CUTTING EDGE
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This e-newsletter - published by the CPRA to keep the medical-scientific and patient communities abreast of research advances on Chronic Overlapping Pain Conditions (COPCs) - contains abstracts of studies on the epidemiology, pathophysiology and clinical management of COPCs published between December 2023 and April 2024.

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Pathophysiology Studies

Is Nociplastic Pain, A New Pain Category, Associated with Biochemical, Hematological, and Inflammatory Parameters?

Telli H, Özdemir Ç.

Objective: The aim of the study was to evaluate the relationship between biochemical, hematological, and inflammatory parameters and pain in patients with nociplastic pain.

Methods: In this cross-sectional study, a total of 8632 patients, aged between 20 and 65, were evaluated according to the nociplastic pain diagnosis criteria determined by IASP. Excluding individuals who did not meet the criteria for nociplastic pain, the study included a total of 660 participants. The biochemical, hematological, and inflammatory parameters of all individuals were examined. The pain levels of the patients were assessed using the Visual Analogue Scale (VAS). The patients were categorized based on nociplastic pain types and pain regions for evaluation.

Results: In this study, the female gender was more prevalent both in all nociplastic pain categories and in all pain region groups ($p < 0.05$). In the nociplastic pain categories, it was observed that vitamin D levels were lower in patients with chronic widespread pain, while ferritin and C-reactive protein levels were higher in patients with chronic primary musculoskeletal pain. Among patients with chronic widespread pain with low hemoglobin and/or ferritin levels, the Visual Analog Scale activity score was higher. For patients with chronic widespread pain and low vitamin D levels and/or high erythrocyte sedimentation rate levels, the Visual Analog Scale rest score was higher. In patients with fibromyalgia and high parathyroid hormone levels, the Visual Analog Scale activity score was higher. For patients with fibromyalgia and high Neutrophil/Lymphocyte ratio levels, the Visual Analog Scale rest score was higher. In patients with chronic primary musculoskeletal pain and high erythrocyte sedimentation rate and/or C-reactive protein levels, the Visual Analog Scale activity score was higher. While vitamin B12 levels were found to be lower in patients with widespread pain, no significant relationship was identified between electrolytes, other blood count results, and nociplastic pain.

Conclusion: In our study, it was observed that levels of vitamin D in individuals with nociplastic pain were low, while erythrocyte sedimentation rate, C-reactive protein, and Neutrophil/Lymphocyte ratio were high, and hemoglobin and ferritin levels were elevated. Furthermore, these findings were found to be associated with both the presence of pain and the severity of pain assessed using the visual analog scale.

Nociplastic Pain Mechanisms and Toll-Like Receptors as Promising Targets for its Management.

Rodríguez-Palma EJ, Huerta de la Cruz S, Islas-Espinoza AM, Castañeda-Corral G, Granados-Soto V, Khanna R.

Nociplastic pain, characterized by abnormal pain processing without an identifiable organic cause, affects a significant portion of the global population. Unfortunately, current pharmacological treatments for this condition often prove ineffective, prompting the need to explore new potential targets for inducing analgesic effects in patients with nociplastic pain. In this context, toll-like receptors (TLRs), known for their role in the immune response to infections, represent promising opportunities for pharmacological intervention because they play a relevant role in both the development and maintenance of pain. Although TLRs have been extensively studied in neuropathic and inflammatory pain, their specific contributions to nociplastic pain remain less clear, demanding further investigation. This review consolidates current evidence on the connection between TLRs and nociplastic pain, with a specific focus on prevalent conditions like fibromyalgia, stress-induced pain, sleep deprivation-related pain, and irritable bowel syndrome. In addition, we explore the association between nociplastic pain and psychiatric comorbidities, proposing that modulating TLRs can potentially alleviate both pain syndromes and related psychiatric disorders. Finally, we discuss the potential sex differences in TLR signaling, considering the higher prevalence of nociplastic pain among women. Altogether, this review aims to shed light on nociplastic pain, its underlying mechanisms, and its intriguing relationship with

TLR signaling pathways, ultimately framing the potential therapeutic role of TLRs in addressing this challenging condition.

Multiple Reports on the Causal Relationship Between Various Chronic Pain and Gut Microbiota: A Two-Sample Mendelian Randomization Study.

Cai Y, Wen S, Hu J, Wang Z, Huang G, Zeng Q, Zou J.

Background: Previous evidence suggests a link between gut microbiota and chronic pain, but the causal relationship is not yet fully understood.
Methods: We categorized gut microbiota based on phylum, class, order, family, and genus levels and gathered pain-related information from the UKB and FinnGen GWAS project. Then, we conducted MR analysis to explore the potential causal relationship between gut microbiota and chronic pain at 12 specific locations.
Results: We have discovered a direct connection between genetic susceptibility in the gut microbiota (gut metabolites) and pain experienced at 12 specific locations. Notably, Serotonin (5-HT) and Glycine were found to be associated with a higher risk of pain in the extremities. On the other hand, certain microbial families and orders were found to have a protective effect against migraines. Specifically, the family Bifidobacteriaceae (IVW, FDR $p = 0.013$) was associated with a lower risk of migraines. Furthermore, the genus Oxalobacter (IVW, FDR $p = 0.044$) was found to be linked to an increased risk of low back pain. Importantly, these associations remained significant even after applying the Benjamini-Hochberg correction test. Our analysis did not find any heterogeneity in the data ($p > 0.05$), as confirmed by the Cochrane's Q-test. Additionally, both the MR-Egger and MR-PRESSO tests indicated no significant evidence of horizontal pleiotropy ($p > 0.05$).
Conclusion: Our MR analysis demonstrated a causal relationship between the gut microbiota and pain, highlighting its potential significance in advancing our understanding of the underlying mechanisms and clinical implications of microbiota-mediated pain.

Central Sensitization in Vulvodynia and Endometriosis: What Have We Been Overlooking So Far?

Cetera GE, Merli CEM, Boero V, Caia C, Facchin F, Barbara G, Monti E, Vercellini P.

Importance: Women experience more frequent and greater pain than men, although they receive less adequate treatment and are perceived as more anxious than males. Recent clinical research has lead to hypothesize a common etiology for overlapping chronic pain conditions and mood disorders, namely, central sensitization, which originates from an alteration of pain processing pathways in the central nervous system.
Objective: The aim of this review was to collect all available evidence regarding the potential role of central sensitization in vulvodynia and endometriosis.
Evidence acquisition: A systematic literature search was performed between July and August 2022 using the electronic database PubMed. The extracted data were summarized using a narrative approach.
Results: Ten articles were chosen for the review. Participants' mean age was 39.2 years (SD = 5.1). Among serum markers of central sensitization, nitric oxide levels were greater in women with endometriosis than in controls, whereas brain-derived neurotrophic factor and S100B levels differed among pain conditions with structural anomalies and those without. Functional magnetic resonance imaging showed different resting state networks between patients with endometriosis and controls. In neurophysiology studies, cases had reduced pain thresholds, compared with healthy controls. Lastly, self-reported questionnaires suggested a central component of pain in women with endometriosis-related dyspareunia and associated bladder/pelvic floor tenderness.
Conclusions and relevance: The management of vulvodynia and endometriosis may benefit from a new perspective, which considers their possible central etiology. It is compelling that treatment of pain starts to be considered a therapeutic goal in its own right.

Causal Effects of Endometriosis on SLE, RA and SS Risk: Evidence from Meta-Analysis and Mendelian Randomization.

Tang T, Zhong Y, Xu S, Yu H.

Background: Endometriosis is an underdiagnosed disorder that affects an estimated 6-10% of women of reproductive age. Endometriosis has been reported in epidemiological studies to be associated with autoimmune diseases. However, the relationship remains controversial.
Methods: A meta-analysis of observational studies was undertaken to evaluate the risk of autoimmune diseases in patients with endometriosis. The relevant studies were retrieved via the databases Medline, Embase and Web of Science until July 20, 2023. Mendelian randomization (MR) was subsequently utilized to scrutinize the causal influence of genetic predisposition toward endometriosis on three autoimmune diseases.
Results: The meta-analysis findings revealed a relationship between endometriosis and the onset of SLE (cohort studies: RR = 1.77, 95% confidence interval (CI): 1.47-2.13, I^2 = 0%; Case-control and cross-sectional studies: OR = 5.23, 95% CI: 0.74-36.98, I^2 = 98%), RA (cohort studies: RR = 2.18, 95% CI: 1.85-2.55, I^2 = 92%; Case-control and cross-sectional studies: OR = 1.40, 95% CI: 1.19-1.64, I^2 = 0%) and SS (cohort studies: RR = 1.49, 95% CI: 1.34-1.66, I^2 = 0%). Similarly, in our MR study, the results of the inverse-variance-weighted (IVW) model suggested that genetic predisposition to endometriosis was causally associated with an increased risk for SLE (OR = 1.915, 95% CI: 1.204-3.045, p = 0.006) and RA (OR = 1.005, 95% CI: 1.001-1.009, p = 0.014).
Conclusions: Both our meta-analysis and MR study indicate that endometriosis increases the risk of autoimmune diseases. These findings not only broaden our understanding of the genetic mechanisms underlying the comorbidity of endometriosis and autoimmune diseases, but also offer a new strategy for autoimmune disease prevention.

