) and a control group (HC, N = 18), acquired during a noxious stimulation paradigm. The analyses were supported by fMRI data from the brainstem and spinal cord in FM and HC, brain fMRI data from participants with provoked vestibulodynia (PVD), and eye-tracking data from an fMRI study of FM. The results demonstrate differences in connectivity, and in blood oxygenation-level dependent (BOLD) responses, between FM and HC. In the FM group, BOLD signals underwent a large increase during the first 40 seconds of each fMRI run, prior to the application of any stimuli, compared to much smaller increases in HC. This indicates a heightened state of neural activity in FM that is sustained during fMRI runs, and dissipates between runs. The exaggerated initial rise was not observed in PVD. Autonomic functioning differed between groups. Pupil sizes were larger in FM than in HC, and the groups exhibited pupil dilation to the same levels during noxious stimulation. The initial BOLD increase varied in relation to state and trait anxiety scores. The results indicate that people with FM enter a heightened state of neural activity associated with anxiety and autonomic functioning, during every fMRI run, concurrent with increased pupil sizes, and heightened pain sensitivity. These findings may relate to the well-known hypervigilance and global hypersensitivity of FM participants.

Adrenergic Dysfunction in Patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Fibromyalgia: A Systematic Review and Meta-Analysis.

Hendrix J, Fanning L, Wyns A, Ahmed I, Patil MS, Richter E, Van Campenhout J, Ickmans K, Mertens R, Nijs J, Godderis L, Polli A.
Eur J Clin Invest. 2025 Jan;55(1):e14318. doi: 10.1111/eci.14318. Epub 2024 Sep 25. PMID: 39319943.

Background: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and fibromyalgia (FM) are comorbid disorders with overlapping symptoms. Research highlights autonomic dysfunction compared to healthy individuals, particularly involving the sympathetic branch. While past reviews focused on neurophysiological assessments, this systematic review summarises biological adrenergic markers, offering deeper insights into the observed sympathetic dysfunction in ME/CFS and FM aiming to identify targetable pathophysiological mechanisms.
Methods: A systematic search was performed on PubMed, Web of Science, Embase and Scopus. Studies investigating peripheral biological markers of adrenergic function in patients with ME/CFS or FM compared to healthy controls at baseline were included. Meta-analyses were performed using R statistical software.
Results: This meta-analysis of 37 studies, encompassing 543 ME/CFS patients and 651 FM patients, compared with 747 and 447 healthy controls, respectively, revealed elevated adrenaline (SMD = .49 [.31-.67]; Z = 5.29, p < .01) and β1 adrenergic receptor expression (SMD = .79 [.06-1.52]; Z = 2.13; p = .03) in blood of ME/CFS patients at rest. Additionally, patients with ME/CFS had a greater increase in the expression of α2A adrenergic receptor (AR, SMD = .57 [.18-.97]; Z = 2.85, p < .01), β2 AR (SMD = .41 [.02-.81]; Z = 2.04; p = .04) and COMT (SMD = .42 [.03-.81]; Z = 2.11; p = .03) after exercise and an increased response of noradrenaline to an orthostatic test (SMD = .11 [-.47 to -.70]; Z = 2.10; p = .04), both found in blood. FM patients showed no significant differences at baseline but exhibited a diminished adrenaline response to exercise (SMD = -.79 [-1.27 to -.30]; Z = -3.14; p < .01).
Conclusion: This systematic review and meta-analysis revealed adrenergic dysfunction mainly in patients with ME/CFS. Higher baseline adrenaline levels and atypical responses to exercise in ME/CFS indicate that sympathetic dysfunction, underscored by adrenergic abnormalities, is more involved in the pathophysiology of ME/CFS rather than FM.

Do Cytokines Play a Role in the Transition from Acute to Chronic Musculoskeletal Pain?
Ebersberger A, Schaible HG.
Pharmacol Res. 2025 Feb;212:107585. doi: 10.1016/j.phrs.2025.107585. Epub 2025 Jan 6. PMID: 39778638.

Musculoskeletal pain has a high prevalence of transition to chronic pain and/or persistence as chronic pain for years or even a lifetime. Possible mechanisms for the development of such pain states are often reflected in inflammatory or neuropathic processes involving, among others, cytokines and other molecules. Since biologics such as blockers of TNF or IL-6 can attenuate inflammation and pain in a subset of patients with rheumatoid arthritis, the question arises to what extent cytokines are involved in the generation of pain in human musculoskeletal diseases. In numerous experimental non-human studies, cytokines have been shown to alter neuronal sensitivity in the peripheral and central nociceptive systems. In this review, we addressed the involvement of cytokines in postoperative pain, complex regional pain syndrome, rheumatoid arthritis, osteoarthritis, temporomandibular joint disease, low back pain and fibromyalgia using PubMed searches including meta-analyses of data. There is evidence that certain pro- and anti-inflammatory cytokines are regulated in all of these diseases, often in both acute and chronic disease states. However, within these data, we found a great deal of heterogeneity in the association between cytokine levels and pain. Neutralization of cytokines showed antinociceptive effects in subgroups of patients with chronic pain (e.g., in a proportion of patients with rheumatoid arthritis), but failed to reduce chronic pain in other diseases (e.g., osteoarthritis). More systematic studies are needed to unravel the pathogenic role of cytokines in human musculoskeletal pain, taking into account the disease process and the mechanisms of pain initiation and maintenance.

Sensory Alterations and Immunological Changes During the Chronification of Postsurgical Pain: A Study Protocol for a Prospective Observational Cohort Study.
van Driel MEC, van Veenendaal N, Vernooij LM, Eijkelkamp N, Koenderman L, Timmerman L, Custers RJH, Delawi D, Huygen FJPM, Rijsdijk M.
BMJ Open. 2025 Jan 7;15(1):e094249. doi: 10.1136/bmjopen-2024-094249. PMID: 39773809; PMCID: PMC11749363.

Introduction: Chronic postsurgical pain (CPSP) represents a widely underdiagnosed and often poorly treated medical problem, affecting 10-50% of all surgical patients, exhibiting neuropathic features in 35-60%. It is hypothesised that surgery-induced tissue damage and the subsequent immune response cause sensory alterations in the early postoperative period, ultimately leading to a chronic neuropathic or nociplastic pain state. The 'Sensory Changes and Immunological parameters in Postsurgical pain' study (SCIP-Pain study) was designed to test this hypothesis and identify sensory alterations and changes in the immunological response that are related to the development of CPSP with neuropathic features.
Methods and analysis: This protocol describes the SCIP-Pain study-an ongoing prospective observational cohort study involving 150 adult patients undergoing elective lower extremity orthopaedic surgery. Study participants complete questionnaires, undergo quantitative sensory testing (QST) and provide blood samples to assess the immunological response at various time points: before surgery, 2 weeks and 3 months after surgery. To reduce dimensionality, cluster analyses will be conducted on QST and immunological parameters. Cluster allocation, along with other preselected candidate predictors, will subsequently be used in a generalised mixed-effects model to predict CPSP with neuropathic features within 3 months after surgery as the primary outcome.

Recognizing Pain Phenotypes: Biopsychosocial Sources of Variability in the Transition to Chronic Postsurgical Pain.
Schreiber KL, Wilson JM, Chen YK.
Reg Anesth Pain Med. 2025 Feb 5;50(2):86-92. doi: 10.1136/rapm-2024-105602. PMID: 39909545; PMCID: PMC11804873.

Chronic postsurgical pain (CPSP) is a cause of new chronic pain, with a wide range of reported incidence. Previous longitudinal studies suggest that development of CPSP may depend more on the constellation of risk factors around a patient (pre-existing pain phenotype) rather than on the extent of surgical injury itself. The biopsychosocial model of pain outlines a broad array of factors that modulate the severity, longevity, and impact of pain. Biological variables associated with CPSP include age, sex, baseline pain sensitivity, and opioid tolerance. Psychological factors, including anxiety, depression, somatization, sleep disturbance, catastrophizing, and resilience, and social factors, like education and social support, may also importantly modulate CPSP. Prevention efforts have targeted acute pain reduction using multimodal analgesia (regional anesthesia and intraoperative analgesic adjuvant medications). However, studies that do not measure or take phenotypic risk factors into account (either using them for enrichment or statistically as effect modifiers) likely suffer from underpowering, and thus, fail to discern subgroups of patients that preventive measures may be most helpful to. Early preoperative identification of a patient's pain phenotype allows estimation of their constellation of risk factors and may greatly enhance successful, personalized prevention of postoperative pain. Effective preoperative employment of behavioral interventions like cognitive-behavioral therapy, stress reduction, and physical and mental prehabilitation may particularly require knowledge of a patient's pain phenotype. Preoperative assessment of patients' pain phenotypes will not only inform high-quality personalized perioperative care clinically, but it will enable enriched testing of novel therapies in future scientific studies.

A Comparison of Genome-wide Association Analyses of Persistent Symptoms after Lyme Disease, Fibromyalgia, and Myalgic Encephalomyelitis - Chronic Fatigue Syndrome.
Hirsch AG, Justice AE, Poissant A, Nordberg CM, Josyula NS, Aucott J, Rebman AW, Schwartz BS.
BMC Infect Dis. 2025 Feb 24;25(1):265. doi: 10.1186/s12879-024-10238-x. PMID: 39994562; PMCID: PMC11853495.

Background: Up to 20% of Lyme disease cases experience post-treatment Lyme disease syndrome (PTLDS). The biological basis for PTLDS is poorly understood and no evidence-based treatment has been identified. Genetic studies have the potential to elucidate PTLDS pathophysiology and identify treatment targets.
Methods: We used electronic health record data (EHR) and genetic data from a linked biorepository to conduct a genome-wide association study (GWAS) for PTLDS among patients from a Pennsylvania health system. We evaluated the validity of the GWAS results in two separate conditions that have hypothesized overlapping pathophysiology, fibromyalgia and myalgic encephalomyelitis - chronic fatigue syndrome (ME/CFS). GWAS analyses were performed using logistic regression in SUGEN, assuming an additive genetic model, and adjusting for age, sex, array, and the first 10 principal components calculated from whole genome genotyping to adjust for ancestry, and accounting for relatedness including all 1st degree relationships. The functional mapping and annotation analysis (FUMA) tool was used to explore top findings from our GWAS.
Results: Among the 161,875 eligible MyCode participants with genotyping, there were 3,585 who met the criteria for treated Lyme disease. A subset of 695 (19.4%) of these patients met the criteria for PTLDS and the remaining 2890 were classified as controls. We identified two PTLDS loci that reached the suggestive significance threshold (P < 5 × 10- 7), with lead variants rs77857587, near IRX1, and rs10833979, near GAS2. Our top index single nucleotide polymorphism (SNP), rs77857587, is in high linkage disequilibrium with a long-range protein quantitative locus SNP, rs111774530, for the MARC2 (Mitochondrial Amidoxime Reducing Component 2) protein. We identified 5,041 cases of fibromyalgia (150,599 controls) and 2,268 cases of ME/CFS (151,594 controls) among the MyCode participants. Neither of the two suggestively significant loci were associated with fibromyalgia or ME/CFS.
Conclusion: We identified two PTLDS loci that reached a suggestive significance threshold. Our top index SNP is associated with the MARC2 protein, a protein that has been linked to multiple immune checkpoints. Further study is needed in a larger population to evaluate whether there is genetic evidence of the role of immune response in the occurrence of PTLDS.

The Association of Lumbar Intervertebral Disc Degeneration with Low Back Pain is Modified by Underlying Genetic Propensity to Pain.
Suri P, Naeini MK, Heagerty PJ, Freidin MB, Smith IG, Elgaeva EE, Compte R, Tsepilov YA, Williams FMK.
Spine J. 2025 Jan;25(1):8-17. doi: 10.1016/j.spinee.2024.05.018. Epub 2024 Jun 26. PMID: 38942297; PMCID: PMC11637947.

Background context: Associations between magnetic resonance imaging (MRI)-detected lumbar intervertebral disc degeneration (LDD) and LBP are often of modest magnitude. This association may be larger in specific patient subgroups.
Purpose: To examine whether the association between LDD and LBP is modified by underlying genetic predispositions to pain.
Study design: Cross-sectional study in UK Biobank (UKB) and Twins UK.
Patient samples: A genome-wide association study (GWAS) of the number of anatomical chronic pain locations was conducted in 347,538 UKB participants. The GWAS was used to develop a genome-wide

polygenic risk score (PRS) in a holdout sample of 30,000 UKB participants. The PRS model was then used in analyses of 645 TwinsUK participants with standardized LDD MRI assessments.
Outcome measures: Ever having had LBP associated with disability lasting ≥1 month (LBP1).
Methods: Using the PRS as a proxy for "genetically-predicted propensity to pain", we stratified TwinsUK participants into PRS quartiles. A "basic" model examined the association between an LDD summary score (LSUM) and LBP1, adjusting for covariates. A "fully-adjusted" model also adjusted for PRS quartile and LSUM x PRS quartile interaction terms.
Results: In the basic model, the odds ratio (OR) of LBP1 was 1.8 per standard deviation of LSUM (95% confidence interval [CI] 1.4-2.3). In the fully-adjusted model, there was a statistically significant LSUM-LBP1 association in quartile 4, the highest PRS quartile (OR=2.5 [95% CI 1.7-3.7], p=2.6×10-6), and in quartile 3 (OR=2.0, [95% CI 1.3-3.0]; p=.002), with small-magnitude and/or nonsignificant associations in the lowest 2 PRS quartiles. PRS quartile was a significant effect modifier of the LSUM-LBP1 association (interaction p≤.05).
Conclusions: Genetically-predicted propensity to pain modifies the LDD-LBP association, with the strongest association present in people with the highest genetic propensity to pain. Lumbar MRI findings may have stronger connections to LBP in specific subgroups of people.

Insights into Chronic Low Back Pain Etiology: Population-based Genome-wide Association Study Identifies 18 Risk Loci.
Martinsen AE, Børte S, Spildrejorde M, Brumpton BM, Heuch I, Zwart JA, Winsvold BS.
Spine (Phila Pa 1976). 2025 Jan 3. doi: 10.1097/BRS.0000000000005254. Epub ahead of print. PMID: 39812312.