Evidence of Shared Genetic Factors in the Etiology of Gastrointestinal Disorders and Endometriosis and Clinical Implications for Disease Management.

Yang F, Wu Y, Hockey R; International Endometriosis Genetics Consortium; Doust J, Mishra GD, Montgomery GW, Mortlock S.

In clinical practice, the co-existence of endometriosis and gastrointestinal symptoms is often observed. Using large-scale datasets, we report a genetic correlation between endometriosis and irritable bowel syndrome (IBS), peptic ulcer disease (PUD), gastro-esophageal reflux disease (GORD), and a combined GORD/PUD medicated (GPM) phenotype. Mendelian randomization analyses support a causal relationship between genetic predisposition to endometriosis and IBS and GPM. Identification of shared risk loci highlights biological pathways that may contribute to the pathogenesis of both diseases, including estrogen regulation and inflammation, and potential therapeutic drug targets (CCKBR; PDE4B). Higher use of IBS, GORD, and PUD medications in women with endometriosis and higher use of hormone therapies in women with IBS, GORD, and PUD, support the co-occurrence of these conditions and highlight the potential for drug repositioning and drug contraindications. Our results provide evidence of shared disease etiology and have important clinical implications for diagnostic and treatment decisions for both diseases.

Neurodevelopmental Disorders as a Risk Factor for Temporomandibular Disorder: Evidence from Mendelian Randomization Studies.

Wu X, Li Z, Cui Y, Yan Z, Lu T, Cui S.

Objective: This study aims to clarify the incidence rate of temporomandibular joint disease in patients with mental disorders.
Methods: Data extracted from the Psychiatric Genomics Consortium and FinnGen databases employed the Mendelian Randomization (MR) method to assess the associations of three

neurodevelopmental disorders (NDDs)-Attention-Deficit/Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), and Tourette's Disorder (TD)-as exposure factors with Temporomandibular Disorder (TMD). The analysis used a two-sample MR design, employing the Inverse Variance Weighted (IVW) method to evaluate the relationships between these disorders and Temporomandibular Disorder. Sensitivity analysis and heterogeneity assessments were conducted. Potential confounding factors like low birth weight, childhood obesity, and body mass index were controlled for.

Results: The study found that ADHD significantly increased the risks for TMD (OR = 1.2342, 95%CI (1.1448-1.3307), $p < 0.00001$), TMD (including avohilmo) (OR = 1.1244, 95%CI (1.0643-1.1880), $p = 0.00003$), TMD-related pain (OR = 1.1590, 95%CI (1.0964-1.2252), $p < 0.00001$), and TMD-related muscular pain associated with fibromyalgia (OR = 1.1815, 95%CI (1.1133-1.2538), $p < 0.00001$), while other disorders did not show significant causal relationships.

Conclusion: This study reveals the elevated risk of various TMD aspects due to ADHD. Furthermore, we discuss the link between low vitamin D levels ADHD and TMD. Future research should address these limitations and delve further into the complex interactions between ADHD, ASD, TD, and TMD.

Causal Association Between Subtypes of Osteoarthritis and Common Comorbidities: A Mendelian Randomisation Study.

Thompson W, Swain S, Zhao SS, Kamps A, Coupland C, Kuo C, Bierma-Zeinstra S, Runhaar J, Doherty M, Zhang W.
Osteoarthr Cartil Open. 2023 Oct 21;5(4):100414. doi: 10.1016/j.ocarto.2023.100414. PMID: 38025156; PMCID: PMC10630649.

Objective: To investigate the causal association between Osteoarthritis (OA) and five comorbidities: depression, tiredness, multisite chronic pain, irritable bowel syndrome (IBS) and gout.

Design: This study used two-sample Mendelian Randomisation (MR). To select the OA genetic instruments, we used data from the largest recent genome-wide association study (GWAS) of OA (GO Consortium), with a focus on OA of the knee (62,497 cases, 333,557 controls), hip (35,445 cases, 316,943 controls) and hand (20,901 cases, 282,881 controls). Genetic associations for comorbidities were selected from GWAS for depression (246,363 cases, 561,190 controls), tiredness (449,019 participants), multisite chronic pain (387,649 participants), IBS (53,400 cases, 433,201 controls) and gout (6543 cases, 456,390 controls). We performed a bidirectional MR analysis using the inverse variance weighted method, for both joint specific and overall OA.

Results: Hip OA had a causal effect on multisite chronic pain (per unit change 0.02, 95% CI 0.01 to 0.04). Multisite chronic pain had a causal effect on knee (odd ratio (OR) 2.74, 95% CI 2.20 to 3.41), hip (OR 2.12, 95% CI 1.54 to 2.92), hand (OR 2.24, 95% CI 1.59 to 3.16) and overall OA (OR 2.44, 95% CI, 2.06 to 2.86). In addition, depression and tiredness had causal effects on knee and hand, but not hip, OA.

Conclusions: Apart from Hip OA to multisite chronic pain, other joint OA did not have causal effects on these comorbidities. In contrast, multisite chronic pain had a causal effect on any painful OA.

Exploring the Complexities of Pain Phenotypes: OMERACT 2023 Chronic Pain Working Group Workshop.

Pickles T, Cowern M, Christensen R, Nielsen SM, Simon LS, Jones CMP, Maxwell LJ, Shea B, Strand V, Touma Z, Toupin-April K, Mease P, Choy E.
Semin Arthritis Rheum. 2023 Dec 15;64:152342. doi: 10.1016/j.semarthrit.2023.152342. Epub ahead of print. PMID: 38128175.

Objective: To educate and discuss pain mechanisms (nociceptive, neuropathic, nociplastic) illuminating its possible impact when measuring different outcomes, which may modify, confound and potentially bias the outcome measures applied across various aspects of Rheumatic Musculoskeletal Diseases (RMDs) clinical trials.

Methods: In the plenary presentations, PM lectured on different pain mechanisms and impact on disease activity assessment. Data from two data sets of RMDs patients, which assessed the

prevalence and impact of nociplastic pain were presented and reviewed. Audience breakout group sessions and polling were conducted.

Results: Mixed pain etiologies may differentially influence disease activity assessment and therapeutic decision-making. Polling demonstrated a consensus on the need to assess different types of pain as a phenotype, as it constitutes an important contextual factor (a variable that is not an outcome of the trial, but needs to be recognized [and measured] to understand the study results), and to standardize across RMDs.

Conclusion: There is need for a standardized pain measure that can differentiate underlying pain mechanisms.

Immune Dysregulation, Inflammation in Characterizing Women with Vulvodynia, Depression, and Both.

Zheng A, Harlow BL, Gereige J.
J Womens Health (Larchmt). 2024 Mar;33(3):364-370. doi: 10.1089/jwh.2023.0422. Epub 2024 Jan 8. PMID: 38190297; PMCID: PMC10924120.

Background: Depression and vulvodynia are often comorbid. The onset of depression and vulvodynia may be immune and/or stress/environmentally induced. We explored whether vulvodynia, depression, or both occur in response to a Th1-mediated versus Th2-mediated immune response.

Materials and Methods: We analyzed data from a case-control study of clinically confirmed vulvodynia and history of depression determined through structured clinical interviews. Immune dysregulation and inflammation were categorized based on the following self-reported conditions: rheumatoid arthritis, Sjogren's disease, scleroderma, systemic lupus erythematosus, inflammatory bowel disease, fibromyalgia, osteoarthritis, polycystic ovarian syndrome, diabetes mellitus, uterine fibroids, asthma, atopic dermatitis, and allergic rhinitis. Logistic regression analyses were adjusted for marital status, body mass index, age, and pack years.

Results: Women with systemic immune dysregulation had higher odds of depression (adjusted odds ratio [aOR] = 1.61, confidence interval [95% CI]: 0.65-3.98), vulvodynia (aOR = 2.45, 95% CI: 1.00-5.96), and comorbid depression and vulvodynia (aOR = 4.93, 95% CI: 2.19-11.10) versus neither condition. Women reporting local immune dysregulation had similar odds of depression (aOR = 1.89, 95% CI: 0.99-3.59), vulvodynia (aOR = 2.12, 95% CI: 1.08-4.18), and comorbid depression and vulvodynia (aOR = 1.96, 95% CI: 0.98-3.90). Women with Th2 inflammation had similar odds of depression (aOR = 2.23, 95% CI: 1.05-4.77) and vulvodynia (aOR = 2.56, 95% CI: 1.20-5.49). Women with Th1 or Th2 inflammation had similar odds of comorbid depression and vulvodynia (aOR = 3.03, 95% CI: 1.48-6.19; aOR = 3.14, 95% CI: 1.49-6.60, respectively).