Study design: Genome-wide association study (GWAS) meta-analysis with downstream analyses.
Objective: To explore the genetic architecture of chronic low back pain (cLBP) and identify underlying biological mechanisms that contribute to its development.
Summary of background data: Chronic low back pain is prevalent and debilitating, with many cases having no identifiable biological cause. Current treatment options provide only limited relief, highlighting the need for a deeper understanding of the genetic and molecular factors involved in cLBP pathogenesis. Identifying these factors may lead to more effective, targeted therapies.
Methods: We conducted a GWAS meta-analysis involving 325,078 participants from the UK Biobank and the HUNT population studies. This was followed by downstream analyses, including gene prioritization, tissue enrichment analysis, and functional gene set analysis. Genetic loci were examined for their association with cLBP, and gene sets were assessed for functional relevance.
Results: Eighteen genetic loci associated with cLBP were identified corresponding to as many prioritized genes, including eight novel genes not previously linked to the condition. Tissue enrichment analysis highlighted significant involvement of hippocampal brain tissue, suggesting central memory processes may contribute to cLBP. Functional gene set analysis identified 37 gene sets, many related to transcription factors involved in bone and cartilage maintenance. Literature on the prioritized genes suggested a potential role for neurological, cartilaginous, and inflammatory mechanisms, including genes implicated in the innervation of intervertebral discs, inflammatory cell death, and central sensitization. Comparison with previous GWASs indicated potential differences between individuals who seek medical care and those who do not.
Conclusion: This study enhances our understanding of the genetic basis of cLBP, revealing distinct biological mechanisms and suggesting the existence of patient subgroups with differing treatment needs. These insights may pave the way for more tailored and effective treatment approaches in the future.

Comparing Autonomic Nervous System Function in Patients with Functional Somatic Syndromes, Stress-related Syndromes and Healthy Controls.
Van Den Houte M, Ramakers I, Van Oudenhove L, Van den Bergh O, Bogaerts K.
J Psychosom Res. 2025 Feb;189:112025. doi: 10.1016/j.jpsychores.2024.112025. Epub 2024 Dec 22. PMID: 39755009.

Background: The goal of this study was to examine autonomic nervous system function by measuring heart rate (HR), heart rate variability (HRV), skin conductance levels (SCL), and peripheral skin temperature (ST) in response to and during recovery from psychosocial stressors in patients with functional somatic syndromes (FSS; fibromyalgia and/or chronic fatigue syndrome), stress-related syndromes (SRS; overstrain or burn-out), and healthy controls (HC).
Methods: Patients with FSS (n = 26), patients with SRS (n = 59), and HC (n = 30) went through a standardized psychosocial stress test consisting of a resting phase (120 s), the STROOP color word task (120 s), a mental arithmetic task (120 s) and a stress talk (120 s), each followed by a 120 s recovery period. HR, HRV, SCL, and ST were monitored continuously.
Results: Average HR and SCL were higher, and HRV was lower, in both patient groups compared to HC during rest (0.50 < Cohen's d < 0.97). A larger SC response to psychosocial stress was found in FSS compared to HC (d = 0.71). However, HR increased less during psychosocial stress and showed a smaller reduction during recovery in both patient groups compared to HC (0.68 < d < 0.98). HRV was lower in both patient groups compared to HC during recovery (0.91 < d < 0.98). There were no differences in ST levels or responses between groups.
Conclusions: Our results indicate a dominance of the sympathetic nervous system in both patient groups compared to controls, suggesting that autonomic nervous system dysfunction is a transdiagnostic feature for stress-related and functional somatic syndromes.

MRI-Derived Abdominal Adipose Tissue is Associated with Multisite and Widespread Chronic Pain.

Kifle ZD, Tian J, Aitken D, Melton PE, Cicuttini F, Jones G, Pan F.
Reg Anesth Pain Med. 2025 Jan 14:rapm-2024-105535. doi: 10.1136/rapm-2024-105535. Epub ahead of print. PMID: 39256036.

Introduction: Musculoskeletal pain typically occurs in multiple sites; however, no study has examined whether excessive visceral and subcutaneous adipose tissue are associated with musculoskeletal pain. This study therefore aimed to describe the associations between MRI-derived abdominal adipose tissue and multisite and widespread chronic musculoskeletal pain.
Methods: Data from the UK Biobank, a large prospective, population-based cohort study, were used. Abdominal MRI scans were performed at two imaging visits to quantify visceral adipose tissue and subcutaneous adipose tissue. Pain in the neck/shoulder, back, hip, knee or 'all over the body' was assessed at the corresponding visits. Mixed-effects ordinal/multinomial/logistic regression models were used for the analyses.
Results: A total of 32 409 participants were included (50.8% women, mean age 55.0±7.4 years). In multivariable analyses, there was a dose-response association of visceral adipose tissue, subcutaneous adipose tissue and their ratio with the number of chronic pain sites in both women (visceral adipose tissue: OR 2.04 per SD (95% CI 1.85 to 2.26); subcutaneous adipose tissue: OR 1.60 (95% CI 1.50 to 1.70); and their ratio: OR 1.60 (95% CI 1.37 to 1.87)) and men (visceral adipose tissue: OR 1.34 (95% CI 1.26 to 1.42); subcutaneous adipose tissue: OR 1.39 (95% CI 1.29 to 1.49); and their ratio: OR 1.13 (95% CI 1.07 to 1.20)). Higher levels of adipose tissue were also associated with greater odds of reporting chronic pain in both sexes. The effect estimates of these adipose measures were relatively larger in women than in men.
Conclusion: Abdominal adipose tissue was associated with chronic musculoskeletal pain, suggesting that excessive and ectopic fat depositions may be involved in the pathogenesis of multisite and widespread chronic musculoskeletal pain. The identified stronger effects in women than men may reflect sex differences in fat distribution and hormones.

Dyspareunia is Rarely Assessed in Rodent Models of Endometriosis and Interstitial Cystitis/Bladder Pain Syndrome.

Nunez-Badinez P, Shah R, Demetriou L, De Leo B, Meijlink J, Birch J, Schmidt N, Nagel J, Vincent K.
Reprod Fertil. 2025 Jan 21;6(1):e230083. doi: 10.1530/RAF-23-0083. PMID: 39704692; PMCID: PMC11770405.

Abstract: Dyspareunia, or pain during sex, is a common and often debilitating symptom in individuals with endometriosis and/or interstitial cystitis/bladder pain syndrome (IC/BPS). Despite its significant impact on quality of life, it is frequently overlooked in research. This review evaluates how dyspareunia has been addressed in preclinical investigations of these conditions. A systematic search was conducted using Embase from 1998 to 2021, identifying original in vivo preclinical studies using female rodents to model (i) endometriosis and (ii) IC/BPS. The search aimed to identify studies that assessed dyspareunia. Study quality and risk of bias were evaluated using a modified CAMARADES checklist. Our analysis found 1,286 studies modelling endometriosis and 674 modelling IC/BPS, but only 18 and 1, respectively, measured dyspareunia. The most common method involved vaginal distention in rats, assessed by either behavioural escape responses or visceromotor reflexes of abdominal muscles. Despite the high prevalence of dyspareunia in these conditions, it is rarely measured in preclinical studies. We identify a significant gap in the literature and offer succinct recommendations for future translational research to address this important symptom.
Lay summary: Dyspareunia describes pain occurring before, during or after sexual intercourse. This poorly understood symptom is particularly common in people suffering from two chronic pain-related conditions: endometriosis and IC/BPS, severely impacting their quality of life. Therefore, effective treatments addressing painful sex in people with these conditions are needed. To see the benefits of medical research at the patient's bedside, it is important to build from basic science research to preclinical animal studies then to human studies. Our study aims to assess the work that has been done so far at the 'preclinical' stage. Developments have been made in the methodology used to investigate this symptom in animals, and a summary of all the key findings may help build a platform to design future studies. Given the urgent need to develop new therapeutic strategies, attention given to painful sex by scientific medical researchers and physicians needs to improve.

Sex-Specific Contrasting Role of BECLIN-1 Protein in Pain Hypersensitivity and Anxiety-Like Behaviors.

Zaheer F, Levine GJ, Simal AL, Fatemi Tabatabaei SR, Martino TA, Descalzi G.
eNeuro. 2025 Feb 3;12(2):ENEURO.0244-24.2024. doi: 10.1523/ENEURO.0244-24.2024. PMID: 39809538; PMCID: PMC11794969.

Chronic pain is a debilitative disease affecting one in five adults globally and is a major risk factor for anxiety (Goldberg and McGee, 2011; Lurie, 2018). Given the current dearth of available treatments for both individuals living with chronic pain and mental illnesses, there is a critical need for research into the molecular mechanisms involved in order to discover novel treatment targets. Cellular homeostasis is crucial for normal bodily functions, and investigations of this process may provide better understanding of the mechanisms driving the development of chronic pain. Using the spared nerve injury (SNI) model of neuropathic pain, we found contrasting roles for BECLIN-1 in the development of pain hypersensitivity and anxiety-like behaviors in a sex-dependent manner. Remarkably, we found that male SNI mice with impaired BECLIN-1 function demonstrated heightened mechanical and thermal hypersensitivity compared with male wild-type SNI mice, while female SNI mice with impaired BECLIN-1 function demonstrated

similar thresholds to the female wild-type SNI mice. We also found that disruptions of BECLIN-1 prevented SNI-induced increases in anxiety-like behaviors in male mice. Our data thus indicate that BECLIN-1 is differentially involved in the nociceptive and emotional components of chronic pain in male but not female mice.

Prolactin-induced Sensitization of Trigeminal Nociceptors Promotes Migraine Co-morbidity in Endometriosis.
Lee GJ, Hode V, Georgieva T, Rau J, Dodick DW, Schwedt TJ, Neugebauer V, Porreca F, Navratilova E.
Cephalalgia. 2025 Jan;45(1):3331024241313378. doi: 10.1177/03331024241313378. PMID: 39814523.

Background: Women with endometriosis are more likely to have migraine. The mechanisms underlying this co-morbidity are unknown. Prolactin, a neurohormone secreted and released into circulation from the anterior pituitary, can sensitize sensory neurons from female, but not male, rodents, monkeys and human donors.
Methods: We used a syngeneic model of endometriosis to determine whether elevated prolactin levels can sensitize trigeminal ganglion neurons and increase vulnerability to migraine pain.
Results: Mice with endometriotic lesions showed increased serum prolactin levels and developed persistent abdominal, but not cephalic, allodynia. However, inhalation of a transient receptor potential ankyrin 1 agonist, umbellulone, a known environmental trigger of headache in some patients, elicited cephalic allodynia in mice with endometriosis but not sham controls, suggesting that endometriosis can promote sensitization of trigeminal neurons and migraine attacks. Endometriosis dysregulated the expression of prolactin receptor isoforms in trigeminal neurons and increased their excitability measured by in vitro patch clamp electrophysiology. Inhibition of pituitary prolactin following a 2-week treatment with a dopamine receptor agonist, cabergoline, prevented cephalic allodynia elicited by activation of trigeminal afferents with umbellulone. Cabergoline treatment also normalized the expression of prolactin receptor isoforms in trigeminal ganglia and the hyperexcitability of trigeminal neurons.
Conclusions: These data demonstrate that circulating prolactin in endometriosis promotes vulnerability to migraine through sensitization of trigeminal afferents. Clinically available dopamine receptor agonists or novel monoclonal antibodies targeting prolactin signaling may be effective for migraine prevention in women with endometriosis.

Characterisation of Periorbital Mechanical Allodynia in the Reserpine-induced Fibromyalgia Model in Mice: The Role of the Schwann Cell TRPA1/NOX1 Signalling Pathway.
Brum ES, Landini L, Souza Monteiro de Araújo D, Marini M, Geppetti P, Nassini R, De Logu F, Oliveira SM.
Free Radic Biol Med. 2025 Mar 1;229:289-299. doi: 10.1016/j.freeradbiomed.2025.01.040. Epub 2025 Jan 20. PMID: 39842732.

Fibromyalgia (FM) is a complex and multifaceted condition characterized by a range of clinical symptoms, including widespread pain and a strong association with migraine headaches. Recent findings have underscored the role of oxidative stress and transient receptor potential ankyrin 1 (TRPA1) channel in migraine and FM. However, the precise mechanisms underlying the comorbidity between migraine and FM are unclear. Periorbital mechanical allodynia (PMA), which recapitulates one of the major symptoms of migraine, and the feed-forward mechanism driven by reactive oxygen species and TRPA1, were investigated in a reserpine-induced FM model in C57BL/6J mice, employing pharmacological interventions and genetic approaches. Reserpine-treated mice developed PMA (which was alleviated by antimigraine drugs) and increased endoneurial macrophages and oxidative stress markers in the trigeminal nerve tissues (neuroinflammation). These responses were absent upon macrophage depletion and by pharmacological inhibition or global genetic deletion of the TRPA1 channel. Furthermore, selective silencing of TRPA1 in Schwann cells attenuated both reserpine-induced PMA and neuroinflammation, while selective silencing of TRPA1 in sensory neurons reduced PMA but not neuroinflammation. In reserpine-treated mice, Schwann cell TRPA1 promoted NADPH oxidase 1-mediated reactive oxygen species generation and macrophage density increase in the mouse trigeminal nerve, which sustains PMA. Targeting TRPA1 channels in Schwann cells could offer a novel therapeutic strategy for FM-related headaches.

CLINICAL STUDIES

Innovations in Acute and Chronic Pain Biomarkers: Enhancing Diagnosis and Personalized Therapy.
Mackey S, Aghaeepour N, Gaudilliere B, Kao MC, Kaptan M, Lannon E, Pfyffer D, Weber K.
Reg Anesth Pain Med. 2025 Feb 5;50(2):110-120. doi: 10.1136/rapm-2024-106030. PMID: 39909549.

Pain affects millions worldwide, posing significant challenges in diagnosis and treatment. Despite advances in understanding pain mechanisms, there remains a critical need for validated biomarkers to enhance diagnosis, prognostication, and personalized therapy. This review synthesizes recent advancements in identifying and validating acute and chronic pain biomarkers, including imaging, molecular, sensory, and neurophysiological approaches. We emphasize the emergence of composite, multimodal strategies that integrate psychosocial factors to improve the precision and applicability of

biomarkers in chronic pain management. Neuroimaging techniques like MRI and positron emission tomography provide insights into structural and functional abnormalities related to pain, while electrophysiological methods like electroencephalography and magnetoencephalography assess dysfunctional processing in the pain neuroaxis. Molecular biomarkers, including cytokines, proteomics, and metabolites, offer diagnostic and prognostic potential, though extensive validation is needed. Integrating these biomarkers with psychosocial factors into clinical practice can revolutionize pain management by enabling personalized treatment strategies, improving patient outcomes, and potentially reducing healthcare costs. Future directions include the development of composite biomarker signatures, advances in artificial intelligence, and biomarker signature integration into clinical decision support systems. Rigorous validation and standardization efforts are also necessary to ensure these biomarkers are clinically useful. Large-scale collaborative research will be vital to driving progress in this field and implementing these biomarkers in clinical practice. This comprehensive review highlights the potential of biomarkers to transform acute and chronic pain management, offering hope for improved diagnosis, treatment personalization, and patient outcomes.