Conclusions: Our results suggest that an imbalance of cytokines, indicated by the presence of one or more immune-related health conditions, is associated with an increased risk of vulvodynia and/or depression.

Longitudinal Cytokine and Multi-Modal Health Data of an Extremely Severe ME/CFS Patient with HSD Reveals Insights into Immunopathology, and Disease Severity.

Jahanbani F, Sing JC, Maynard RD, Jahanbani S, Dafoe J, Dafoe W, Jones N, Wallace KJ, Rastan A, Maecker HT, Röst HL, Snyder MP, Davis RW.
Front Immunol. 2024 Apr 8;15:1369295. doi: 10.3389/fimmu.2024.1369295. PMID: 38650940; PMCID: PMC11033372.

Introduction: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) presents substantial challenges in patient care due to its intricate multisystem nature, comorbidities, and global prevalence. The heterogeneity among patient populations, coupled with the absence of FDA-approved diagnostics and therapeutics, further complicates research into disease etiology and patient managment. Integrating longitudinal multi-omics data with clinical, health, textual, pharmaceutical, and nutraceutical data offers a promising avenue to address these complexities, aiding in the identification of underlying causes and providing insights into effective therapeutics and diagnostic strategies.

Methods: This study focused on an exceptionally severe ME/CFS patient with hypermobility spectrum disorder (HSD) during a period of marginal symptom improvements. Longitudinal

cytokine profiling was conducted alongside the collection of extensive multi-modal health data to explore the dynamic nature of symptoms, severity, triggers, and modifying factors. Additionally, an updated severity assessment platform and two applications, ME-CFSTrackerApp and LexiTime, were introduced to facilitate real-time symptom tracking and enhance patient-physician/researcher communication, and evaluate response to medical intervention.

Results: Longitudinal cytokine profiling revealed the significance of Th2-type cytokines and highlighted synergistic activities between mast cells and eosinophils, skewing Th1 toward Th2 immune responses in ME/CFS pathogenesis, particularly in cognitive impairment and sensorial intolerance. This suggests a potentially shared underlying mechanism with major ME/CFS comorbidities such as HSD, Mast cell activation syndrome, postural orthostatic tachycardia syndrome (POTS), and small fiber neuropathy. Additionally, the data identified potential roles of BCL6 and TP53 pathways in ME/CFS etiology and emphasized the importance of investigating adverse reactions to medication and supplements and drug interactions in ME/CFS severity and progression.

Discussion: Our study advocates for the integration of longitudinal multi-omics with multi-modal health data and artificial intelligence (AI) techniques to better understand ME/CFS and its major comorbidities. These findings highlight the significance of dysregulated Th2-type cytokines in patient stratification and precision medicine strategies. Additionally, our results suggest exploring the use of low-dose drugs with partial agonist activity as a potential avenue for ME/CFS treatment. This comprehensive approach emphasizes the importance of adopting a patient-centered care approach to improve ME/CFS healthcare management, disease severity assessment, and personalized medicine. Overall, these findings contribute to our understanding of ME/CFS and offer avenues for future research and clinical practice.

Elevated DAS28-ESR in Patients with Rheumatoid Arthritis who Have Comorbid Fibromyalgia is Associated More with Tender Joint Counts than with Patient Global Assessment or Swollen Joint Counts: implications for Assessment of Inflammatory Activity.

Kannayiram S, Schmukler J, Li T, Goodson N, Sridhar A, Pincus T.
Clin Exp Rheumatol. 2024 May;42(5):1083-1090. doi: 10.55563/clinexprheumatol/vfvso2. Epub 2024 Mar 22. PMID: 38525998.

Objectives: More than 20% of rheumatoid arthritis (RA) patients have comorbid fibromyalgia (FM+), which may elevate DAS28-ESR (disease activity score 28-erythrocyte sedimentation rate) and other indices, resulting in challenges to assess inflammatory disease activity. Although several reports indicate that elevated patient global assessment (PATGL) may elevate DAS28 in the absence of inflammatory activity, less information is available concerning the other three components, tender joint count (TJC), swollen joint count (SJC), and erythrocyte sedimentation rate (ESR), to possibly elevate DAS28 in FM+ vs. FM- RA patients.

Methods: A PubMed search identified 14 reports which presented comparisons of DAS28-ESR and its four components in RA FM+ vs. FM- groups. Median DAS28, component arithmetic differences, pooled effect sizes and 95% confidence intervals were analysed in the FM+ vs. FM- groups.

Results: In FM+ vs. FM- groups, median DAS28 was 5.3 vs. 4.2, SJC 4.0 vs. 3.0, TJC 13.2 vs. 5.3, PATGL 61.6 vs. 39.9, ESR 26.3 vs. 26.5. DAS28-ESR was classified as "high" (>5.1) in 11/14 FM+ groups and "moderate" (3.2-5.1) in all 14 FM- groups. Effect sizes in FM+ vs. FM-groups for DAS28-ESR, SJC, TJC, PATGL, and ESR were large (≥0.8) in 10/14, 1/13, 12/13, 7/13, and 1/13 comparisons, respectively, and pooled effect sizes 0.84 (0.3, 1.4), 0.33 (-0.4, 1.0), 1.27 (0.01, 2.5), 0.91 (-0.6, 2.4), and 0.07 (-0.6, 0.7), respectively.

Conclusions: DAS28-ESR is elevated significantly in FM+ vs. FM- RA patients; pooled effect sizes were highest for TJC, followed by PATGL, SJC and ESR. The findings appear relevant to response and remission criteria, treat-to-target, and general management of RA.

Healthy Women Show More Experimentally Induced Central Sensitization Compared with Men.

Guekos A, Saxer J, Salinas Gallegos D, Schweinhardt P.
Pain. 2024 Jun 1;165(6):1413-1424. doi: 10.1097/j.pain.0000000000003144. Epub 2024 Jan 11. PMID: 38231588; PMCID: PMC11090033.

Women more often experience chronic pain conditions than men. Central sensitization (CS) is one key mechanism in chronic pain that can differ between the sexes. It is unknown whether CS processes are already more pronounced in healthy women than in men. In 66 subjects (33 women), a thermal CS induction protocol was applied to the dorsum of one foot and a sham protocol to the other. Spatial extent [cm2] of secondary mechanical hyperalgesia (SMH) and dynamic mechanical allodynia were assessed as subjective CS proxy measures, relying on verbal feedback. Changes in nociceptive withdrawal reflex magnitude (NWR-M) and response rate (NWR-RR) recorded through surface electromyography at the biceps and rectus femoris muscles were used as objective CS proxies. The effect of the CS induction protocol on SMH was higher in women than in men (effect size 2.11 vs 1.68). Nociceptive withdrawal reflex magnitude results were statistically meaningful for women (effect size 0.31-0.36) but not for men (effect size 0.12-0.29). Differences between men and women were not meaningful. Nociceptive withdrawal reflex response rate at the rectus femoris increased in women after CS induction and was statistically different from NWR-RR in men (median differences of 13.7 and 8.4% for 120 and 140% reflex threshold current). The objective CS proxy differences indicate that dorsal horn CS processes are more pronounced in healthy women. The even larger sex differences in subjective CS proxies potentially reflect greater supraspinal influence in women. This study shows that sex differences are present in experimentally induced CS in healthy subjects, which might contribute to women's vulnerability for chronic pain.

Chimeric and Mutant CARD9 Constructs Enable Analyses of Conserved and Diverged Autoinhibition Mechanisms in the CARD-CC Protein Family.

Staal J, Driege Y, Van Gaever F, Steels J, Beyaert R.

Caspase recruitment domain-containing protein (CARD)9, CARD10, CARD11, and CARD14 all belong to the CARD-coiled coil (CC) protein family and originated from a single common ancestral protein early in vertebrate evolution. All four proteins form CARD-CC/BCL10/MALT1 (CBM) complexes leading to nuclear factor-kappa-B (NF-κB) activation after upstream phosphorylation by various protein kinase C (PKC) isoforms. CBM complex signaling is critical for innate and adaptive immunity, but aberrant activation can cause autoimmune or autoinflammatory diseases, or be oncogenic. CARD9 shows a superior auto-inhibition compared with other CARD-CC family proteins, with very low spontaneous activity when overexpressed in HEK293T cells. In contrast, the poor auto-inhibition of other CARD-CC family proteins, especially CARD10 (CARMA3) and CARD14 (CARMA2), is hampering characterization of upstream activators or activating mutations in overexpression studies. We grafted different domains from CARD10, 11, and 14 on CARD9 to generate chimeric CARD9 backbones for functional characterization of activating mutants using NF-κB reporter gene activation in HEK293T cells as readout. CARD11 (CARMA1) activity was not further reduced by grafting on CARD9 backbones. The chimeric CARD9 approach was subsequently validated by using several known disease-associated mutations in CARD10 and CARD14, and additional screening allowed us to identify several previously unknown activating natural variants in human CARD9 and CARD10. Using Genebass as a resource of exome-based disease association statistics, we found that activated alleles of CARD9 correlate with irritable bowel syndrome (IBS), constipation, osteoarthritis, fibromyalgia, insomnia, anxiety, and depression, which can occur as comorbidities.

Brainstem Nuclei Responsive to Cystometry in Both Endometriosis and Cystitis Rat Models: C-fos Immunohistochemistry Study.

Bashkami AA, Kaddumi EG, Al-Saghbini M, Kenana AJ.

Purpose: Although the co-occurrence of interstitial cystitis (IC) and endometriosis (ENDO) is remarkably high, the exact pathophysiology for this co-occurrence is unknown. The convergence of the inputs from the involved structures to the same neuronal centers may suggest neuronal hyperexcitability as a mechanism for this co-occurrence.

Methods: The present study aimed to investigate the association between IC and ENDO, by studying the changes in brainstem responses to cystometry in a rat model of ENDO and cyclophosphamide (CYP)-induced IC using c-fos immunohistochemistry.

Results: Following cystometry the brainstem areas that had significant increase in c-fos expression in ENDO alone included: periaqueductal gray (PAG) nuclei, dorsal raphe nucleus, raphe obscurus nucleus, kolliker- Fuse areas, and area postrema. However, the brainstem areas that had increased significantly in the c-fos expression in the ENDO and CYP treated animals included: gigantocellular nucleus, lateral paragigantocellular nucleus, caudoventrolateral nucleus, rostroventrolateral/caudoventrolateral nucleus, lateral reticular nucleus, locus coeruleus, lateral PAG, raphe pallidus nucleus, raphe magnus nucleus, rostroventrolateral nucleus, dorsal motor nucleus of vagus, and solitary tract nucleus. Whereas only lateral parabrachial nucleus showed significant increase in c-fos expression in CYP treated animals alone.

Conclusions: The results of the present study demonstrate the overlap of brainstem nuclei that are excited by urinary bladder under ENDO and IC conditions. The pattern of hyperexcitability of the brainstem nuclei may help in understating the pathophysiology of IC and ENDO conditions.

Clinical Studies

Current Understanding of Nociplastic Pain.
Yoo YM, Kim KH.
Korean J Pain. 2024 Apr 1;37(2):107-118. doi: 10.3344/kjp.23326. Epub 2024 Mar 20. PMID: 38504389; PMCID: PMC10985487.

Nociplastic pain by the "International Association for the Study of Pain" is defined as pain that arises from altered nociception despite no clear evidence of nociceptive or neuropathic pain. Augmented central nervous system pain and sensory processing with altered pain modulation are suggested to be the mechanism of nociplastic pain. Clinical criteria for possible nociplastic pain affecting somatic structures include chronic regional pain and evoked pain hypersensitivity including allodynia with after-sensation. In addition to possible nociplastic pain, clinical criteria for probable nociplastic pain are pain hypersensitivity in the region of pain to non-noxious stimuli and presence of comorbidity such as generalized symptoms with sleep disturbance, fatigue, or cognitive problems with hypersensitivity of special senses. Criteria for definitive nociplastic pain is not determined yet. Eight specific disorders related to central sensitization are suggested to be restless leg syndrome, chronic fatigue syndrome, fibromyalgia, temporomandibular disorder, migraine or tension headache, irritable bowel syndrome, multiple chemical sensitivities, and whiplash injury; non-specific emotional disorders related to central sensitization include anxiety or panic attack and depression. These central sensitization pain syndromes are overlapped to previous functional pain syndromes which are unlike organic pain syndromes and have emotional components. Therefore, nociplastic pain can be understood as chronic altered nociception related to central sensitization including both sensory components with nociceptive and/or neuropathic pain and emotional components. Nociplastic pain may be developed to explain unexplained chronic pain beyond tissue damage or pathology regardless of its origin from nociceptive, neuropathic, emotional, or mixed pain components.

Nociceptive, Neuropathic, or Nociplastic Low Back Pain? The Low Back Pain Phenotyping (BACPAP) Consortium's International and Multidisciplinary Consensus Recommendations.
Nijs J, Kosek E, Chiarotto A, Cook C, Danneels LA, Fernández-de-Las-Peñas C, Hodges PW, Koes B, Louw A, Ostelo R, Scholten-Peeters GGM, Sterling M, Alkassabi O, Alsobayel H, Beales D, Bilika P, Clark JR, De Baets L, Demoulin C, de Zoete RMJ, Elma Ö, Gutke A, Hanafi R, Hotz Boendermaker S, Huysmans E, Kapreli E, Lundberg M, Malfliet A, Meziat Filho N, Reis FJJ, Voogt L, Zimney K, Smeets R, Morlion B, de Vlam K, George SZ.
Lancet Rheumatol. 2024 Mar;6(3):e178-e188. doi: 10.1016/S2665-9913(23)00324-7. Epub 2024 Feb 1. PMID: 38310923.

The potential to classify low back pain as being characterised by dominant nociceptive, neuropathic, or nociplastic mechanisms is a clinically relevant issue. Preliminary evidence

suggests that these low back pain phenotypes might respond differently to treatments; however, more research must be done before making specific recommendations. Accordingly, the low back pain phenotyping (BACPAP) consortium was established as a group of 36 clinicians and researchers from 13 countries (five continents) and 29 institutions, to apply a modified Nominal Group Technique methodology to develop international and multidisciplinary consensus recommendations to provide guidance for identifying the dominant pain phenotype in patients with low back pain, and potentially adapt pain management strategies. The BACPAP consortium's recommendations are also intended to provide direction for future clinical research by building on the established clinical criteria for neuropathic and nociplastic pain. The BACPAP consortium's consensus recommendations are a necessary early step in the process to determine if personalised pain medicine based on pain phenotypes is feasible for low back pain management. Therefore, these recommendations are not ready to be implemented in clinical practice until additional evidence is generated that is specific to these low back pain phenotypes.

Application of a Clinical Approach to Diagnosing Primary Pain: Prevalence and Correlates of Primary Back and Neck Pain in a Community Physiatry Clinic.
Schubiner H, Lowry WJ, Heule M, Ashar YK, Lim M, Mekaru S, Kitts T, Lumley MA.
J Pain. 2024 Mar;25(3):672-681. doi: 10.1016/j.jpain.2023.09.019. Epub 2023 Sep 28. PMID: 37777033.

Chronic back or neck pain (CBNP) can be primary (nociplastic or neuroplastic; without clear peripheral etiology) or secondary (to nociceptive or neuropathic causes). Expanding on available models of nociplastic pain, we developed a clinic-ready approach to diagnose primary/nociplastic pain: first, a standard physical exam and review of imaging to rule out secondary pain; and second, a detailed history of symptom presentation to rule in primary pain. We trained a physician who evaluated 222 patients (73.9% female, age M = 59.6) with CBNP; patients separately completed pain and psychosocial questionnaires. We estimated the prevalence of primary CBNP and explored biomedical, imaging, and psychological correlates of primary CBNP. Although almost all patients (97.7%) had at least 1 spinal anomaly on imaging, the diagnostic approach estimated that 88.3% of patients had primary pain, 5.0% had secondary pain, and 6.8% had mixed pain. Patients with primary pain were more likely than the other 2 groups of patients (combined as "non-primary pain") to report certain functional conditions, central sensitization, and features such as sensitivity to light touch, spreading pain, and pain worsening with stress; however, no difference was detected in depression, anxiety, and pain catastrophizing between those with primary and nonprimary pain. These findings are consistent with prior estimates that 85 to 90% of CBNP is "nonspecific." Further research is needed to validate and perhaps refine this diagnostic approach, which holds the potential for better outcomes if patients are offered treatments targeted to primary pain, such as pain neuroscience education and several emerging psychological therapies. PERSPECTIVE: We developed an approach to diagnose chronic primary pain, which was applied in a physiatry clinic to 222 patients with CBNP. Most patients (88.3%) had primary pain, despite almost universal anomalies on spinal imaging. This diagnostic approach can guide educational and psychological treatments tailored for primary pain.

Case Report: Initial Successful Treatment of Migraine and Irritable Bowel Syndrome with a Low-FOMAP Diet.
Bonakdar RA, Sweeney MM, Garvey C, White AA, VanNoord MU.
J Am Nutr Assoc. 2023 Dec 18:1-6. doi: 10.1080/27697061.2023.2288081. Epub ahead of print. PMID: 38108544.

Objective: Migraine and irritable bowel syndrome (IBS) can be difficult-to-treat comorbidities that may be driven by underlying gut-brain axis dysfunction. This report describes utilization of a low-FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet (LFD) in a patient with refractory migraine and co-occurring IBS.
Methods: After unremarkable physical and neurological examinations, a 57-year-old woman with IBS and chronic migraine was started on a LFD under the guidance of a registered dietician. Psychometrically validated surveys administered at baseline and initial follow-up assessed patient-reported outcomes related to migraine and IBS symptoms.