The Number of Central Nervous System-Driven Symptoms Predicts Subsequent Chronic Primary Pain: Evidence from UK Biobank.
Kelleher E, Kaplan CM, Kheirabadi D, Schrepf A, Tracey I, Clauw DJ, Irani A. Br J Anaesth. 2025 Mar;134(3):772-782. doi: 10.1016/j.bja.2024.12.009. Epub 2025 Jan 27. PMID: 39875287.

Background: Chronic primary pain describes conditions where pain is the principal problem rather than a consequence of another disease. Primary pain is thought to be primarily owing to nociplastic pain (i.e. pain as a result of altered nociception despite the absence of tissue damage). Primary pain is often accompanied by other bothersome central nervous system (CNS)-driven symptoms, including disturbed sleep, mood, and cognition; however, it is unclear whether these symptoms precede onset of primary pain.
Methods: In a prospective cohort study of the UK Biobank, we examined adults with no self-reported recent or chronic pain at baseline. Using linked primary care record data, we investigated the association between the number of CNS-driven symptoms and subsequent incidence of primary pain conditions. Multivariable regression analyses adjusted for sociodemographic and lifestyle factors.
Results: Of 502 369 participants, 70 630 (14.0%) met the inclusion criteria, with a mean (range) age of 56.7 (40-70) yr, 51% being female. After 7.4 (range 0.5-11.02) yr, 12.2% developed a primary pain condition. We observed a positive relationship between the number of CNS-driven symptoms at baseline and risk of future primary pain (HR 1.43, 95% CI 1.34-1.52, P<0.001). Participants with more CNS-driven symptoms at baseline were also more likely to have chronic and more severe nociplastic pain, but not non-nociplastic pain at follow-up.
Conclusions: In adults with no current self-reported pain, those with a greater number of CNS-driven symptoms at baseline were more likely to develop a primary pain condition. This suggests a potential opportunity for early intervention in mitigating the burden of primary pain.

Relationship Between Treatment Hours of Selected Disciplines and Change in Pain Impact During the Year Following Referral to an Interdisciplinary Pain Management Center: A Latent Class Analysis.
Burke LA, Flynn DM, Ransom JC, Steffen AD, Shah SH, Doorenbos AZ.
J Integr Complement Med. 2025 Jan;31(1):44-53. doi: 10.1089/jicm.2024.0333. Epub 2024 Aug 22. PMID: 39169874; PMCID: PMC11844771.

Introduction: Pain management clinics differ in treatments offered, and little evidence exists regarding which combinations of therapies result in best outcomes. This study analyzed clinical encounters and pain outcomes data for associations between treatment composition and outcomes.
Methods: Retrospective observational study of 2,142 predominantly active-duty US service members referred to an interdisciplinary pain management center between 2014 and 2021. Latent class analysis was used to identify treatment groups with distinct outcome patterns during the year following initial assessment. The primary outcome measure was the National Institutes of Health Task Force on Research Standards for Chronic Low-Back Pain impact score.
Results: Four distinct treatment groups were identified: 1 group engaged in conventional medical therapies alone (n = 726, median 3.5 treatment hours), and 3 groups used a combination of conventional, psychological, rehabilitative, and complementary therapies, with different levels of treatment hours: low (n = 814, median 15.7 h), medium (n = 177, median 40.1 h), and high (n = 425, median 72.5 h). All groups showed significant improvement in pain impact score from baseline up to 9 months but not at 12 months following initial assessment. At the 6-month time point, the group with high multimodal treatment hours had the most improvement in pain impact (-3.1 [95% CI -3.8, -2.4]) compared with the group using only conventional therapies (-1.0 points [95% CI -1.8, -0.1]) or with low multimodal treatment hours (-1.3 points [95% CI -1.9, -0.7]). There were no between-group differences at the 9- or 12-month time points.
Conclusion: These results suggest that a combination of pain therapy approaches results in greater reduction in pain impact than the use of conventional medical treatment alone for up to 6 months after initiating therapy and that there may be a threshold of treatment hours that must be exceeded to achieve this benefit.

Fibromyalgia Severity and Symptoms are Associated with the Disorders of Gut-Brain Interaction.
Erdrich S, Harnett JE.
Eur J Pain. 2025 Jan;29(1):10.1002/ejp.4766. doi: 10.1002/ejp.4766. PMID: 39665371; PMCID: PMC11635909.

Introduction: Fibromyalgia remains an idiopathic common disorder characterised by widespread pain with no universally accepted treatment. Irritable bowel syndrome is prevalent among women living with fibromyalgia. The prevalence of other disorders of gut-brain interaction (DGBI) and associations with fibromyalgia symptoms and severity is unknown.
Objectives: To evaluate the prevalence of the range of DGBI and associations with the symptoms and severity of fibromyalgia in women.
Methods: A prospective observational study was conducted in New Zealand in 2022. A comprehensive survey included validated measures to identify DGBI (Rome IV) and items assessing the severity of fibromyalgia and pain symptoms, sleep quality, quality of life, mental health and migraine. Analysis was conducted employing Spearman's rho, Mann-Whitney U, Kruskal-Wallis and chi-square tests.
Results: A total of 111 adult women with fibromyalgia enrolled in the study. Of these, 98 (93%) met the criteria for at least one DGBI, and 67 (68%) satisfied criteria for more than one. All groups of DGBI, and 11 specific DGBI were significantly associated with measures of pain, fibromyalgia severity, sleep problems and migraine ($p < 0.05$). Severity of pain and symptoms associated with fibromyalgia, including sleep problems, were also significantly associated with the functional bowel disorder severity index.
Conclusion: This study demonstrated that the prevalence of DGBI in women with fibromyalgia extends beyond irritable bowel syndrome. Presence of multiple DGBI correlates with pain, severity indices of fibromyalgia and sleep problems. Further research is required to examine the aetiology of DGBI in this population.
Significance statement: This observational study has identified important relationships between the broader DGBI, fibromyalgia pain and associated symptoms, particularly migraine and sleep disturbance. Notable correlations between the severity indices of each are demonstrated, suggesting that improvements in one domain may reduce pain and improve overall well-being. These findings highlight the importance of addressing each clinical feature of the condition when supporting patients with fibromyalgia.

Rome Foundation Working Team Report on Overlap in Disorders of Gut-Brain Interaction.
Barbara G, Aziz I, Ballou S, Chang L, Ford AC, Fukudo S, Nurko S, Olano C, Saps M, Sayuk G, Siah KTH, Van Oudenhove L, Simrén M.
Nat Rev Gastroenterol Hepatol. 2025 Jan 27. doi: 10.1038/s41575-024-01033-9. Epub ahead of print. PMID: 39870943.

In patients with disorders of gut-brain interaction (DGBI), overlapping non-gastrointestinal conditions such as fibromyalgia, headaches, gynaecological and urological conditions, sleep disturbances and fatigue are common, as is overlap among DGBI in different regions of the gastrointestinal tract. These overlaps strongly influence patient management and outcome. Shared pathophysiology could explain this scenario, but details are not fully understood. This overlap has been shown to be of great relevance for DGBI. In addition, symptoms considered to be caused by a DGBI could have a detectable organic cause, and in patients with a diagnosed organic gastrointestinal disease, symptoms not clearly explained by the pathology defining this organic disease are common. Thus, the aims of this Rome Foundation Working Team Report were to review the literature on overlapping conditions among patients with paediatric and adult DGBI and, based on the available epidemiological and clinical evidence, make recommendations for the current diagnostic and therapeutic approach, and for future research. Specifically, we focused on other DGBI in the same or different gastrointestinal anatomical region(s), DGBI overlap with organic bowel diseases in remission, and DGBI overlap with non-gastrointestinal, non-structural conditions.

Nociplastic Pain Among Individuals with Chronic Ocular Surface Pain: One Cause for "Pain Without Stain"?
De Lott LB, Kaplan C, Harte S, Clauw DJ, Galor A, Vehof J, Shtein RM.
Surv Ophthalmol. 2025 Jan 13:S0039-6257(25)00015-3. doi: 10.1016/j.survophthal.2025.01.004. Epub ahead of print. PMID: 39814104.

Chronic ocular surface pain (COSP) refers to interrelated symptoms such as burning, aching, and irritation and can occur as an isolated condition or comorbid with numerous ocular disorders, including dry eye syndrome Treatments for COSP are largely aimed at the ocular surface and modulating pain arising from damaged corneal nerves; however, the average impact of these treatments on COSP are low to absent. A potential explanation for this is that, in a subset of patients with COSP, individuals have amplified and/or dysregulated neural signaling and sensory processing within the central nervous system (CNS). As in other chronic pain conditions, this might be the pathogenic mechanism primarily responsible for maintaining pain - a phenomenon now referred to as nociplastic pain. The key clinical features of nociplastic pain include symptoms out of proportion to signs, regional or widespread pain, the presence of other chronic pain conditions, and non-pain CNS mediated symptoms (e.g., sleep disorders). We provide an overview for eye care clinicians of nociplastic pain and delineate the emerging evidence for the presence of nociplastic pain among some individuals with COSP. We highlight gaps in our current understanding of nociplastic pain in COSP and provide clinicians with specific tools that may aid in the assessment and management of nociplastic pain.

Towards a Better Definition of Nociplastic Pain Conditions: A Psychological Grounded Study on Fibromyalgia, Chronic Headache and Vulvodynia.
Mesce M, Nimbi FM, Sarzi-Puttini P, Lai C, Galli F.
Eur J Psychotraumatol. 2025 Dec;16(1):2461434. doi: 10.1080/20008066.2025.2461434. Epub 2025 Feb 13. PMID: 39943899; PMCID: PMC11827037.

Background: This study investigates the psychological underpinnings of chronic pain conditions,

specifically fibromyalgia, chronic headache, vulvodynia, and mixed condition (consisting of fibromyalgia in comorbidity with chronic headache and/or vulvodynia), with a focus on nociplastic pain mechanisms.
Objective: The aim of the study is to better understand the psychological functioning of women with different chronic pain conditions to identify and discuss similarities and differences. In particular, we aim to explore any significant differences in the domain of traumatic experiences, in global defensive functioning, and in the domain of alexithymia among the evaluated groups. Further, the 4 groups with chronic pain will be compared with a healthy control group.
Methods: A sample of 1006 Italian women diagnosed with chronic pain participated in the study, categorized into four clinical groups and a healthy control group. Measures were assessed using self-report measures, in particular: Traumatic Experiences Checklist, Defense Mechanism Rating Scales, and Toronto Alexithymia Scale.
Results: There are significant differences among groups, with mixed conditions exhibiting the highest levels of traumatic experiences, particularly emotional neglect and physical threats. Fibromyalgia and mixed condition groups displayed greater reliance on neurotic defense mechanisms. Additionally, fibromyalgia and mixed condition participants exhibited higher levels of alexithymia, indicating difficulties in emotional processing.
Conclusions: These findings underscore the complex interplay between psychological factors and nociplastic pain conditions, emphasizing the importance of personalized psychological interventions in managing nociplastic pain. The study highlights the need for multidisciplinary approaches to nociplastic pain treatment, considering the diverse psychological profiles of affected individuals.

11th Revision of the International Classification of Diseases Chronic Primary Pain Diagnoses in Children and Adolescents: Representation of Pediatric Patients in the New Classification System.
Rau LM, Korwisi B, Barke A, Frosch M, Zernikow B, Wager J.
Pain. 2025 Feb 1;166(2):328-337. doi: 10.1097/j.pain.0000000000003386. Epub 2024 Sep 6. PMID: 39258738.

Chronic pain is common among children and adolescents; however, the diagnoses in the newly developed 11th revision of the International Classification of Diseases (ICD-11) chronic pain chapter are based on adult criteria, overlooking pediatric neurodevelopmental differences. The chronic pain diagnoses have demonstrated good clinical applicability in adults, but to date, no field study has examined these diagnoses to the most specific diagnostic level in a pediatric sample. The current study aimed to explore pediatric representation within the ICD-11, with focus on chronic primary pain. Healthcare professionals (HCPs) at a specialized pediatric pain center documented the symptoms of and assigned both ICD-10 and ICD-11 diagnoses to N = 402 patients. Using criteria-based computer algorithms, specific ICD-11 pain diagnoses were allocated for each documented pain location, with residual diagnoses (ie, "unspecified") assigned if criteria were not (fully) met. Within the ICD-11, the algorithms assigned specific pain diagnoses to most patients (73.6%). In ICD-10, HCPs could not specify a diagnosis for 5.2% of patients; the ICD-11 algorithm allocated a residual chronic primary pain diagnosis in 51.2%. Residual categories were especially prevalent among younger children, boys, patients with headaches, and those with lower pain severity. Overall, clinical utility of the ICD-11 was high, although less effective for chronic back pain and headache diagnoses. The latter also exhibited the lowest agreement between HCPs and algorithm. The current study underscores the need for evidence-based improvements to the ICD-11 diagnostic criteria in pediatrics. Developing pediatric coding notes could improve the visibility of patients internationally and improve the likelihood of receiving reimbursement for necessary treatments through accurate coding.

Where Do We Start? Health Care Transition in Adolescents and Young Adults with Chronic Primary Pain.
Feinstein AB, Brown K, Dunn AL, Neville AJ, Sokol O, Poupore-King H, Sturgeon JA, Kwon AH, Griffin AT.
Pain. 2025 Feb 1;166(2):236-242. doi: 10.1097/j.pain.0000000000003324. Epub 2024 Jul 9. PMID: 38981053.

No abstract available.

Understanding What it is Like to Experience Pain as You Grow Up: A Poetic Meta-Ethnography.
Toye F, Hannink E, Woolverton A, Barker KL.
Pain. 2025 Jan 1;166(1):24-33. doi: 10.1097/j.pain.0000000000003420. Epub 2024 Oct 18. PMID: 39432809; PMCID: PMC11647824.

A recent Lancet Commission raised concerns about the management of child and adolescent pain. We aimed to undertake a comprehensive review of qualitative research to understand children and adolescent pain experiences across contexts. We used the 7 stages of meta-ethnography to synthesise findings. We combined the strengths of arts-based methods, translating themes into poems in a range of languages. We screened 7471 titles, 464 abstracts, and 302 full texts, including 189 reports (177 unique samples) incorporating 5875 young people. Age range across studies was 2 to 38 years, with 93% including those between the age of 11 and 20 years old. Studies spanned 30 years (1993-2023) with 121 (64%) published in the last 10 years. Almost all (93%) were set-in high-income countries. We report 6 themes focusing on transition to adulthood: (1) I want to stay within the safety of home; (2) don't exclude me from my own care; (3) it might hurt but it's for my own good; (4) I rely on others but I want some independence; (5) I am no longer a child but I am not an adult yet; and (6) I wasn't prepared for the transfer to adult health care. Our findings focus on the complex transition into adulthood and the importance of creating a genuine healthcare partnership with young people by acknowledging their perspectives, creating a safe and supportive environment, and preparing them for the transition to adult pain care. Arts-based methods have

the potential to make findings from qualitative evidence syntheses accessible and impactful for compassionate health care.

Temporomandibular Joint Arthritis in Rheumatic Diseases Patients: Which are the Effective Rehabilitative Approaches for Pain Relief? A Systematic Review.

Aiello V, Ferrillo M, Marotta N, Agostini F, Curci C, Calafiore D, Fortunato L, Ammendolia A, Longo UG, de Sire A.

BMC Musculoskelet Disord. 2025 Feb 18;26(1):159. doi: 10.1186/s12891-024-08196-1. PMID: 39966784; PMCID: PMC11834569.

Background: Temporomandibular disorders (TMD) are a set of musculoskeletal conditions involving the temporomandibular joint, masticatory muscles, and/or associated structures, characterized by symptoms as pain, joint stiffness with limited mouth opening, and joint sounds as crepitus. Rheumatic diseases (RD) are a heterogeneous group of conditions affecting the musculoskeletal system, including temporomandibular joint (TMJ). To date, there is a lack of systematic reviews that properly investigated the efficacy of conservative approaches in reducing pain in rheumatic patients affected by TMJ arthritis. Therefore, this systematic review aimed to evaluate the effectiveness of rehabilitative approaches in pain relief in rheumatic patients with TMJ arthritis.
Methods: PubMed, Scopus, and Web of Science were searched from inception until February 25th, 2024, to identify studies including patients with diagnosis of rheumatic disease affecting the temporomandibular joint who underwent specific rehabilitative approaches to reduce pain intensity. The risk of bias of studies was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist.
Results: Out of 479 search results, 115 duplicates were removed, and 364 studies were considered as eligible for inclusion and screened for title and abstract. Out of these, we included 19 papers for full-text screening. Then, 5 papers were included in the synthesis by this systematic review. Four studies assessed patients affected by rheumatoid arthritis, one systemic sclerodermia, and one included patients affected by ankylosing spondylitis, psoriatic arthritis, Sjogren's syndrome, fibromyalgia, common variable immunodeficiency, and chronic polyarthritis. In the included studies, the interventions consisted of intraarticular TMJ injection of corticosteroids performed with or without anesthetics, or irrigation in three studies, dextrose subcutaneous TMJ perineural injection, and lower-level laser therapy (LLLT).
Conclusions: This systematic review showed that rehabilitative approaches (e.g., intra-articular injections and LLLT) might be effective in terms of pain relief in TMD RD-related. However, the heterogeneity of the rehabilitative approaches performed, and the low quality of the included studies do not allow to draw certain conclusions regarding the efficacy of these approaches. Further high-quality studies are mandatory to improve the robustness of the efficacy of the different rehabilitative techniques for pain relief in TMD patients affected by rheumatic diseases.

Persistent Pain after Total Temporomandibular Joint Replacement Surgery: Clinical Characteristics, Comorbidities, and Risk Factors.

Handa S, Youness M, Keith DA, Rosén A.

Int J Oral Maxillofac Surg. 2025 Feb;54(2):166-173. doi: 10.1016/j.ijom.2024.08.038. Epub 2024 Sep 5. PMID: 39237445.

Chronic post-surgical pain (CPSP) after temporomandibular joint (TMJ) surgery is an under-recognized problem. The aim of this study was to document the characteristics of CPSP and identify patient risk factors and comorbidities associated with the development of CPSP after total TMJ replacement (TJR). This was a retrospective cohort study of patients who underwent TJR between 2000 and 2018 at Massachusetts General Hospital, Boston, USA. The primary outcome was the presence of CPSP and use of pain medications after TJR. The secondary outcome was the risk factors associated with the development of CPSP. A total 88 patients were included (79 females, 9 males). The mean follow-up was 4.2 years. Overall, 68 (77.3%) had CPSP and 20 (22.7%) had no CPSP. Of those with CPSP, 32.4% had severe pain and 45.6% continued to take pain medications. Of the 27 patients with data available on the characteristics of the pain, the majority had myofascial pain, while some developed neuropathic pain. A significant difference was noted between the CPSP and non-CPSP groups in terms of preoperative pain, smoking behavior, and use of opioids, non-steroidal anti-inflammatory drugs, muscle relaxants, and neuropathic pain medications.

Identifying Patient Subgroups in the Heterogeneous Chronic Pain Population Using Cluster Analysis.

Rijsdijk M, Smits HM, Azizoglu HR, Brugman S, van de Burgt Y, van Charldorp TC, van Gelder DJ, de Grauw JC, van Lange EA, Meye FJ, Strick M, Walravens HWA, Winkens LHH, Huygen FJPM, Drylewicz J, Willemen HLDM.

J Pain. 2025 Jan 23;28:104792. doi: 10.1016/j.jpain.2025.104792. Epub ahead of print. PMID: 39855407.

Chronic pain is an ill-defined disease with complex biopsychosocial aspects, posing treatment challenges. We hypothesized that treatment failure results, at least partly, from limited understanding of diverse patient subgroups. We aimed to identify subgroups using psychological variables, allowing for more tailored interventions. In a retrospective cohort study, we extracted patient-reported data from two Dutch tertiary multidisciplinary outpatient pain clinics (2018-2023) for unsupervised hierarchical clustering. Clusters were defined by anxiety, depression, pain catastrophizing, and kinesiophobia. Sociodemographics, pain characteristics, diagnosis, lifestyle, health-related quality of life and treatment efficacy were compared among clusters. A prediction model was built utilizing a minimum set of questions to reliably assess cluster allocation. Among 5,466 patients with chronic pain, three clusters emerged. Cluster 1 (n=750) was

characterized by high psychological burden, low health-related quality of life, lower educational levels and employment rates, and more smoking. Cluster 2 (n=1,795) showed low psychological burden, intermediate health-related quality of life, higher educational levels and employment rates, and more alcohol consumption. Cluster 3 (n=2,909) showed intermediate features. Pain reduction following treatment was least in cluster 1 (28.6% after capsaicin patch, 18.2% after multidisciplinary treatment), compared to >50% for both treatments in clusters 2 and 3. A model incorporating 15 psychometric questions reliably predicted cluster allocation. In conclusion, our study identified distinct chronic pain patient clusters through 15 psychological questions, revealing one cluster with notably poorer response to conventional treatment. Our prediction model, integrated in a web-based tool, may help clinicians improve treatment by allowing patient-subgroup targeted therapy according to cluster allocation. PERSPECTIVE: Hierarchical clustering of chronic pain patients identified three subgroups with similar pain intensity and diagnoses but distinct psychosocial traits. One group with higher psychological burden showed poorer treatment outcomes. A web-based tool using this model could help clinicians tailor therapies by matching interventions to specific patient subgroups for improved outcomes.

Characterizing Phenotypes and Clinical and Health Utilization Associations of Young People with Chronic Pain: Latent Class Analysis Using the Electronic Persistent Pain Outcomes Collaboration Database.

Slater H, Waller R, Briggs AM, Lord SM, Smith AJ.

Pain. 2025 Jan 1;166(1):67-86. doi: 10.1097/j.pain.0000000000003326. Epub 2024 Jul 9. PMID: 39688968; PMCID: PMC11647817.

Using the Australiasian electronic Persistent Pain Outcomes Collaboration, a binational pain registry collecting standardized clinical data from paediatric ePPOC (PaedsePPOC) and adult pain services (AdultePPOC), we explored and characterized nationally representative chronic pain phenotypes and associations with clinical and sociodemographic factors, health care utilization, and medicine use of young people. Young people ≥15.0 and <25.0 years captured in PaedePPOC and AdultePPOC Australian data registry were included. Data from 68 adult and 12 paediatric pain services for a 5-year period January 2018 to December 2022 (first episode, including treatment information) were analysed. Unsupervised latent class analysis was applied to explore the existence of distinct pain phenotypes, with separate models for both services. A 3-phenotype model was selected from both paediatric and adult ePPOC data, with 693 and 3518 young people included, respectively (at least one valid indicator variable). Indicator variables for paediatric models were as follows: pain severity, functional disability (quasisurrogate "pain interference"), pain count, pain duration, pain-related worry (quasisurrogate "catastrophizing"), and emotional functioning; and, for adult models: pain severity, pain interference, pain catastrophizing, emotional functioning, and pain self-efficacy. From both services, 3 similar phenotypes emerged ("low," "moderate," "high"), characterized by an increasing symptom-severity gradient in multidimensional pain-related variables, showing meaningful differences across clinical and sociodemographic factors, health service utilization, and medicines use. Derived phenotypes point to the need for novel care models that differentially respond to the needs of distinct groups of young people, providing timely, targeted, age-appropriate care. To effectively scale such care, digital technologies can be leveraged to augment phenotype-informed clinical care.

Refining Chronic Pain Phenotypes: A Comparative Analysis of Sociodemographic and Disease-Related Determinants Using Electronic Health Records.

Begum T, Veeranki B, Chike OJ, Tamang S, Simard JF, Chen J, Chaichian Y, Mackey S, Darnall BD, Falasinnu T.

J Pain. 2025 Jan 3;28:104775. doi: 10.1016/j.jpain.2025.104775. Epub ahead of print. PMID: 39756769.

The use of electronic health records (EHR) for chronic pain phenotyping has gained significant attention in recent years, with various algorithms being developed to enhance accuracy. Structured data fields (e.g., pain intensity, treatment modalities, diagnosis codes, and interventions) offer standardized templates for capturing specific chronic pain phenotypes. This study aims to determine which chronic pain case definitions derived from structured data elements achieve the best accuracy, and how these validation metrics vary by sociodemographic and disease-related factors. We used EHR data from 802 randomly selected adults with autoimmune rheumatic diseases seen at a large academic center in 2019. We extracted structured data elements to derive multiple phenotyping algorithms. We confirmed chronic pain case definitions via manual chart review of clinical notes, and assessed the performance of derived algorithms, e.g., sensitivity/recall, specificity, positive predictive value (PPV). The highest sensitivity (67%) was observed when using ICD codes alone, while specificity peaked at 96% with a quadrimodal algorithm combining pain scores, ICD codes, prescriptions, and interventions. Specificity was generally higher in males and younger patients, particularly those aged 18-40 years, and highest among Asian/Pacific Islander and privately insured patients. PPV was highest among patients who were female, younger, or privately insured. PPV and sensitivity were lowest among males, Asian/Pacific Islander, and older patients. Variability of phenotyping results underscores the importance of refining chronic pain phenotyping algorithms within EHRs to enhance their accuracy and applicability. While our current algorithms provide valuable insights, enhancement is needed to ensure more reliable chronic pain identification across diverse patient populations. PERSPECTIVES: This study evaluates chronic pain phenotyping algorithms using electronic health records, highlighting variability in performance across sociodemographic and disease-related factors. By combining structured data elements, the findings advance chronic pain identification, promoting equitable healthcare practices and highlighting the need for tailored algorithms to address subgroup-specific biases and improve outcomes.

A Machine Learning Approach to Stratify Patients with Hypermobile Ehlers-Danlos Syndrome/Hypermobility Spectrum Disorders According to Disorders of Gut Brain Interaction, Comorbidities and Quality of life.

Choudhary A, Fikree A, Ruffle JK, Takahashi K, Palsson OS, Aziz I, Aziz Q. A Neurogastroenterol Motil. 2025 Jan;37(1):e14957. doi: 10.1111/nmo.14957. Epub 2024 Nov 14. PMID: 39543811; PMCID: PMC11650402.

Background: A high prevalence of disorders of gut-brain interaction (DGBI) exist in patients with hypermobile Ehlers-Danlos Syndrome (hEDS) and hypermobility spectrum disorders (HSD). However, it is unknown if clusters of hEDS/HSD patients exist which overlap with different DGBIs and whether this overlap influences presence of comorbidities and quality of life. We aimed to study these knowledge gaps.
Methods: A prospectively collected hEDS/HSD cohort of 1044 individuals were studied. We undertook Uniform Manifold Approximation and Projection-enabled (UMAP) dimension reduction to create a representation of nonlinear interactions between hEDS/HSD and DGBIs, from which individuals were stratified into clusters. Somatization, Postural Tachycardia Syndrome (PoTS), autonomic symptoms, psychological factors and quality of life were statistically compared between clusters.
Key results: The mean age of patients was 40 ± 13.2 years; 87.8% were female. Patients segregated into three clusters: Cluster 0 (n = 466): hEDS/HSD+ functional foregut disorders (FFD) + irritable bowel syndrome (IBS); Cluster 1 (n = 180): hEDS/HSD+ IBS and Cluster 2 (n = 337): hEDS/HSD alone. In cluster 0, we demonstrated increased somatization (p <0.0001), anxiety (p <0.0001), depression (p <0.0001), PoTS prevalence (p = 0.003), autonomic symptoms (p <0.0001) and reduced quality of life (p <0.0001) compared to cluster 2. Cluster 0 had greater comorbidity burden than cluster 1.
Conclusions: Within hEDS/HSD, subgroups exist with a high prevalence of FFD and IBS. These subgroups have a higher prevalence of psychological disorders, dysautonomia and poorer quality of life compared with hEDS/HSD alone. Further research should focus on healthcare utilization, management and prognosis in hEDS/HSD and DGBI overlap.

Importance of Pain Drawing Profiles and Their Association with Pain Intensity/Interference and Clinical TMD Diagnoses Among Tertiary Care TMD Pain Patients.