Results: At baseline, the patient reported 80/90 migraine days with average pain of 8/10, a Migraine Disability Assessment (MIDAS) score of 33, and Headache Impact Test-6 (HIT-6) score of 64, the latter 2 scores indicating severe disability. Baseline IBS symptom severity was noted at 9/10. Within 1 week on a LFD, the patient's IBS symptoms and migraines improved in both frequency and intensity of episodes. After 5 weeks on a LFD elimination, the patient's clinical improvement continued and she reported significant reduction in migraines, with average pain of 1/10 and IBS severity of 3/10. The patient also improved from severe to minimal levels of disability on validated measures (MIDAS, HIT-6, and IBS Patient Global Impression of Change).

Conclusion: This is the first case report detailing successful initial treatment of migraine and co-occurring IBS utilizing a dietician-guided LFD. There are a number of important reasons for potential improvement in these gut-brain axis disorders which are reviewed as well as an implication for long-term management and food reintroduction. Larger, randomized trials evaluating a LFD in diverse individuals with migraine and co-occurring IBS are warranted to help confirm these results.

Functional Somatic Syndromes are Associated with Inferior Outcomes and Increased Complications after Hip and Knee Arthroplasty: A Systematic Review.
Masood R, Mandalia K, Pagani NR, Moverman MA, Puzzitiello RN, Menendez ME, Salzler MJ.
Arthroplasty. 2024 Jan 3;6(1):2. doi: 10.1186/s42836-023-00223-1. PMID: 38173047; PMCID: PMC10765755.

Background: Functional somatic syndromes (FSSs), defined as chronic physical symptoms with no identifiable organic cause, may impact results after hip and knee arthroplasty. The purpose of this study was to perform a systematic review assessing the relationship between FSSs and clinical outcomes after primary total hip arthroplasty (THA), total knee arthroplasty (TKA), and unicompartmental knee arthroplasty (UKA).

Methods: The PubMed and Web of Science databases were queried from January 1955 through December 2021 for studies investigating the impact of at least one FSS (fibromyalgia, irritable bowel syndrome (IBS), chronic headaches, and chronic low back pain) on outcomes after primary THA/TKA/UKA. Outcomes of interest included patient-reported outcome measures (PROMs), postoperative opioid use, complications, revisions, and costs of care.

Results: There were twenty-eight studies, including 768,909 patients, of which 378,384 had an FSS. Five studies reported preoperative PROMs prior to THA/TKA, all of which showed worse PROMs among patients with at least 1 FSS diagnosis. Thirteen studies reported postoperative PROMs after THA/TKA, all of which demonstrated worse PROMs among patients with at least 1 FSS diagnosis. Patients with FSS diagnoses were more likely to continue using opioids at 3, 6, and 12 months following TKA, THA, and UKA. Medical and surgical complications, as well as revision rates, were higher among patients with FSSs.

Conclusion: Patients with FSSs have inferior PROMs and are at increased risk for prolonged postoperative opioid use, medical and surgical complications, and revision after hip and knee arthroplasty. Improved understanding of the factors influencing the success of hip and knee arthroplasty is critical. Future studies should address the biopsychosocial determinants of health that can impact outcomes after total joint arthroplasty.

Relationship Between Nociplastic Pain Involvement and Medication Use, Symptom Relief, and Adverse Effects Among People Using Medical Cannabis for Chronic Pain.
Scott JR, Williams DA, Harte SE, Harris RE, Litinas E, Sisley S, Clauw DJ, Boehnke KF.
Clin J Pain. 2024 Jan 1;40(1):1-9. doi: 10.1097/AJP.0000000000001164. PMID: 37823303.

Objectives: Cannabis is increasingly being used for chronic pain management, but cannabis' effects remain poorly characterized in chronic nociplastic pain (NPP), which is posited to be caused by disturbances in nervous system pain processing. In this cross-sectional study (n=1213), we used the 2011 Fibromyalgia (FM) Survey Criteria as a surrogate measure for degree of NPP among individuals using medical cannabis for chronic pain.

Methods: Using a quartile-split, we investigated associations between the degree of NPP and medication use, cannabis use characteristics, and symptom relief. Continuous variables were assessed using one-way analysis of variance and categorical variables with Pearson χ^2 test and binomial logistic regression for calculation of odds ratios.

Results: Participants were predominately female (59%), with a mean ± SD age of 49.4±13.6 years. Higher FM scores were associated with less self-reported improvement in pain and health since initiating medical cannabis use, as well as more cannabis-related side effects. Paradoxically, higher FM scores were also associated with higher usage of concomitant medication use (including opioids and benzodiazepines) but also with substituting cannabis for significantly more medication classes, including opioids and benzodiazepines.

Discussion: This article presents evidence that individuals in higher NPP quartiles have higher analgesic intake, higher odds of substituting cannabis for medications, higher side effect burden, and lower therapeutic effect from cannabis. These seemingly contradictory findings may reflect higher symptom burden, polypharmacy at baseline, or that NPP may be challenging to treat with cannabis. Further research is necessary to further explain cannabinoid effects in NPP.

Functional Somatic Syndromes Are Associated with Varied Postoperative Outcomes and Increased Opioid Use After Spine Surgery: A Systematic Review.

Masood R, LeRoy TE, Moverman MA, Feldman MW, Rogerson A, Salzler MJ.
Global Spine J. 2023 Nov 21:21925682231217706. doi: 10.1177/21925682231217706. Epub ahead of print. PMID: 38124313.

Study design: Systematic Review.

Objective: To perform a systematic review assessing the relationship between functional somatic syndromes (FSSs) and clinical outcomes after spine surgery.

Methods: A systematic review of online databases (PubMed and Web of Science) through December 2021 was conducted via PRISMA guidelines to identify all studies investigating the impact of at least one FSS (fibromyalgia, irritable bowel syndrome (IBS), chronic headaches/migraines, interstitial cystitis, chronic fatigue syndrome, multiple chemical sensitivity) on outcomes after spine surgery. Outcomes of interest included patient reported outcome measures (PROMs), postoperative opioid use, cost of care, complications, and readmission rates.

Results: A total of 207 records were identified. Seven studies (n = 40,011 patients) met inclusion criteria with a mean MINORS score of 16.6 out of 24. Four studies (n = 21,086) reported postoperative opioid use; fibromyalgia was a strong risk factor for long-term opioid use after surgery whereas the association with chronic migraines remains unclear. Two studies (n = 233) reported postoperative patient reported outcome measures (PROMs) with mixed results suggesting a possible association between fibromyalgia and less favorable PROMs. One study (n = 18,692) reported higher postoperative complications in patients with fibromyalgia.

Conclusion: Patients with fibromyalgia and possibly migraines are at higher risk for prolonged postoperative opioid use and less favorable PROMs after spine surgery. There is limited research on the relationship between other Functional somatic syndromes (FSSs) and outcomes following spine surgery. Growing evidence suggests the variation in outcomes after spine procedures may be attributed to non-identifiable organic patient factors such as FSSs.

Correlation Between Endometriosis and Migraine Features: Results from a Prospective Case-Control Study.

Selntigia A, Exacoustos C, Ortoleva C, Russo C, Monaco G, Martire FG, Rizzo G, Della-Morte D, Mercuri NB, Albanese M.
Cephalalgia. 2024 Mar;44(3):3331024241235210. doi: 10.1177/03331024241235210. PMID: 38436302.

Background: Endometriosis and migraine frequently coexist, but only a limited number of studies have focused on their mutual association. The aim of our study was to investigate, in untreated women with comorbid endometriosis/adenomyosis and migraine, the correlation between headache features and endometriotic subtypes and their possible relationship with pain severity and disease disability.

Methods: Fifty women affected by endometriosis/adenomyosis and migraine matched (1:2) with 100 patients with endometriosis alone and 100 patients with only migraine were recruited and underwent pelvic ultrasound imaging and neurological examination.

Results: Severe adenomyosis, posterior and anterior deep infiltrating endometriosis (p = 0.027, p = 0.0031 and p = 0.029, respectively) occurred more frequently in women with migraine.

Dysmenorrhea was the most commonly reported symptom in women with endometriosis and migraine and the mean VAS scores of all typical endometriotic symptoms were significantly higher in the presence of comorbidity. Women with both migraine and endometriosis reported significant higher pain intensity (p = 0.004), higher monthly migraine days (p = 0.042) and increased HIT 6-scores (p = 0.01), compared with those without endometriosis.

Conclusions: Our results demonstrated that the co-occurrence of migraine in untreated women with endometriosis is associated with more severe gynecological infiltrations and correlated with increased pain intensity and disease disability.

Impact of Family History for Endometriosis, Migraine, Depression and Early Menopause on Endometriosis Symptoms, Localization and Stage: A Case Control Study.