Iljin A, Näpänkangas R, Sipilä K, Tolvanen M, Teerijoki-Oksa T, Vuollo V, Suvinen T. J Oral Rehabil. 2025 Feb 24. doi: 10.1111/joor.13952. Epub ahead of print. PMID: 39994953.

Background: Body pain widespreadness may be related to biopsychosocial impact in TMD (temporomandibular disorders) pain patients.
Objectives: The aim was to assess, by using pain drawings (PDs), the whole-body pain locations/widespreadness and their association with pain-related intensity/interference and clinical Axis I diagnoses among Finnish tertiary care TMD pain patients using the DC/TMD-FIN (Diagnostic Criteria for TMD-FIN).
Methods: Based on PDs, 197 TMD pain patients were divided into PD profile subgroups: PD-1 (local head/face pain), PD-2 (regional head and neck/shoulder pain) and PD-3 (widespread pain). Using the Graded Chronic Pain Scale 2.0 (GCPS 2.0) assessing pain-related intensity/interference, the patients were classified into TMD subtypes (1 = uncompromised, 2 = moderately, 3 = severely compromised). Based on quantitative analysis of PDs, PD score was calculated, considering the pain widespreadness. Differences between PD profile subgroups in TMD subtypes, PD scores and Axis I diagnoses were evaluated with Independent Samples Kruskal-Wallis and chi-squared tests and pairwise comparisons with Mann-Whitney U test with Bonferroni correction. PD score sum was explored by linear regression with age, sex, Axis I diagnoses and TMD subtype as independent variables.
Results: Patients were evenly distributed by PD profiles. Patients with widespread PD-3 profiles were significantly more often classified into TMD subtype 3, had higher PD scores and more pain-related Axis I diagnoses as compared to local PD-1 and regional PD-2.
Conclusion: Among TMD pain patients widespread pain associates with biopsychosocial impact. PD is an important adjunct tool in biopsychosocial Axis II assessment of TMD pain patients for treatment planning and personalised care.

Risk Factors Affecting the Therapeutic Effect of Onabotulinum Toxin A on Chronic Migraine.

Mendes-Andrade L, Inês Mendes-Andrade, Medeiros B, Pinto M, Costa A. Pain Manag. 2025 Feb;15(2):65-71. doi: 10.1080/17581869.2025.2458448. Epub 2025 Jan 27. PMID: 39871598; PMCID: PMC11864016.

Background: OnabotulinumtoxinA demonstrates effectiveness in chronic migraine prevention but is hindered by variable patient responses. This study aims to identify modifiable and non-modifiable risk factors influencing the response to onabotulinumtoxinA.
Methods: We conducted a retrospective cohort study at a tertiary hospital involving chronic migraine patients treated with onabotulinumtoxinA. Data on risk factors and patient perceptions were collected through medical records and questionnaires.
Results: A total of 131 patients were included. At 12 months, a significant reduction in headache frequency was observed: from 26 episodes pre-treatment to 13 at 3 months, 12 at 6 months, 11 at 9 months, and 10 at 12 months. A third of patients stopped overusing medication after treatment. Univariate logistic regressions revealed that fibromyalgia was associated with a reduced likelihood of achieving ≥50% response to onabotulinumtoxinA (OR (odds ratio) = 0.213, p = 0.031), while secondary education was associated with an increased likelihood of response (OR = 4.400, p = 0.029). Adjusted logistic regression confirmed that fibromyalgia significantly reduced the likelihood of ≥50% response (aOR (adjusted odds ratio) = 0.064, p = 0.033).

Conclusions: This study confirms the real-world effectiveness of onabotulinumtoxinA in reducing headache frequency. Furthermore, patients with fibromyalgia may have a diminished likelihood of responding positively, underscoring the importance of personalized treatment strategies.

Longitudinal Outcomes Among Patients with Fibromyalgia, Chronic Widespread Pain, or Localized Chronic Low Back Pain.
Licciardone JC, Brownell E, Nwaichi U, Patel A, Do K.
J Osteopath Med. 2025 Feb 27. doi: 10.1515/jom-2024-0087. Epub ahead of print. PMID: 40009484.

Objectives: The objective of this study was to compare longitudinal outcomes of patients with FM, CWP, or localized chronic low back pain (LBP) to determine whether FM is an extreme manifestation of the CWP continuum.
Methods: A retrospective cohort study was conducted within a national pain research registry from August 2019 to July 2023. A total of 310 participants with FM (and CWP), CWP (without FM), or LBP were followed for 12 months to measure pain intensity, back-related disability, and health-related quality of life (HRQOL). Multivariable analyses were performed with generalized estimating equations (GEEs), including baseline and longitudinal covariates to adjust for potential confounding.
Results: The mean age of the participants was 52.3 (standard deviation [SD], 13.6) years, and 238 (76.8 %) were female. There were 64 (20.6 %) participants with FM, 56 (18.1 %) with CWP, and 190 (61.3 %) with LBP. There were no differences in pain intensity among the groups. Compared with back-related disability in the LBP group (mean, 12,7; 95 % confidence interval [CI], 11.4-14.1), the FM group (mean, 15.3; 95 % CI, 13.7-17.0; p=0.006) and CWP group (mean, 16.2; 95 % CI, 14.8-17.7; p<0.001) had greater disability. There were no clinically relevant differences in pain and disability between the FM and CWP groups. Compared with the LBP group, the FM group had worse outcomes on five HRQOL scales, and the CWP group had worse outcomes on all seven scales. Clinically relevant HRQOL differences between the FM and CWP groups involved anxiety and depression, with results favoring the FM group.
Conclusions: These findings do not support the view that FM is an extreme manifestation of the CWP continuum, involving greater pain, disability, or HRQOL deficits.

Exploring the Influence of Social Support, Disease Activity, and Fibromyalgia on the Emotional Well-Being of Women with Systemic Lupus Erythematosus.
Alnaimat F, Hamdan O, Natsheh T, Hamad RB, Amrieh ZA, Ahmad D, Mohammed MH, Al-Awamleh N.
BMC Rheumatol. 2025 Feb 27;9(1):26. doi: 10.1186/s41927-025-00476-0. PMID: 40012000; PMCID: PMC11866860.

Background: Systemic Lupus erythematosus (SLE) is an autoimmune disorder in which females are affected more commonly than males. In addition to the physical burden of the disease, patients with SLE are at higher risk of psychological disorders. In Jordan, there is a paucity of studies assessing the emotional well-being and psychosocial burden of SLE. This study aims to explore fibromyalgia, mental health-related problems and their association with SLE disease activity and its various manifestations.
Methods: This cross-sectional study enrolled all sequential female patients diagnosed with SLE who attended a single-provider rheumatology clinic at the Jordan University Hospital (JUH), in Amman, Jordan. Data was collected between September 2023 and March 2024. A structured questionnaire was utilized to collect demographic data as well as SLE disease features. Comorbid psychiatric disorders were assessed using PHQ-9 and GAD-7 for depression and anxiety, respectively, fibromyalgia by FiRST, disease activity by SLEDAI score, quality of life by SF-12 and perceived social support were evaluated using MSPSS.
Results: We analyzed the data of 63 female patients diagnosed with SLE. The mean age was 40.3 ± 15.3 years with a mean age of 28.3 ± 12.1 years at diagnosis. The most common manifestations were mucocutaneous and hematological manifestations each affecting 84.1% of patients. Regarding treatments, 79.4% of patients were using hydroxychloroquine and 73.0% of patients were using glucocorticoids. According to PHQ-9, 34.9% of patients had depression and 7.9% of patients had severe depression. positive FiRST screening suggestive of fibromyalgia was found in 31.7%. The mean PCS-12 scores were 41.9 ± 9.8 and the mean MCS-12 was 51.9 ± 3.4 indicating a moderate level of physical and mental health, respectively. Using multivariate logistic regression, vascular involvement (OR = 14.9, 95% CI: 1.1-202.4) were associated with depression while patients with high PCS-12 scores (OR = 0.889, 95% CI: 0.79-0.96) had lower odds of positive FiRST screening.
Conclusion: Our study showed that patients with SLE are at an increased risk of comorbid psychiatric disorders, which adds to the complexity of the disease. The management of SLE should adopt a multidisciplinary approach to address both the physical and psychosocial burdens.

Factors Associated with Receiving a Functional Disorder Diagnostic Label: A Systematic Review.
Tattan M, Rosmalen J, Hanssen D.
PLoS One. 2025 Jan 27;20(1):e0317236. doi: 10.1371/journal.pone.0317236. PMID: 39869577; PMCID: PMC11771906.

Objectives: Functional Disorders (FD) are highly prevalent conditions that are diagnosed based on the presence of specific patterns of somatic symptoms. Examples of FDs include Fibromyalgia and Irritable Bowel Syndrome. Many patients who meet the criteria do not receive a formal diagnostic label. This systematic review aims to assess factors associated with receiving an FD diagnostic label.
Methods: A systematic search of PubMed, PsycINFO, and Embase was performed following the PRISMA guidelines. All research methodologies and languages were included with a focus on experiences and impacts of receiving/having an FD diagnostic label. Excluded studies were those not mentioning diagnostic labels, only involving single pain symptoms, and studies solely focusing on functional neurological

symptoms. Screening, data extraction and quality ratings (using the QuADS instrument) were performed by two independent reviewers.
Results: 15 Studies were identified (10 quantitative and 5 qualitative). Our results show that female patients were more likely to receive an FD diagnostic label for their symptoms; other associations were less consistent and only found for specific labels or research designs. In general, quality of life and healthcare use did not seem to differ between patients with and without an FD diagnostic label. From the healthcare professional's perspective there was doubt about giving an FD diagnostic label, mainly due to concerns of harm for patients. Quality of included studies was rated low to moderate.
Conclusion: Better understanding of factors associated with receiving or having an FD diagnostic label, independently from symptom development can help healthcare professionals make evidence-based decisions in labelling or not; however, high quality studies on this topic are urgently needed.

Crohn's Disease, Irritable Bowel Syndrome, and Chronic Fatigue: The Importance of Communication and Symptom Management-A Case Report.
Haedrich J, Huber R.
J Med Case Rep. 2025 Jan 9;19(1):9. doi: 10.1186/s13256-024-05010-3. PMID: 39789666; PMCID: PMC11721286.

Background: Crohn's disease and irritable bowel syndrome may both cause abdominal pain and diarrhea. Irritable bowel syndrome not only is an important differential diagnosis for Crohn's disease but also occurs in one out of three patients with Crohn's disease in remission in parallel. If not adequately diagnosed and treated, additional functional symptoms such as fatigue and/or muscle pain may develop, indicating a more severe course.
Case presentation: A 64-year-old Caucasian male with long-standing, widely inactive Crohn's disease presented with persistent diarrhea, bloating, abdominal pain, general fatigue, unexplained hip pain, and frequent shivering with cold extremities, which had worsened following a gastrointestinal infection and psychological stress. A plausible explanation of his symptoms, based on an understanding of mind-body interactions, the autonomic nervous system, and temperature regulation, combined with symptom relief, was associated with rapid and sustainable improvement. After 2.5 years of follow-up, the patient is almost symptom-free.
Conclusions: This case report exemplifies the interrelation between organic (Crohn's disease) and functional diseases (irritable bowel syndrome, chronic fatigue syndrome, and somatoform pain). It further demonstrates that these connections may be overlooked in daily practice and that providing a plausible explanation in combination with symptom relief may be important for patients with functional syndromes.

The Role of Central Sensitization in Autoimmune Connective Tissue Diseases: A Comparative Cross-Sectional Study.
Bazancir-Apaydin Z, Apaydin H, Armagan B, Orhan K, Erten S.
Int J Rheum Dis. 2025 Jan;28(1):e70069. doi: 10.1111/1756-185X.70069. PMID: 39835488; PMCID: PMC11748102.

Objective: To investigate the central sensitization (CS) in patients with autoimmune connective tissue diseases (ACTDs) and its relationship with disease activity, laboratory findings, medical treatments, organ involvements, and comorbidity.
Methods: One hundred and eleven patients with ACTDs and 40 healthy individuals were included. All patients were divided into three groups in terms of their diseases: Sjögren's syndrome (SS), rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE). The CS was assessed using the central sensitization inventory (CSI-A and CSI-B scores). The disease activity, laboratory findings, medical treatments, organ involvements, and comorbidity of all patients were evaluated.
Results: Overall, 41.4% patients with ACTDs had CS. SS group had the highest CS positivity (n = 21, 58.3%) compared to the RA (n = 14, 36.8%) and SLE (n = 11, 29.7%) groups. The SS group had a significantly higher CSI-A score ($p < 0.016$) than the RA and SLE group, which had similar scores. CSI-A ($p = 0.008$, $r = -0.63$) and CSI-B ($p = 0.001$, $r = -0.76$) scores were moderately to high correlated with vitamin D3 levels in SLE group. CSI-B score was moderately correlated with folic acid levels ($p = 0.03$, $r = 0.50$) and TSH ($p = 0.005$, $r = 0.55$) in SS group. The CSI-A score ≥ 40 subgroup had more female gender, frequency of COPD or asthma, more coexisting fibromyalgia, higher VAS score, more common exocrine gland involvement, and higher corticosteroid dose compared to the CSI score < 40 subgroup.
Conclusions: CS is commonly seen in patients with ACTDs, especially in SS. CS is associated with vitamin D3, folic acid, and TSH levels in ACTD subgroups and the patients with clinical CS have a specific profile.

Subgroup Characteristics of Middle-Aged and Older Women with Chronic Low Back Pain by Multiple Factors: A Hierarchical Cluster Analysis.
Miyachi R, Nishimura T, Noguchi M, Goda A, Takeda H, Takeshima E, Kanazawa Y, Imai T, Tanaka W.
J Funct Morphol Kinesiol. 2025 Jan 14;10(1):30. doi: 10.3390/jfmk10010030. PMID: 39846671; PMCID: PMC11755572.