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

Introduction: Endometriosis is a common disabling pain condition in women of childbearing age, frequently showing familial clustering. Nevertheless, little is known about whether familial predispositions influence its severity or presentation. In this study, we investigate disease characteristics in endometriosis patients with a family history (FH) for endometriosis or the comorbidities migraine, depression and early menopause (EMP).

Materials and methods: We performed an observational case-control study enrolling women with histologically confirmed endometriosis in a tertiary center. Based on surgical findings, patient records and phone interviews, we examined the relations between a FH for endometriosis, migraine, depression or EMP and endometriotic signs and symptoms, such as response to combined hormonal contraceptives (CHC) and analgesics, disease localization, infiltration depth, Enzian- and rASRM-scores.

Results: A positive FH for endometriosis, migraine, depression or EMP was reported by 10.2 %, 33.4 %, 32.6 % and 9.9 % of the 344 patients. A positive FH of endometriosis was associated with an increased risk for high rASRM-scores (rASRM 3 + 4: OR 2.74 (95 % CI 1.16-6.49), p = 0.017) and the presence of endometriomas (OR 2.70 (1.22-5.95), p = 0.011). A positive FH for migraine was associated with less response of endometriosis symptoms to CHC (OR 0.469 (0.27-0.82) p = 0.025). Depression in the family was linked to less severe rASRM-scores (rASRM 3 + 4: OR 0.63 (0.39-0.99), p = 0.046) and less endometriomas (OR 0.58 (0.67-0.92), p = 0.02), but increased the risk of both migraine (OR 1.66 (1.01-2.73), p = 0.043) and depression (OR 3.04 (1.89-4.89), p < 0.001) while showing a better response to CHC (OR 2.0 (1.15-3.48, p < 0.001). Patients with EMP in their family reported more current endometriosis symptoms at present (OR 3.72 (1.67-8.30), p = 0.001), more dysmenorrhea (OR 2.13 (1.04-4.35), p = 0.037), more frequent severe dysmenorrhea (OR 2.32 (1.14-4.74), p = 0.019) and suffered significantly more often > 5 days of non-cyclic pain (OR 3.58 (1.72-7.44), p < 0.001).

Conclusions: Around 30% reported a positive FH for migraine or depression. Patients with a positive FH for endometriosis, migraine, depression or EMP differ in symptoms and surgical findings when compared to controls. While a FH for endometriosis is associated with higher rASRM scores and more endometriomas, women with a FH for depression had lower rASRM scores and less endometriomas while responding better to CHC. In contrast, women with a FH for migraine showed less response to CHC.

Patterns of Comorbidities Differentially Affect Long-term Functional Evolution and Disease Activity in Patients with 'Difficult to Treat' Rheumatoid Arthritis.

Bertsias A, Flouri ID, Repa A, Avgoustidis N, Kalogiannaki E, Pitsigavdaki S, Bertsias G, Sidiropoulos P.

Background: Characterisation of the long-term outcome of patients with 'difficult to treat' (D2T) rheumatoid arthritis and factors contributing to its evolution are unknown. Herein, we explored the heterogeneity and contributing factors of D2T long-term outcome.

Methods: Patients included from a prospective single centre cohort study. The EULAR definition of D2T was applied. Longitudinal clustering of functional status (modified Health Assessment

Questionnaire (mHAQ)) and disease activity (Disease Activity Score-28 (DAS28)) were assessed using latent-class trajectory analysis. Multiple linear mixed models were used to examine the impact of comorbidities and their clusters on the long-term outcome.

Results: 251 out of 1264 patients (19.9%) were identified as D2T. Younger age, fibromyalgia, osteoarthritis, DAS28-erythrocyte sedimentation rate (ESR) at first biological or targeted synthetic disease-modifying antirheumatic drug (b/ts-DMARD) initiation and failure to reduce DAS28-ESR scores within the first 6 months of b/ts-DMARD therapy were significant predictors of patients becoming D2T. Long-term follow-up (total of 5872 person-years) revealed four groups of functional status evolution: 18.2% had stable, mildly compromised mHAQ (mean 0.41), 39.9% had gradual improvement (1.21-0.87) and two groups had either slow deterioration or stable significant functional impairment (HAQ>1). Similarly, four distinct groups of disease activity evolution were identified. Among the different clusters of comorbidities assessed, presence of 'mental-health and pain-related illnesses' or 'metabolic diseases' had significant contribution to mHAQ worsening (p<0.0001 for both) and DAS28 evolution (p<0.0001 and p=0.018, respectively).

Conclusion: D2T patients represent a heterogeneous group in terms of long-term disease course. Mental-health/pain-related illnesses as well as metabolic diseases contribute to long-term adverse outcomes and should be targeted in order to optimise the prognosis of this subset of rheumatoid arthritis.

Is Reduced Heart Rate Variability Associated with Functional Somatic Disorders? A Cross-sectional Population-based Study; DanFunD.

Jørgensen T, Dantoft TM, Petersen MW, Gormsen L, Winter-Jensen M, Fink P, Linneberg A, Benros ME, Eplov LF, Bjerregaard AA, Schovsbo SU, Brinth LS.

Objectives: It has been hypothesised that functional somatic disorders (FSD) could be initiated by sympathetic predominance in the autonomic nervous system as measured by low heart rate variability (HRV). Earlier studies on the association between HRV and FSD are small case-control studies hampered by selection bias and do not consider the great overlap between the various FSDs. The aim of the present study is to assess any associations between HRV and various FSDs and whether chronic stress confounds such an association.

Design: A cross-sectional general population-based study.

Setting: The Danish Study of Functional Somatic Disorders conducted 2013-2015 in 10 municipalities in the western part of Greater Copenhagen, Denmark.

Participants: A total of 6891 men and women aged 18-72 years were included in the analyses after exclusion of 602 persons with missing HRV data. Various delimitations of FSD (chronic fatigue, chronic widespread pain, irritable bowel and bodily distress syndrome) were identified by validated questionnaires and diagnostic interviews. HRV parameters in time and frequency domains were calculated from successive beat-to-beat heart rate (HR) data using the 'E-motion' HR monitor device during 7 min of supine rest. Chronic stress was assessed by Cohen's self-perceived stress scale.

Outcome measures: Logistic regression analyses were used to calculate possible associations between the various delimitations of FSD and HRV adjusting for chronic stress.

Results: Persons with FSD had a slightly higher mean HR and lower HRV as measured by time domain parameters, whereas associations with frequency domain parameters were not consistent. Adjusting for chronic stress attenuated associations slightly.

Conclusion: The study supports a sympathetic predominance in persons with FSD, which could not be entirely explained by chronic stress. However, it is not possible to conclude whether the association is a causal factor to or a consequence of FSD.

Beyond Vulvodynia: From a Correct Diagnosis to a Multidisciplinary Care Program. A Referral Center Experience.

Boero V, Cetera GE, Caia C, Merli CEM, Gramegna G, Pesce E, Barbara G, Ermelinda M, Vercellini P.

Background: Vulvodynia is a chronic pain condition without an identifiable cause. As such, it is a diagnosis of exclusion, and all other causes of vulvar pain should be excluded. Although a standard treatment for vulvodynia has not been established yet, multidisciplinary care programs appear to be effective.

Purpose: The aim of this retrospective monocentric study was to analyze the prevalence of vulvodynia among women referred to our institution for a suspected diagnosis and to evaluate the efficacy of a multidimensional treatment plan. The primary outcome was the prevalence of vulvodynia following differential diagnosis. Secondary outcomes included: prevalence of the differential diagnoses, symptom resolution rate following treatment, and the relation between persistence of symptoms and (a) patients' age; (b) coexisting chronic overlapping pain conditions (COPCs).

Results: After having ruled out all other causes of vulvar pain, only 40.1% of women were considered as affected by vulvodynia. The most frequent differential diagnoses included lower genital tract infections (25.3%), vulvar lichen sclerosus (17.6%) and vulvovaginal atrophy (8.2%). Following a multidisciplinary care program, resolution of symptoms was observed in 13.6% cases, improvement in 64.3% and persistence in 21.9%. We did not find a statistically significant association between persistence of symptoms and age > 38 years (OR 2.10; $p = 0.30$). Women with one or more COPCs other than vulvodynia had a 75% increased risk of not obtaining a resolution of symptoms (OR 1.75; $p = 0.44$).

Conclusion: A thorough differential diagnosis and a multidisciplinary care program may represent a first way out of the muddle in the management of these patients.

Measuring Persistent Somatic Symptom Related Stigmatisation: Development of the Persistent Somatic Symptom Stigma scale for Healthcare Professionals (PSSS-HCP).

Objective: Persistent somatic symptoms (PSS) describe recurrent or continuously occurring symptoms such as fatigue, dizziness, or pain that have persisted for at least several months. These include single symptoms such as chronic pain, combinations of symptoms, or functional disorders such as fibromyalgia or irritable bowel syndrome. While stigmatisation by healthcare professionals is regularly reported, there are limited measurement instruments demonstrating content validity. This study develops a new instrument to measure stigmatisation by healthcare professionals, the Persistent Somatic Symptom Stigma scale for Healthcare Professionals (PSSS-HCP).

Methods: Development was an iterative process consisting of research team review, item generation and cognitive interviewing. We generated a longlist of 60 items from previous reviews and qualitative research. We conducted 18 cognitive interviews with healthcare professionals in the United Kingdom (UK). We analysed the relevance, comprehensibility and comprehensiveness of items, including the potential for social desirability bias.

Results: After research team consensus and initial feedback, we retained 40 items for cognitive interviewing. After our first round of interviews (n = 11), we removed 20 items, added three items and amended five items. After our second round of interviews (n = 7), we removed four items and amended three items. No major problems with relevance, comprehensibility, comprehensiveness or social desirability were found in remaining items.

Conclusions: The provisional version of the PSSS-HCP contains 19 items across three domains (stereotypes, prejudice, discrimination), demonstrating sufficient content validity. Our next step will be to perform a validation study to finalise item selection and explore the structure of the PSSS-HCP.

Neuropathic and Nociplastic Pain Profiles are Common in Adult Chronic Nonbacterial Osteitis (CNO).

Chronic nonbacterial osteitis (CNO) is a rare musculoskeletal disease causing chronic bone pain. It is known that chronic musculoskeletal pain may involve other mechanisms than nociceptive pain only. We investigate the prevalence of neuropathic and nociplastic pain in adult CNO and their association with clinical characteristics and treatment outcomes. Survey study among the Dutch adult CNO cohort (n = 84/195 participated), including PAIN-detect for neuropathic pain, and the Central Sensitization Inventory (CSI), Fibromyalgia Rapid Screening Tool (FiRST), and ACTTION-APS Pain Taxonomy (AAPT) for nociplastic pain. Clinical characteristics and CNO-related bone pain scores were compared between patients with exclusive nociceptive pain and those with nociceptive pain plus neuropathic and/or nociplastic pain (mixed pain). 31% (95% CI 21-41) of patients classified as likely having neuropathic pain according to PAIN-detect. 53% (41-64) of patients displayed central sensitization on CSI, 61% (50-72) screened positive for fibromyalgia on FiRST and 14% (7-23) of patients fulfilled the AAPT criteria, all indicative of nociplastic pain. Mixed pain was associated with longer diagnostic delay (mean difference 2.8 years, 95% CI 0.4-5.2, p = 0.023), lower educational level (72% versus 20%, p < 0.001), and opioid use (37% versus 13%, p = 0.036). Despite comparable disease severity and extent, patients with mixed pain reported significantly higher CNO-related bone pain scores. This study demonstrates the high prevalence of mixed pain in adult CNO, in which neuropathic and nociplastic pain exist alongside nociceptive inflammatory bone pain. Disease burden in CNO may extend beyond inflammatory activity, highlighting the need for a multifaceted management approach.

Epidemiology Studies

Veterans with Chronic Pain: Examining Gender Differences in Pain Type, Overlap, and the Impact of Post-Traumatic Stress Disorder.

Hadlandsmyth K, Driscoll MA, Johnson NL, Mares JG, Mengeling MA, Thomas EBK, Norman SB, Lund BC.

Background: Women are more likely to experience multiple overlapping pain conditions (MOPCs) relative to men. Post-traumatic stress disorder can negatively impact the severity and trajectory of chronic pain and its treatment. Specific associations between gender, post-traumatic stress disorder (PTSD), and MOPCs require further examination.
Methods: A cohort of all Veterans in 2021 who met criteria for one or more of 12 chronic pain types was created using national Veterans Health Administration administrative data. MOPCs were defined as the number of pain types for which each patient met criteria. Multivariable logistic regression models estimated gender differences in frequency for each of the 12 pain subtypes, after controlling for demographics and comorbidities. Negative binomial regression was used to estimate gender differences in the count of MOPCs and to explore moderation effects between gender and PTSD.
Results: The cohort included 1,936,859 Veterans with chronic pain in 2021, which included 12.5% women. Among those with chronic pain, women Veterans had higher rates of MOPCs (mean = 2.3) relative to men (mean = 1.9): aIRR = 1.31, 95% CI: 1.30-1.32. PTSD also served as an independent risk factor for MOPCs in adjusted analysis (aIRR = 1.23, 95% CI: 1.23-1.24). The interaction term between gender and PTSD was not significant (p = 0.87). Independent of PTSD, depressive disorders also served as a strong risk factor for MOPCs (aIRR = 1.37, 95% CI: 1.36-1.37).
Conclusions: Individuals with MOPCs and PTSD may have complex treatment needs. They may benefit from highly coordinated trauma-sensitive care and integrated interventions that simultaneously address pain and PTSD.
Significance: Women were significantly more likely than men to experience MOPCs. PTSD was also significantly, independently, associated with MOPCs. Patients, particularly women, may benefit from tailored interventions that address both trauma and MOPCs.

Age and Sex Differences in Comorbidities in Adult Temporomandibular Disorders: A Cross-Sectional Study Using Korea National Health and Nutrition Examination Survey (KNHANES).

Park HJ, Auh QS.

Objectives: To investigate the relationship between Temporomandibular disorder (TMD) and associated comorbidities in groups matched according to age and sex.

Methods: Using data from the cross-sectional fifth Korea National Health and Nutrition Examination Survey (KNHANES). Of the 25,534 eligible KNHANES, 17,762 adults aged ≥19 years who responded to survey questionnaire on TMD and comorbidities. Subjects were classified into eight groups according to age and sex. Logistic regression analyses were performed to evaluate the association between TMD and comorbidities according to age and sex.

Results: Of the enrolled participants, 2,107 (11.86%) complained of ≥1 TMD symptoms. In all groups, odds ratios (ORs) for prevalence of TMD were >1 in those with tinnitus. Rhinitis was closely associated with TMD in 6 groups. ORs for TMD with comorbidities according to age and sex were as follows: hypertension, men aged 50-64 years (OR 0.62; CI 0.41-0.94); ischemic heart disease, men aged 35-49 years (4.38; 1.54-12.47); osteoarthritis, women aged 50-64 years (1.38; 1.03-1.86); diabetes mellitus, men aged 35-49 years (0.21; 0.05-0.88); depression, men aged 50-64 years (1.68; 1.00-2.83), women aged 35-49 years (1.39; 1.05-1.85) and women aged 65-80 years (2.01; 1.46-2.77); migraine, men aged 50-64 years (1.60; 1.14-2.25), women aged d35-49 years (1.44; 1.14-1.81) and women aged 35-49 years (1.43; 1.07-1.90); cold hypersensitivity in the hands and feet, men aged 19-34 years (1.64; 1.05-2.58), men aged 35-49 years (1.68; 1.04-2.70), men aged 65-80 years (1.74; 1.09-2.75) and women aged 35-49 years (1.45; 1.15-1.84); olfaction disorder, men aged 50-64 years (2.49; 1.39-4.43); voice disorder, men aged 50-64 years (2.25; 1.28-3.96) and women aged 65-80 years (1.69; 1.09-2.63).

Conclusions: This study confirmed that the types and effects of comorbidities related to prevalence of TMD may differ according to the patient's age and sex and this result will increase the predictability of the onset of TMD.

Orofacial Pain and Risk of Dysphagia in Women with Fibromyalgia: A Cross-Sectional Observational Study.

Del Carmen Villaverde-Rodríguez M, Correa-Rodríguez M, Casas-Barragán A, Tapia-Haro RM, Aguilar-Ferrándiz ME.

Objective: This study aims to analyze the frequency of dysphagia risk and swallowing-associated quality of life (QoL) in a sample of women with fibromyalgia syndrome (FMS) and examine the potential relationship between risk of dysphagia and chronic orofacial pain (COP) in a sample of women with FMS.

Method: A cross-sectional observational study was conducted in 46 women with FMS. COP was assessed by mouth opening, the orofacial visual analog scale (VAS), and the craniofacial pain and disability inventory (CF-PDI). Risk of dysphagia was assessed using the Eating Assessment Tool (EAT-10) and the volume-viscosity swallowing test (V-VST). Swallowing-associated QoL was determined using the Swallowing Quality of Life (SWAL-QOL) questionnaire.

Results: Thirty patients were identified as being at risk for dysphagia (65.21%) using the EAT-10 and, according to the SWAL-QOL, 41.30% of patients had alterations in QoL associated with swallowing. The EAT-10 correlated positively with orofacial VAS, CF-PDI-total, CF-PDI-pain and disability, and CF-PDI-jaw-functional status. In relation to SWAL-QOL, negative correlations were observed for orofacial VAS, CF-PDI-total, CF-PDI-pain and disability, and CF-PDI-jaw-functional status. Patients at risk of dysphagia (EAT-10 and V-VST) had significantly higher scores in orofacial VAS ($p = .002$ and $p = .015$), CF-PDI-total ($p = .006$ and $p = .014$), and CF-PDI-pain and disability ($p = .004$ and $p = .013$).