Background/objectives: Chronic low back pain (CLBP) after middle age is a complex multifactorial condition, and subgrouping is recommended to determine effective treatment strategies. Multidimensional data help create new groupings to increase the effectiveness of interventions in middle-aged and older adults with CLBP. This study aimed to investigate the relationship between the factors associated with CLBP after middle age and to create and characterize a new subgroup based on these factors.
Methods: A cross-sectional observational study was conducted and included 46 women aged ≥40 years

with CLBP who participated in health events. Trunk muscle mass, lumbar movement control ability, autonomic balance, lumbar tenderness threshold, lumbar proprioception, and severity of central sensitization were assessed.
Results: Partial correlation analysis revealed a significant negative correlation between lumbar movement control ability and autonomic balance. A significant positive correlation was observed between trunk muscle mass and the lumbar tenderness threshold. Hierarchical clustering analysis identified three subgroups. The cluster 1 participants had low trunk muscle mass, low tenderness threshold, and low severity of central sensitization. The cluster 2 participants had low trunk muscle mass and tenderness threshold and high severity of central sensitization. The cluster 3 participants had high trunk muscle mass and tenderness threshold and were sympathetically predominant. Trunk muscle mass, pressure pain threshold, severity of central sensitization, and autonomic balance were significantly different between the clusters.
Conclusions: Three characteristic subgroups were identified. The results contribute to treatment and prevention strategies for middle-aged and older adults with CLBP based on the characteristics of the subgroups rather than a uniform approach.

Sex-Specific Sensory Profiles Discriminate Between Sensitization at Twelve Weeks in Patients with Acute Low Back Pain: A Retrospective Study.
Gräper PJ, Scafoglieri A, Hallegraeff JM.
J Clin Med. 2025 Jan 19;14(2):621. doi: 10.3390/jcm14020621. PMID: 39860628; PMCID: PMC11765823.

Background/objective: Low back pain (LBP) is the leading cause of disability worldwide, resulting in enormous socio-economic and personal consequences. Sensory profiles during the acute back pain stage will predict central sensitization symptoms in the chronic pain stage, as central sensitization is the main mechanism behind nociplastic pain and pain chronicity. Therefore, our objective was to establish overall and sex-specific sensory profile cut-off points that distinguish symptoms of central sensitization at 12 weeks, using a retrospective prognostic cohort study design.
Methods: Two hundred and seventeen patients with acute LBP (<6 weeks) were assessed using Receiver Operator Characteristic analyses. Measurements were taken at baseline using the Adolescent/Adult Sensory Profile and follow-up by the Central Sensitization Inventory at 12 weeks, based on the established Central Sensitization Inventory cut-off points for the overall population at ≥30 and ≥40, female patients at ≥33, and male patients at ≥25.
Results: In female patients, a Sensory Sensitive cut-off point of ≥30.5 significantly distinguished central sensitization symptoms at 12 weeks, resulting in the following values: Area Under the Curve = 0.81 (95% CI = 0.73; 0.89), sensitivity = 0.89, specificity = 0.63, prevalence = 0.36, positive predictive value = 0.56, negative predictive value = 0.80, and Youden's index = 0.52.
Conclusions: The Sensory Sensitive profile distinguishes female patients with acute LBP with and without central sensitization symptoms at 12 weeks. This cut-off point may be useful in identifying individual sensory preferences and addressing maladaptive behavioral responses to sensory stimulation in clinical practice to prevent chronicity.

Nociplastic Pain: Controversy of the Concept.
Macionis V.
Korean J Pain. 2025 Jan 1;38(1):4-13. doi: 10.3344/kjp.24257. PMID: 39743317; PMCID: PMC11695249.

Classically, pain can be of a nociceptive or neuropathic nature, which refers to non-neural or neural tissue lesions, respectively. Chronic pain in conditions such as migraine, fibromyalgia, and complex regional pain syndrome (CRPS), is thought to perpetuate without a noxious input. Pain in such patients can be assigned neither to the nociceptive nor neuropathic category. Therefore, a third pain descriptor, named "nociplastic pain", has been adopted by the International Association for the Study of Pain. The current controversy-focused narrative review updates little debated aspects of the new pain concept. The most disputable feature of nociplastic pain is its autonomous persistence, i.e., existence without causative tissue damage, presumably because of a malfunction of pain pathways and processing. This contradicts the fact that nociplastic pain is accompanied by persistent central sensitization that has been shown to require a continuing noxious input, e.g ., nerve injury. Even if sensitization occurs without a lesion, e.g ., in psychogenic and emotional pain, peripheral stimulus is necessary to produce pain. A logical weakness of the concept is that the word "plastic" in biology refers to adaptation rather than to maladaptation. The pathophysiologic mechanism of nociplastic pain may, in fact, be associated with background conditions that elude diagnosis because of the limitations of current diagnostic means. Misapplication of the nociplastic pain category may weaken diagnostic alertness toward occult causes of pain. Possible diagnostic errors could be avoided by understanding that nociplastic pain is a mechanism of pain rather than a diagnosis. Clinical use of this pain descriptor deserves a wider critical discussion.

Comorbid Bladder Pain Syndrome and Vulvodynia - A Cross-sectional Analysis of the UNICORN-4 Study.
Okui N.
BMC Womens Health. 2025 Feb 19;25(1):72. doi: 10.1186/s12905-025-03602-9. PMID: 39972456; PMCID: PMC11837444.

Background: Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC) and vulvodynia often coexist, exacerbating patient symptoms and complicating the diagnosis and treatment. This study aimed to identify distinct subtypes within a BPS/IC and vulvodynia cohort and evaluate their symptom profiles, psychological characteristics, and sexual function indicators.

Methods: A cross-sectional analysis was conducted on 150 female patients diagnosed with BPS/IC and vulvodynia. The patients completed validated questionnaires assessing bladder symptoms, psychological distress (PHQ-9 and GAD-7), and sexual function (FSFI and FSDS-R). Hierarchical and K-means clustering were used to identify patient subgroups.
Results: Three distinct clusters were identified. Cluster 1 exhibited moderate bladder-specific symptoms and psychological distress. Cluster 2 had severe bladder symptoms and the highest psychological distress. Cluster 3, defined as the vulvodynia-predominant subtype, featured severe vulvodynia, significant psychological distress, and minimal bladder symptoms, aligning with a non-urologic pelvic pain phenotype. Sexual function was significantly impaired across all clusters, with Cluster 3 showing the most severe dysfunction.
Conclusions: This study highlights the heterogeneity within BPS/IC and vulvodynia populations. The identification of a vulvodynia-predominant subtype and non-urologic pelvic pain phenotype emphasizes the need for personalized treatment strategies addressing both physical and psychological factors, particularly sexual dysfunction and psychological distress.

Joint Terminology Report: Terminology Standardization for Female Bladder Pain Syndrome. Developed by the Joint Writing Group of the International Urogynecological Association and the American Urogynecologic Society.
Int Urogynecol J. 2025 Feb;36(2):265-277. doi: 10.1007/s00192-024-05923-z. Epub 2025 Jan 3. PMID: 39751633.

Female bladder pain syndrome (FBPS), previously known as interstitial cystitis/bladder pain syndrome, is a life-altering and morbid condition that occurs primarily in female patients and can be variable in presentation. Given the absence of pathognomonic symptoms and sensitive diagnostic tests, significant symptomatic overlap with numerous other pelvic conditions (such as pelvic floor tension myalgia or endometriosis) occurring in women makes diagnosis of FBPS challenging. The frequent co-occurrence of FBPS with other pain conditions and functional somatic syndromes further complicates diagnosis and management. The challenges have limited the progress made in understanding the pathophysiology of the condition and improving approaches to treatment and prevention. Improvement in standardization of the terminology used to describe this unique condition is needed to improve the accuracy of diagnosis and the clinical care for affected patients. Given the variability in presentation and the differing definitions for the condition world-wide, the American Urogynecologic Society and the International Urogynecologic Association convened a joint writing group to standardize terminology around common signs and symptoms of the condition and to clarify the diagnosis as it pertains to female patients with the condition. After careful consideration of a broad range of available data and clinical experiences, consensus opinion recommended adopting the term "FBPS" instead of the misleading "interstitial cystitis" to describe a chronic, intermittent condition of at least 3 months' duration affecting women involving symptoms of pain or discomfort localized to the bladder, often with bladder filling, which are not attributed to other pathology. This term will allow clinicians, researchers, and learners alike to standardize their understanding of FBPS.

Heart Rate Variability is Not Associated with Multiple Chemical Sensitivity in a Cross-sectional Population-based Study - The Danish Study of Functional Disorders.
Bjerregaard AA, Brinth L, Petersen MW, Schovsbo SU, Eplov L, Brix S, Linneberg A, Gormsen L, Jørgensen T, Dantoft TM.
J Psychosom Res. 2025 Jan;188:111992. doi: 10.1016/j.jpsychores.2024.111992. Epub 2024 Nov 19. PMID: 39579587.

Objective: Multiple chemical sensitivity (MCS), a functional somatic disorder (FSD), is a multisystem, polysymptomatic disease, characterized by various individual symptoms attributed to low level of volatile chemical exposures. Symptoms relate to the autonomic nerve system (ANS) among others which is mandatory in the MCS delimitations. An accepted measure of ANS is heart rate variability (HRV). The aim was to explore associations between HRV and MCS in the general Danish population.
Methods: In the Danish Study of Functional Disorders, 7493 adults filled in questionnaires and participated in a physical health examination (2012-2015). The "E motion" heart rate monitor device assessed time and frequency measures of HRV. For this study, 143 were categorized with MCS of which, 84 were subcategorized as MCS without comorbid FSD. The remaining population (n = 5525) was used as comparison group. Logistic regression models to assess odds ratio (OR) with 95 % confidence intervals (95 % CI) of MCS, and MCS without comorbid FSD for each HRV exposure adjusted for age, sex, and chronic stress.
Results: Compared to the general population, median resting heart rate was higher (64.7 vs 63.1 bpm, p = 0.007) and median normal-to-normal intervals was lower (930 vs 952 ms, p = 0.007) in MCS individuals. Resting heart rate was associated with MCS (OR: 1.019, 95 %CI: 1.003; 1.037); but not after adjustment for chronic stress. No other associations with other HRV measures nor in MCS without comorbid FSD were found.
Conclusion: HRV was not associated with MCS. The magnitude of the differences between groups was small and of uncertain clinical significance.

Network Structure of Functional Somatic Symptoms.
Litzenburger A, Rothacher Y, Hanusch KU, Ehlert U, Nater UM, Fischer S.
J Psychosom Res. 2025 Jan;188:111968. doi: 10.1016/j.jpsychores.2024.111968. Epub 2024 Nov 1. PMID: 39532031.

Objective: The overlap among functional somatic syndromes (FSS) is substantial, which is why various

empirical attempts at an improved understanding of related symptoms have been undertaken. Network analyses are particularly valuable from a clinical point of view, since they focus on the extent to which symptoms expression is co-dependent. The aim of this study was to provide the first estimation of the network structure of symptoms in 17 FSS.
Methods: N = 3054 young adults participated in an online survey. The Questionnaire on Functional Somatic Syndromes (FSSQ) was used to diagnose FSS and to assess related symptoms. The Patient Health Questionnaire (PHQ-9) was used to assess (comorbid) depression. Various R packages were used for network analysis, which yielded correlations between symptoms (edges), symptom groups (communities), and measures of centrality for individual symptoms (e.g., node strength).
Results: The final network had a relatively small number of edges, with small (46.5 %) or small- to medium-sized (47.1 %) correlations. Ten communities were identified: cognitive problems/fatigue/depression, sensory problems, facial pain, head/neck/upper back pain, dizziness/nausea, throat pain/problems with swallowing, chest pain, widespread pain, abdominal pain/problems with digestion, and genital pain. The highest node strength in the network was found for the symptoms "tired", "down, depressed, or hopeless", and "tired after minimal exertion".
Conclusions: The network analyses pointed to ten distinct groups of moderately associated symptoms in individuals with FSS. Fatigue and depression emerged as important symptoms connecting groups. Future studies should test whether (transdiagnostic) interventions specifically targeting these symptoms are particularly potent in alleviating FSS.

Entangled Illnesses: Embodied Experiences of Managing Multimorbidity.
Oikkonen V, Helosvuori E, Ganesh A, Rokkonen LA.
Sociol Health Illn. 2025 Feb;47(2):e70006. doi: 10.1111/1467-9566.70006. PMID: 39874027.

Multimorbidity, meaning multiple long-term conditions impacting a person's health, has become a rising societal and public health issue. The article contributes to the sociological study of chronic illness and multimorbidity by analysing how the blurriness of illnesses and entanglement of symptoms in multimorbidity is experienced and negotiated by people with coexisting chronic conditions. Drawing on qualitative interviews with people who live with endometriosis, fibromyalgia or hormonal migraine in Finland, we show how people with multiple chronic conditions distinguish between evolving symptoms based on past embodied experiences to make decisions about how to best manage their health. We argue that coexisting illnesses become entangled in ambiguous and open-ended ways, which, if left unaddressed, complicates treatment. Our analysis of illness experiences is aligned with the growing body of literature that argues that the single-disease model underlying healthcare systems fails to address the needs of patients living with multiple chronic conditions. Our emphasis on evolving entanglements between illnesses and the blurriness of conditions makes visible crucial discrepancies between lived illness and existing biomedical models and healthcare structures.

Communication and Empathy within the Patient-Physician Relationship among Patients with and without Chronic Pain.
Licciardone JC, Middleton CN, Aboutaj A, Allouche T, Siddiqui I.
J Osteopath Med. 2024 Oct 3;125(2):79-86. doi: 10.1515/jom-2024-0112. PMID: 39356631.

Context: Chronic pain may affect the relationship between patients and their treating physicians. Objectives: This study was designed to compare four aspects of physician communication and physician empathy reported by patients with chronic pain and in chronic pain-free controls.
Methods: A cross-sectional study was conducted within a national pain research registry from July 2020 through January 2024. Patients with chronic low back pain of greater than 3 months duration were matched to chronic pain-free controls utilizing propensity scores derived from a logistic regression model based on 11 variables that included sociodemographic characteristics, cigarette smoking status, history of comorbid medical conditions, and duration of the current patient-physician relationship. Patients reported on the primary outcomes of physician communication utilizing the Communication Behavior Questionnaire (CBQ) and physician empathy utilizing the Consultation and Relational Empathy (CARE) measure. Group means were compared for each aspect of physician communication (patient participation and patient orientation, effective and open communication, emotionally supportive communication, and communication about personal circumstances) and physician empathy, and Cohen's d statistic was utilized to assess the clinical relevance of between-group differences. Secondary exploratory analyses were also performed to compare patients treated by osteopathic physicians vs. allopathic physicians and to determine whether study group X physician type interaction effects were present.
Results: The 387 patients in each study group were matched within a caliper width of 0.001 on the propensity score. Overall, patients ranged from 21 to 79 years of age (mean, 50.7 years; standard deviation [SD], 15.1 years), and 617 (79.7 %) of them were female. Patients in the chronic pain group reported poorer scores for all aspects of physician communication and physician empathy than the chronic pain-free controls. All between-group differences were clinically relevant. There were no differences in physician communication or physician empathy according to physician type in the exploratory analyses, and study group X physician type interaction effects were not observed.
Conclusions: In this cross-sectional study, patients with chronic pain reported having physicians with poorer communication and less empathy than chronic pain-free controls. Longitudinal research is needed to more clearly determine the temporal relationship between patients' chronic pain and physician communication and physician empathy during medical encounters.

'What Script Am I Meant to Use?': A Qualitative Study in Chronic Primary Pain.
Blythe N, Hughes C, Hart ND.

BJGP Open. 2025 Jan 2;8(4):BJGPO.2024.0101. doi: 10.3399/BJGPO.2024.0101. PMID: 39054301; PMCID: PMC11687266.

Background: Chronic primary pain (CPP) as a diagnosis has been introduced in the recent International Classification of Diseases, 11th Revision (ICD-11). CPP captures the experience of pain as the primary problem, without an underlying attributable cause. Dissemination of UK guidance regarding CPP represents the first time it has been recognised as a condition in its own right. Little is known about GP views concerning caring for patients with CPP, and how related guidance is viewed and applied in practice.
Aim: To explore GP perspectives in relation to caring for people with CPP, including challenges encountered and use of related guidelines in practice.
Design & setting: A UK-wide qualitative interview study in primary care.
Method: Purposive and snowball sampling were used to recruit 15 GP participants from England, Northern Ireland, Wales, and Scotland. Semi-structured interviews were undertaken and analysed using reflexive thematic analysis.
Results: The following three main themes were generated: (1) 'How to start? Problematic beginnings', which referred to difficulties regarding diagnosis; (2) 'Where to go? Mapping the management challenge'; and (3) 'How to get there? Navigating strategies and response', which explored GP awareness and acceptability of UK guidelines for chronic pain. Areas identified for potential improvement included increased access to non-pharmacological management (NPM) and secondary care services, support with deprescribing, and an expanded multidisciplinary team input.
Conclusion: CPP is complex to both diagnose and manage. Although guidelines provide a useful framework, they pose challenges when translating into day-to-day practice.

Sex Differences in Pain, Suicidal Ideation, and Suicide Attempts in Patients with Migraine.
Kuan AS, Wang YF, Chen SP, Chuang YF, Wang SJ.
Headache. 2025 Jan 24. doi: 10.1111/head.14906. Epub ahead of print. PMID: 39853772.

Objective: To examine sex-specific associations between non-cephalic pain and suicidal ideation and suicide attempts in patients with migraine, controlling for depression and other risk factors for suicide.
Background: In patients with migraine, co-occurring pain conditions are common and are associated with worse physical and psychosocial function, but the association with suicide has not been determined.
Methods: In this cross-sectional analysis, we included 10,690 patients with migraine who were consecutively recruited from headache clinics. All participants provided information on sociodemographic status, headache, Widespread Pain Index (WPI), suicidal ideation, and suicide attempts. Relative risks (RRs and 95% confidence intervals [CIs]) for factors associated with suicidal ideation and suicide attempts were calculated.
Results: In this migraine cohort, more females reported non-cephalic pain than males (78.7% [6511/8271] vs. 66.7%, [1613/2419]; $p < 0.001$). The prevalences of suicidal ideation and suicide attempts were higher in female patients than male patients in those aged 20-59 years ($p < 0.001$), and the differences diminished after the age of 60 years. In female patients, a WPI ≥4 was associated with increased suicidal ideation and suicide attempts, and dysmenorrhea was associated with suicidal ideation (RR 1.27, 95% CI 1.12-1.43), while lower back pain was associated with both suicidal ideation (RR1.35, 95% CI 1.18-1.55) and suicide attempts (RR 1.48, 95% CI 1.19-1.84). In male patients, a WPI ≥2 was associated with increased suicidal ideation, and no individual pain site was associated with suicidal ideation or suicide attempts. In both sexes, there was a dose-response association between the number of pain sites and suicidal ideation and suicide attempts; and pain that had lasted for 2 years and extreme pain intensity were associated with suicide attempts.
Conclusion: Non-cephalic pain was associated with suicidal ideation and suicide attempts, with observed differences in pain threshold and individual pain sites found between sexes. Patients with migraine and co-occurring pain conditions, chronic pain, or extreme pain are distinct subgroups of patients at risk of suicide who require sex-specific and integrated risk assessment by multidisciplinary teams.

The Diagnostic Journey of Dysautonomia Patients: Insights from a Patient-Reported Outcome Study.
O'Dell JA, Walker A, Latham AJ, Parisian DJ, Branch LE, Vanderburg DD, Cox AA, Chavis S, Smith SE.
J Patient Exp. 2025 Jan 21;12:23743735251314651. doi: 10.1177/23743735251314651. PMID: 39839488; PMCID: PMC11748159.

Dysautonomia refers to any disorder involving altered function of the autonomic nervous system. Dysautonomia can be debilitating as it often affects multiple organ systems. The diagnostic journey for individuals affected by dysautonomia can be hindered by symptom overlap with other conditions and by limited access to autonomic specialists. The present patient-reported outcome study aims to characterize the diagnostic journey of 672 adult individuals affected by different types of dysautonomia. The average time to diagnosis was 7.7 years (SD 10 years) and diagnosis was made primarily by cardiologists, followed by neurologists, and internists or primary care physicians. Common comorbid conditions are Ehlers-Danlos syndrome, mast cell disorders, vitamin deficiency, fibromyalgia, and myalgic encephalomyelitis, all of which can contribute to the symptoms burden and can potentially confound the diagnostic process. We suggest that the prolonged time to diagnosis contributes to morbidity and compounds the psychological and economic burden of dysautonomia. Raising awareness about the numerous obstacles that hinder the diagnostic process among both clinicians and dysautonomia patients is the first step to reduce morbidity and improve clinical outcomes.

Journey of Hope for Patients with Fibromyalgia: From Diagnosis to Self-Management-A Qualitative

Study.
Aldarwesh A.
Healthcare (Basel). 2025 Jan 13;13(2):142. doi: 10.3390/healthcare13020142. PMID: 39857169; PMCID: PMC11765407.

Background/objectives: Fibromyalgia syndrome (FMS) is a chronic, debilitating condition characterized by widespread pain, fatigue, and psychological distress. There is a lack of qualitative studies on the unique experiences of patients with FMS in Arab countries, particularly through social media. Despite the availability of diagnostic criteria, diagnosing and managing patients remains challenging. This study aimed to describe the experiences of patients with FMS in Arab countries, their understanding of the illness, and perceptions of treatment.
Methods: A qualitative study was conducted using a content analysis of patients' narratives published in a supportive group, describing their experiences with fibromyalgia. The dataset included 2305 quotes from 192 main posts and 2113 comments collected between 2019 and 2024.
Results: The analysis of the posts and associated comments revealed six main themes: patients' experiences with the syndrome, symptoms, searching for a doctor, pharmacological management, self-management, and the impact of fibromyalgia and peer support. Most posts and comments focused on patients' experiences with self-management approaches and coping strategies, highlighting significant noncompliance with therapeutic modalities. Factors influencing patients' experiences and decisions included their relationship with physicians, medication side effects, personal fears, and physical and mental health.
Conclusions: Patients with FMS in Arab countries face similar challenges to those in other regions, including physical, psychological, social, and economic impacts. Many patients reject conventional therapeutic management strategies and adopt coping mechanisms to mitigate adverse effects and healthcare costs. The findings suggest that the physician-patient relationship, as well as the physician's knowledge and attitude toward fibromyalgia syndrome, are the cornerstones of gaining patients' trust.

EPIDEMIOLOGY STUDIES

Prevalence and Epidemiological Characteristics of Chronic Pain in the Spanish Population. Results from the Pain Barometer.
Dueñas M, De Sola H, Salazar A, Esquivia A, Rubio S, Failde I.
Eur J Pain. 2025 Jan;29(1):e4705. doi: 10.1002/ejp.4705. Epub 2024 Jul 24. PMID: 39046161; PMCID: PMC11609938.

Background: Chronic pain (CP) is a public health problem worldwide.
Aim: To update the prevalence of CP and compare the clinical and social characteristics of people with CP with those with non-chronic continuous pain and a group without pain.
Methods: An observational cross-sectional study was carried out in a representative sample of 7058 adults from the Spanish population. Sociodemographic data, the presence of CP and non-chronic continuous pain, characteristics of pain, limitations on activities of daily living (ADL), the presence and level of anxiety and depression (HADS), quality of life (SF-12v2) and social support (DUKE) were collected. Descriptive and bivariate analyses were performed.
Results: The prevalence of CP was 25.9% (95% CI;24.8-26.9) and that of non-chronic continuous pain was 7.7% (95% CI;7.1-8.3). Women presented a higher prevalence of both CP (30.5% vs. 21.3%) and non-chronic continuous pain (8.8% vs. 6.6%). CP was more common in the group between 55 and 75 years old (30.6%, 95% CI = 28.6-32.6%), non-chronic continuous pain affected most the population between 18 and 34 years old (11.2%, 95% CI = 9.6-12.7%). The median duration of CP was 4 years. The lumbar was the most frequent pain site (58.1%), and 27.1% did not know the cause. A greater frequency of limitations on ADL, more anxiety and depression, and worse quality of life were shown among the subjects with CP.
Conclusion: CP affects one in four Spanish people and impairs the mental, physical and social health. Differences exist by sex and age in its frequency. Identifying subjects with non-chronic continuous pain is fundamental to prevent their pain from becoming chronic.
Significance statement: Indicating the main aspects where this work adds significantly to existing knowledge in the field, and if appropriate to clinical practice. Due to its high prevalence and impact on quality of life, chronic pain has become one of the main health problems nowadays. Attention must be paid to it both from a clinical and social perspective, trying to raise awareness among the population of its possible causes and consequences. In routine clinical practice, greater consideration is given to groups of people with a higher prevalence of chronic pain, such as women and people with middle age, and with no chronic pain to prevent the appearance of chronic pain.

Correlates of Chronic Pain Onset and Recovery in the CoLaus Cohort.
Dirupo G, Rossel JB, Fournier N, D'Andrea A, Vollenweider P, Decosterd I, Suter MR, Berna C.
Eur J Pain. 2025 Feb;29(2):e4712. doi: 10.1002/ejp.4712. Epub 2024 Aug 7. PMID: 39113471; PMCID: PMC11671331.

Background: Only few previous cohort studies examined simultaneously predictors of chronic pain (CP) onset and recovery. Furthermore, these studies used various sociodemographic and pain-related characteristics, without standardized measures of sleep and depression. The present study aimed at

expanding and strengthening these findings in a large Swiss population.
Methods: We analysed data from a longitudinal cohort (n = 4602) collected at two time points separated by 5 years in Lausanne, Switzerland. We studied through two independent multivariable logistic regression models, the predictors of CP onset and recovery, including socio-demographic data as well as standardized measures of sleep and mood.
Results: Chronic pain was reported by 43.1% and 44.4% of participants, with 11.6% at the second follow-up reporting moderate or intense pain. Neuropathic pain, regardless of intensity, had a more negative impact on quality of life. An inferential model (n = 1331) identified the male sex as predictive for recovering from CP. Older age, being overweight or obese (compared to normal weight), higher depression scores and pain medication intake were predictive for sustained pain at the second follow-up. A second model (n = 1886) identified being overweight or obese (compared to normal weight), low quality of sleep and being a former smoker (compared to a non-smoker) as predictive for developing CP, while the male sex was lowering the risk.
Conclusions: While sex and weight are associated with both recovery and new CP onset, separate variables also need to be considered in these processes, underlining specific factors to be addressed, depending on the context, whether preventive or therapeutic.
Significance statement: Multivariable models in a Swiss cohort (N = 4602) associate male sex, not taking pain medication, normal weight, lower depression scores and younger age with recovery from chronic pain, while females, obese or overweight, having worse sleep and former smokers are associated with onset of new chronic pain. These common and separate factors need to be considered in treatment and prevention efforts.

High-impact Chronic Pain in a Cohort of Urologic Chronic Pelvic Pain Syndrome Patients: A Retrospective MAPP Research Network Study.
Wang T, Bergmans R, Minc A, Krieger J, Harris RE, Lai HH, Clemens JQ, Harte SE, Kaplan C, Williams DA, Naliboff B, Gallop R, Till S, Schrepf A.
Clin J Pain. 2025 Jan 30. doi: 10.1097/AJP.0000000000001275. Epub ahead of print. PMID: 39881480.

Objectives: An emerging concept in the chronic pain literature, high-impact chronic pain (HICP), refers to pain that occurs very frequently and results in major disruption of daily life. Previous epidemiologic investigations have noted that lower educational attainment, age, and race appear to be associated with the frequency of HICP, but condition-specific investigations of HICP have been less common.
Methods: Here we investigate HICP status and its clinical/demographic correlates in the Multidisciplinary Approach to the study of chronic Pelvic Pain research network Symptom Pattern Study.
Results: Participants were 476 urologic pelvic pain syndrome (UCPPS) patients, 64% of whom were female. Of these, 22% were classified as having HICP, based on responses to the several questions about pain interference in daily life. We confirmed that African-American individuals and those with lower educational attainment were more likely to experience HICP (both $P<0.05$). Additionally, those with HICP demonstrated much greater levels of disability, genitourinary pain, urinary symptoms, widespread pain, pelvic floor tenderness, and were more likely experience pain in response to consuming standardized amounts of water (all $P<0.05$). Binary logistics regression showed that genitourinary pain, widespread pain, and race were the strongest prediction of pain in multivariate models. Furthermore, HICP status was associated with more self-reported healthcare utilization over the subsequent 18 months ($P<0.05$).
Discussion: These findings suggest that HICP affects more than 1 out of 5 UCPPS patients, with significant associated morbidity. Demographic and clinical characteristics associated with HICP may be useful for identifying at-risk UCPPS patients.

Is There a Comorbid Relationship between Temporomandibular Disorders and Otologic Signs/Symptoms?: An Umbrella Review.
Chew AQA, Saigo L, Yap AU.
Cranio. 2025 Jan;43(1):8-21. doi: 10.1080/08869634.2022.2069639. Epub 2022 May 11. PMID: 35543516.