Conclusions: In this sample of women with FMS, we identified a high rate of dysphagia risk. Also, a high percentage of these women presented alterations in QoL associated with swallowing. Patients at risk for dysphagia had significantly higher orofacial VAS and CF-PDI-total scores,

supporting the relationship between dysphagia risk and COP in FMS. Further research to establish the need for appropriate assessment referrals in clinical practice to determine whether dysphagia is present in this population is needed.

Validity and Diagnostic Overlap of Functional Somatic Syndrome Diagnoses.

van der Meulen ML, Bos M, Bakker SJL, Gans ROB, Rosmalen JGM.

Objective: We present the first study that investigates the validity and the diagnostic overlap of the three main functional somatic syndrome (FSS) diagnoses, i.e. chronic fatigue syndrome (CFS), fibromyalgia (FM), and irritable bowel syndrome (IBS), irrespective of help-seeking behaviour or diagnostic habits, and irrespective of differences in diagnostic thresholds for chronicity or symptom interference.
Methods: This cross-sectional analysis was performed in 89,781 participants of the general-population cohort Lifelines. Diagnostic criteria for CFS (Centers for Disease Control and Prevention), FM (American College of Rheumatology) and IBS (Rome IV) were assessed by questionnaire. Additional items were added to enable studying the effects of differences in thresholds for minimum symptom chronicity (varying from three for FM to six months for CFS and IBS), and symptom interference (required for CFS but not for FM and IBS).
Results: The diagnostic criteria were met by 3.1% for CFS, 6.6% for FM, and 5.5% for IBS participants. The number of participants that met criteria for all three diagnoses was 45 times higher than what would have been expected based on chance. After alignment of the chronicity and symptom interference criteria to circumvent differences in diagnostic thresholds, the overlap between diagnoses increased to 152 times. Furthermore, there was a similar pattern of symptom occurrence, particularly for those fulfilling diagnostic criteria for CFS and FM.
Conclusion: The diagnostic overlap of different FSS was much higher than would be expected by chance, and substantially increased when FSS were more chronic and serious in nature.

Multimorbidity in Rheumatoid Arthritis: Literature Review and Future Directions.

Katz J, Bartels CM.

Purpose of review: To offer a narrative review of literature and an update on rheumatoid arthritis (RA) multimorbidity research over the past five years as well as future directions.
Recent findings: Patients with RA experience higher prevalence of multimorbidity (31-86% vs 18-71% in non-RA) and faster accumulation of comorbidities. Patients with multimorbidity have worse outcomes compared to non-RA multimorbid patients and RA without multimorbidity including mortality, cardiac events, and hospitalizations. Comorbid disease clusters often included: cardiopulmonary, cardiometabolic, and depression and pain-related conditions. High-frequency comorbidities included interstitial lung disease, asthma, chronic obstructive pulmonary disease, cardiovascular disease, fibromyalgia, osteoarthritis, and osteoporosis, thyroid disorders, hypertension, and cancer. Furthermore, patients with RA and multimorbidity are paradoxically at increased risk of high RA disease activity but experience a lower likelihood of biologic use and more biologic failures. RA patients experience higher prevalence of multimorbidity and worse outcomes versus non-RA and RA without multimorbidity. Findings call for further studies.

Shared Comorbidity of Depression, Migraine, Insomnia, and Fibromyalgia in a Population-Based Sample.

Lee W, Shin HJ, Min IK, Kim CS, Kim KM, Heo K, Chu MK.

Background: Depression, migraine, insomnia, and fibromyalgia are reportedly comorbidities. Nevertheless, no study has evaluated the comorbidity of all four of these disorders. This study aimed to investigate the comorbidity of these four disorders.

Methods: Cross-sectional analyses were performed using data of the Circannual Change in Headache and Sleep study, an online nationwide population-based survey. Validated questionnaires were used to diagnose the disorders and measure quality of life. The change of clinical characteristics by addition of any comorbidity was analyzed using the Jonckheere-Terpstra trend test.

Results: The prevalence rates of depression, migraine, insomnia, and fibromyalgia were 7.2 %, 5.6 %, 13.3 %, and 5.8 %, respectively. Among the 3030 included participants, 494 (16.3 %), 164 (5.4 %), 40 (1.3 %), and 6 (0.2 %) had one, two, three, and four of these conditions, respectively. The number of headache days per 30 days (Jonckheere-Terpstra trend test, p = 0.011) and migraine-related disability (migraine disability assessment score, p = 0.021) increased with an increase in the number of comorbidities but not with the intensity of headache (visual analog scale, p = 0.225) among participants with migraine. The severity of insomnia (Insomnia Severity Index, p < 0.001) and fibromyalgia (fibromyalgia severity score, p = 0.002) increased with additional comorbidities; however, depression (Patient Health Questionnaire-9, p = 0.384) did not show such an increase.

Limitations: The diagnoses of conditions were based on self-reported questionnaires.

Conclusions: The findings confirmed significant comorbidity between depression, migraine, insomnia, and fibromyalgia. Health professionals should be aware of the probable comorbidity of depression, migraine, insomnia, and fibromyalgia when caring for individuals with any of these four disorders.

Association Between Migraine and Epilepsy: A Meta-Analysis.

Wu X, Zhuang J.
Front Neurol. 2024 Jan 5;14:1276663. doi: 10.3389/fneur.2023.1276663. PMID: 38249732; PMCID: PMC10796653.

Background: Epidemiological studies have demonstrated a comorbid association between migraine and epilepsy. However, despite the long history of this association, the exact nature of the relationship between migraine and epilepsy remains largely unresolved. Therefore, it is crucial to conduct a meta-analysis in order to thoroughly investigate the relationship between migraine and epilepsy.

Methods: Odds ratios (ORs) or relative risks (RRs) and 95% confidence intervals (CIs) regarding association between migraine and epilepsy were summarized using STATA 12.0 software.

Results: There was an 80% increase in the lifetime prevalence of migraine among patients with epilepsy, compared to those without epilepsy with a random effects model (OR/RR: 1.80, 95% CI: 1.35 to 2.40, I^2 = 97.5%, *p* < 0.001). There was an 80% increase in the lifetime prevalence of epilepsy among patients with migraine, compared to those without migraine with a random effects model (OR/RR: 1.80, 95% CI: 1.43 to 2.25, I^2 = 80.6%, *p* < 0.001).

Conclusions: It is important to note the comorbid association between migraine and epilepsy examined in the study.

Do People with ME/CFS and Joint Hypermobility Represent a Disease Subgroup? An Analysis Using Registry Data.

Mudie K, Ramiller A, Whittaker S, Phillips LE.
Front Neurol. 2024 Mar 13;15:1324879. doi: 10.3389/fneur.2024.1324879. PMID: 38545281; PMCID: PMC10965591.

Background: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a chronic, multifaceted disease that affects millions globally. Despite its significant impact, the disease's etiology remains poorly understood, and symptom heterogeneity poses challenges for diagnosis and treatment. Joint hypermobility, commonly seen in hypermobile Ehlers-Danlos Syndrome (hEDS), has been observed in ME/CFS patients but its prevalence and clinical significance within this population are not well-characterized.

Objective: To compare the characteristics of ME/CFS patients with and without joint hypermobility (JH+ and JH-) as assessed using the Beighton scoring system, and to explore whether JH+ ME/CFS patients exhibit distinct disease characteristics, comorbidities, and health-related quality of life (HRQOL).

Methods: The study used cross-sectional, self-reported data from 815 participants of the You + ME Registry. Participants were categorized as JH+ or JH- based on self-assessed Beighton scores and compared across demographics, comorbidities, family history, and symptoms. HRQOL was assessed using the Short Form-36 RAND survey and Karnofsky Performance Status.

Results: 15.5% (N = 126) of participants were classified as JH+. JH+ participants were more likely to be female, report Ehlers-Danlos Syndrome (EDS), Postural Orthostatic Tachycardia Syndrome (POTS), and a family history of EDS. They experienced worse HRQOL, particularly in physical functioning and pain, and a higher number of autonomic, neurocognitive, headache, gut, and musculoskeletal symptoms. Sensitivity analysis suggested that ME/CFS with concurrent JH+ and EDS was associated with more severe symptoms and greater functional impairment.

Conclusion: ME/CFS patients with joint hypermobility, particularly those with EDS, demonstrate distinct clinical characteristics, including more severe symptomatology and reduced HRQOL. These findings highlight the need for comprehensive clinical assessments of ME/CFS patients with joint hypermobility. Understanding these relationships could aid in subgroup identification, improving diagnosis, and informing targeted therapeutic approaches. Further research is warranted to explore these associations and their implications for clinical practice.

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