Objective: This umbrella review (UR) explored the possible associations between temporomandibular disorders (TMDs) and otologic signs/symptoms (OSs) and established the potential impact of TMD interventions on OSs.
Methods: A systematic review of systematic reviews (SRs)/meta-analyses (MAs) was conducted according to the PRISMA guidelines and Joanna Briggs Institute UR protocol. Electronic search of the PubMed, Scopus, Web of Science, and Open Grey databases was conducted and the quality of the identified studies was assessed using the AMSTAR2 criteria.
Results: Out of 923 and 157 articles screened for the first and second focus questions respectively, a total of 8 SRs/MAs fulfilled the eligibility criteria. The prevalence of OSs in TMD patients and contrariwise varied substantially up to 85.0-95.0%. Available evidence indicates that TMDs are associated with OSs, and TMD treatment reduced OSs.
Conclusion: Findings suggest that a comorbid relationship between TMDs and OSs exists, and therapeutic TMD interventions improve OSs.

Prevalence, Treatment, and Unmet Needs of Migraine in the Middle East: A Systematic Review.
Alsaadi T, Al Madani A, Alhatou M, Nada M, Albilali A, Al-Qassabi A, Mohamed H, Mohamed H, El Masry R, Saifuddin GA, AlRukn SA.
Pain Ther. 2025 Feb;14(1):145-183. doi: 10.1007/s40122-024-00686-3. Epub 2024 Dec 30. PMID: 39738973; PMCID: PMC11751246.

Introduction: Migraine is a debilitating neurological disorder characterized by recurrent throbbing,

moderate-to-severe headaches that disrupt daily chores, leisure, and social activities of patients, impacting their overall quality of life (QoL). Despite the high disease burden, there is a scarcity of data on migraines within the Middle East (ME) region. Thus, a systematic literature review (SLR) was conducted to examine epidemiological data, treatment patterns, QoL, and unmet needs regarding migraines in the ME region.
Methods: Electronic searches were carried out using the MEDLINE® and Embase® databases via the OvidSP® platform for articles published prior to April 2024. The inclusion and exclusion criteria for the selection of studies were based on the Patients, Intervention, Comparator, Outcomes, and Study design framework, which identified 42 studies.
Results: The prevalence of migraines reported from the region ranged between 2.6 and 32%, and the average age of patients with migraines reported in these studies ranged from 27 to 37.5 years. The data indicated a gender disparity in migraine prevalence, with women exhibiting a 2- to 2.5-fold higher prevalence. Common comorbidities reported were depression, anxiety, and irritable bowel disease. Migraines significantly impact patients' physical and emotional well-being, leading to disabilities and loss of productivity. The most common triggers of migraines were sleep disorders, dietary habits, and stress. The current treatment landscape for acute migraines encompasses anti-inflammatory agents, analgesics, triptans, ditans, calcitonin-gene-related peptides, and antiemetics. However, migraines in the region are often underestimated, underreported, and undertreated. Several unmet needs persist in the region, including delayed referral along with delayed diagnosis, misdiagnosis, poor treatment adherence, limited accessibility to treatments, and a lack of awareness among health care providers and patients.
Conclusions: The SLR highlights knowledge gaps in clinical aspects and the treatment of migraines and enables clinicians to make informed decisions to ensure optimal patient outcomes in diverse clinical settings.

Frequency of Central Sensitization and Nociplastic Pain in Patients with Plantar Fasciitis : Central Sensitization and Nociplastic Pain in Plantar Fasciitis.
Demir Karakılıç G, Melek Aykut Selçuk M, Öztürk EA.
Int Orthop. 2025 Feb 27. doi: 10.1007/s00264-025-06462-y. Epub ahead of print. PMID: 40014141.

Purpose: If the pain persists for a long time in the treatment of plantar fasciitis (PF) or if there is no response to treatment, central sensitization (CS) may develop and the pain may transform into nociplastic pain (NP). This study aimed to evaluate the frequency of CS and NP in patients with PF.
Methods: This cross-sectional study was undertaken between November 2023 and March 2024. The Foot Function Index (FFI) scale, which evaluates the foot's functionality, was applied to the patient group. The Visual Analog Scale (VAS), which evaluates pain intensity; the Pain-DETECT scale, which evaluates NP; and the Central Sensitization Scale (CSI), which evaluates CS, were applied to patient and control groups.
Results: A total of 206 people were included in the study; 106 were in the patient group with PF, and 100 constituted the control group. While we detected NP in 67 (63.2%) patients according to Pain-DETECT and CS was detected in 91 (85.8%) patients according to CSI among 106 patients with chronic PF; we detected NP in seven (7%) patients according to Pain-DETECT and CS in 44 (44.0%) patients according to CSI among 100 control patients. VAS-score and FFI-pain are moderately and positively correlated with pain-DETECT scores and fairly and positively correlated with CSI scores in the PF group. The pain-DETECT score is moderately and positively correlated with the CSI score in the two groups.
Conclusions: This is the first study to evaluate the presence of CS and NP in PF patients. We found NP and CS to be common in patients with chronic PF. Effective pain management in patients with PF before it becomes chronic can prevent the development of CS and NP.

Dyspareunia and Pelvic Pain in Women with Chronic Migraine: A Retrospective, Observational Analysis.
Smirnoff L, Moskatel LS.
Headache. 2025 Feb 4. doi: 10.1111/head.14905. Epub ahead of print. PMID: 39902805.

Background: Dyspareunia and pelvic pain are commonly comorbid conditions with migraine, with chronic migraine potentially contributing to the exacerbation of sexual dysfunction and pain.
Methods: We conducted a retrospective cohort study of female patients seen at the Stanford Headache Clinic between January 1, 2022, and March 24, 2024, for the management of chronic migraine for dyspareunia and pelvic pain and stratified for comorbidities related to both conditions.
Results: Patients with chronic migraine were overall found to be at higher likelihood of having a comorbid pelvic pain condition after adjusting for age, race-ethnicity, and marital status (adjusted odds ratio [aOR] 2.46; 95% confidence interval [CI]: 2.17-2.79, $p < 0.001$), with interstitial cystitis (aOR 3.04; 95% CI: 1.98-4.66, $p < 0.001$), vaginismus (aOR 2.51; 95% CI: 1.29-4.88, $p = 0.007$), dyspareunia (aOR 1.97; 95% CI: 1.57-2.49, $p < 0.001$), and vulvodynia (aOR 1.88; 95% CI: 1.04-3.40, $p = 0.036$) all increased in the chronic migraine population. Furthermore, conditions that are commonly comorbid with migraine, such as irritable bowel syndrome, fibromyalgia, and mood disorders, independently contributed to increased risk of pelvic pain conditions and dyspareunia.
Conclusions: Conditions that cause pelvic pain and sexual dysfunction in women are disproportionally common in women with chronic migraine and may contribute to disability and difficulties in interpersonal relationships. Early screening for disorders of pelvic pain in patients with chronic migraine and appropriate referrals can improve the quality of life of these patients.

Comorbidity Analysis and Clustering of Endometriosis Patients Using Electronic Health Records.
Khan U, Oskotsky TT, Yilmaz BD, Roger J, Gjoni K, Irwin JC, Opoku-Anane J, Elhadad N, Giudice LC, Sirota M.
medRxiv [Preprint]. 2025 Feb 19:2025.02.13.25322244. doi: 10.1101/2025.02.13.25322244. PMID:

39990556; PMCID: PMC11844609.

Endometriosis is a prevalent, complex, inflammatory condition associated with a diverse range of symptoms and comorbidities. Despite its substantial burden on patients, population-level studies that explore its comorbid patterns and heterogeneity are limited. In this retrospective case-control study, we analyzed comorbidities from over forty thousand endometriosis patients across six University of California medical centers using de-identified electronic health record (EHR) data. We found hundreds of conditions significantly associated with endometriosis, including genitourinary disorders, neoplasms, and autoimmune diseases, with strong replication across datasets. Clustering analyses identified patient subpopulations with distinct comorbidity patterns, including psychiatric and autoimmune conditions. This study provides a comprehensive analysis of endometriosis comorbidities and highlights the heterogeneity within the patient population. Our findings demonstrate the utility of EHR data in uncovering clinically meaningful patterns and suggest pathways for personalized disease management and future research on biological mechanisms underlying endometriosis.

The Association Between Urological Conditions Across the Life Course and Provoked Vulvodynia.
Harlow BL, Mühlrad H, Yan J, Lu D, Bohm-Starke N.
J Womens Health (Larchmt). 2025 Feb 17. doi: 10.1089/jwh.2024.0933. Epub ahead of print. PMID: 39957362.

Objective: Vulvodynia is a condition characterized by chronic pain and discomfort in the vulvar region often accompanied with physical and psychological comorbidities. Interstitial cystitis (IC)/bladder pain syndrome (BPS), a chronic condition characterized by bladder pain and urinary urgency, has repeatedly been shown to comorbidly be present in a large proportion of women with vulvodynia. However, recent studies have shown that women with vulvodynia experienced additional bladder-related symptoms beyond that of just IC/BPS.
Materials and Methods: Using Swedish National Registry data, we assessed the association between urological symptoms in the presence and absence of IC/BPS in women with vulvodynia/vaginismus relative to women with no vulvar pain history.
Results: After adjustment for birth year, parity, education, and residential location, women with vulvar pain had a 2.2-fold greater risk of cystitis or urethritis as expected (95% confidence interval [CI] 1.9-2.6). However, when women with cystitis codes were excluded, those with urethra disorders or other urinary symptoms codes were 1.9 times more likely to be vulvar pain cases (95% CI 1.7-2.1).
Conclusions: These findings support the belief that vulvodynia is not limited to being comorbid with IC/BPS but may also likely be associated with a wide range of urological disorders.

Obesity and Fibromyalgia are Associated with Difficult-to-Treat Rheumatoid Arthritis (D2T-RA) Independent of Age and Gender.
Luciano N, Barone E, Brunetta E, D'Isanto A, De Santis M, Ceribelli A, Caprioli M, Guidelli GM, Renna D, Selmi C.
Arthritis Res Ther. 2025 Jan 3;27(1):2. doi: 10.1186/s13075-024-03432-4. PMID: 39754234; PMCID: PMC11697877.

Background: There is still a significant proportion of patients with rheumatoid arthritis (RA) in whom multiple therapeutic lines are ineffective. These cases are defined by the EULAR criteria as Difficult-to-Treat RA (D2T-RA) for which there is limited knowledge of predisposing factors.
Objective: To identify the clinical features associated with D2T-RA in real-life practice.
Methods: We retrospectively collected demographic, clinical, and serological data on 458 patients consecutively seen for RA between January 2019 and January 2023. We compared patients fulfilling the D2T-RA criteria with the remaining RA cohort using univariate comparisons and logistic regression to determine the impact of clinical features, comorbidities on outcome variable, adjusted for confounders.
Results: Seventy-one/458 (16%) patients fulfilled the 2021 EULAR criteria for D2T-RA with no significant differences for age (median 62 years interquartile range -IQR- 58- 65 vs. 62 IQR 60 - 63 in non-D2T), gender prevalence (23% in both groups) and positivity rates for rheumatoid factors (62% vs. 62% in non-D2T) and Anti-Citrullinated Protein Antibodies (ACPA) (69% vs. 61% in non-D2T). Conversely, D2T-RA cases had significant longer disease duration (median 15 years IQR 13-17 vs. 10 years IQR 9-11 in non-D2T; $p < 0.0001$). D2T-RA also had more erosions at baseline (24% vs. 11% in non-D2T; $p < 0.0001$) and higher disease activity index (CDAI) at the last follow up visit (15.7 ± 10.5 vs. 7.5 ± 8.8 in non-D2T; $p < 0.0001$). D2T-RA cases suffered with higher frequency of obesity (33% vs. 19% in non-D2T, $p = 0.021$) and fibromyalgia (25% vs. 10% in non-D2T, $p < 0.0001$). The multivariate analysis confirmed the correlations of D2T-RA with disease duration (Odds ratio -OR- 1.06, 95% confidence interval -CI-1.03-1.09; $p < 0.0001$), baseline erosions (OR 2.73, 95% CI 1.28-5.82; $p = 0.009$), obesity (OR 2.22, 95% CI 1.10-4.50; $p = 0.026$) and fibromyalgia (OR 3.91, 95% CI 1.76-8.70; $p = 0.001$), independent of age and gender.
Conclusions: High disease activity, baseline erosions and disease duration are significantly associated with the D2T phenotype of RA while we confirm the importance of obesity and fibromyalgia.

Potential Difficult-to-Treat Psoriatic Arthritis Real-World Prevalence and Contributing Factors.
Alp G, Kara M, Cinakli H.
Clin Exp Rheumatol. 2025 Jan;43(1):41-47. doi: 10.55563/clinexprheumatol/pqpzef. Epub 2024 Aug 8. PMID: 39152760.

Objectives: The challenge of achieving low disease activity or remission in psoriatic arthritis (PsA) is an unmet need for many patients. Persistent disease activity in PsA may require treatment adjustments due to

its complex pathogenesis and varied tissue involvement, highlighting the need for dedicated definitions. This study evaluates patients' frequency and contributing factors with potential "difficult-to-treat PsA (D2TPsA)", similar to the EULAR definition of D2T rheumatoid arthritis.
Methods: A retrospective study was conducted at two tertiary centres to define potential D2TPsA, defined as failure of ≥1 conventional synthetic disease-modifying anti-rheumatic drug (DMARD) and ≥2 biological or targeted synthetic DMARDs with different mechanisms of action.
Results: Of the 171 patients included in the study, 116 (67.8%) were women; the average age was 48.16 ±11.23 years. D2TPsA was detected in 33 patients (19.3%). This group exhibited a longer disease duration, higher disease burden (median number of tender and swollen joints, patient and physician global evaluation, morning stiffness, erythrocyte sedimentation rate and C-reactive protein, DAPSA), HLA-B27 positivity, and higher prevalence of peripheral involvement. Secukinumab usage and mean glucocorticosteroid dosage were significantly higher in the D2TPsA group. Comorbidities such as fibromyalgia (FM) and diabetes mellitus (DM) and the median number of comorbidities were significantly higher in D2TPsA. In multivariate analysis, FM, DM, and HLA-B27 positivity were independently associated with D2TPsA.
Conclusions: This study underscores the impact of comorbidities on PsA disease activity and emphasises the need for further research to differentiate treatment challenges influenced by comorbidities from true treatment resistance.