



# Issue 26 - December 2023

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 July and November 2023.

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# Pathophysiology Studies

Genomic Characterisation of the Overlap of Endometriosis with 76 Comorbidities Identifies Pleiotropic and Causal Mechanisms Underlying Disease Risk. McGrath IM; International Endometriosis Genetics Consortium; Montgomery GW, Mortlock S.

Hum Genet. 2023 Jul 6. doi: 10.1007/s00439-023-02582-w. Epub ahead of print. PMID: 37410157.

Comorbid conditions can be driven by underlying pleiotropic and causal mechanisms that can provide insights into shared molecular and biological processes contributing to disease risk. Endometriosis is a chronic condition affecting one in nine women of reproductive age and poses many challenges including lengthy diagnostic delays and limited treatment efficacy owing to poor understanding of disease aetiology. To shed light on the underlying biological mechanisms and to identify potential risk factors, we examine the epidemiological and genomic relationship between endometriosis and its comorbidities. In the UK Biobank 292 ICD10 codes were epidemiologically correlated with endometriosis diagnosis, including gynaecological, immune, infection, pain, psychiatric, cancer, gastrointestinal, urinary, bone and cardiovascular traits. A subset of the identified comorbidities (n = 76) underwent followup genetic analysis. Whilst Mendelian randomisation suggested causality was not responsible for most comorbid relationships, 22 traits were genetically correlated with endometriosis, including pain, generational and gastrointestinal traits, suggestive of a shared genetic background. Pleiotropic genetic variants and genes were identified using gene-based and colocalisation analysis. Shared genetic risk factors and potential target genes suggest a diverse collection of biological systems are involved in these comorbid relationships including coagulation factors, development of the female reproductive tract and cell proliferation. These findings highlight the diversity of traits with epidemiological and genomic overlap with endometriosis and implicate a key role for pleiotropy in the comorbid relationships.

#### DNA Methylation Signatures of Functional Somatic Syndromes: Systematic Review.

Fischer S, Kleinstäuber M, Fiori LM, Turecki G, Wagner J, von Känel R. Psychosom Med. 2023 Oct 1;85(8):672-681. doi: 10.1097/PSY.0000000000001237. Epub 2023 Aug 21. PMID: 37531610.

Objective: Functional somatic syndromes (FSS) are highly prevalent across all levels of health care. The fact that they are characterized by medically unexplained symptoms, such as fatigue and pain, raises the important question of their underlying pathophysiology. Psychosocial stress represents a significant factor in the development of FSS and can induce long-term modifications at the epigenetic level. The aim of this review was to systematically review, for the first time, whether individuals with FSS are characterized by specific alterations in DNA methylation. Methods: MEDLINE and PsycINFO were searched from the first available date to September 2022. The inclusion criteria were as follows: a) adults fulfilling the research diagnostic criteria for chronic fatigue syndrome, fibromyalgia syndrome, and/or irritable bowel syndrome; b) healthy control group; and c) candidate-gene or genome-wide study of DNA methylation. Results: Sixteen studies (N = 957) were included. In candidate-gene studies, specific sites within NR3C1 were identified, which were hypomethylated in individuals with chronic fatigue syndrome compared with healthy controls. In genome-wide studies in chronic fatigue syndrome, a hypomethylated site located to LY86 and hypermethylated sites within HLA-DQB1 were found. In genome-wide studies in fibromyalgia syndrome, differential methylation in sites related to HDAC4, TMEM44, KCNQ1, SLC17A9, PRKG1, ALPK3, TFAP2A, and LY6G5C was found. Conclusions: Individuals with chronic fatigue syndrome and fibromyalgia syndrome seem to be characterized by altered DNA methylation of genes regulating cellular signaling and immune functioning. In chronic fatigue syndrome, there is preliminary evidence for these to be implicated in key pathophysiological alterations, such as hypocortisolism and low-grade inflammation, and to contribute to the debilitating symptoms these individuals experience.

# Insights from Mendelian Randomization and Genetic Correlation Analyses into the Relationship between Endometriosis and its Comorbidities.

McGrath IM, Montgomery GW, Mortlock S. Hum Reprod Update. 2023 Sep 5;29(5):655-674. doi: 10.1093/humupd/dmad009. PMID: 37159502; PMCID: PMC10477944.

Background: Endometriosis remains a poorly understood disease, despite its high prevalence and debilitating symptoms. The overlap in symptoms and the increased risk of multiple other traits in women with endometriosis is becoming increasingly apparent through epidemiological data. Genetic studies offer a method of investigating these comorbid relationships through the assessment of causal relationships with Mendelian randomization (MR), as well as identification of shared genetic variants and genes involved across traits. This has the capacity to identify risk factors for endometriosis as well as provide insight into the aetiology of disease. Objective and rationale: We aim to review the current literature assessing the relationship between endometriosis and other traits using genomic data, primarily through the methods of MR and genetic correlation. We critically examine the limitations of these studies in accordance with the assumptions of the utilized methods. Search methods: The PubMed database was used to search for peer-reviewed original research articles using the terms 'Mendelian randomization endometriosis' and "genetic correlation" endometriosis'. Additionally, a Google Scholar search using the terms "endometriosis" "mendelian randomization" "genetic correlation" was performed. All relevant publications (n = 21) published up until 7 October 2022 were included in this review. Upon compilation of all traits with published MR and/or genetic correlation with endometriosis, additional epidemiological and genetic information on their comorbidity with endometriosis was sourced by searching for the trait in conjunction with 'endometriosis' on Google Scholar. Outcomes: The association between endometriosis and multiple pain, gynaecological, cancer, inflammatory, gastrointestinal, psychological, and anthropometric traits has been assessed using MR analysis and genetic correlation analysis. Genetic correlation analyses provide evidence that genetic factors contributing to endometriosis are shared with multiple traits: migraine, uterine fibroids, subtypes of ovarian cancer, melanoma, asthma, gastrooesophageal reflux disease, gastritis/duodenitis, and depression, suggesting the involvement of multiple biological mechanisms in endometriosis. The assessment of causality with MR has revealed several potential causes (e.g. depression) and outcomes (e.g. ovarian cancer and uterine fibroids) of a genetic predisposition to endometriosis; however, interpretation of these results requires consideration of potential violations of the MR assumptions. Wider implications: Genomic studies have demonstrated that there is a molecular basis for the cooccurrence of endometriosis with other traits. Dissection of this overlap has identified shared genes and pathways, which provide insight into the biology of endometriosis. Thoughtful MR studies are necessary to ascertain causality of the comorbidities of endometriosis. Given the significant diagnostic delay of endometriosis of 7-11 years, determining risk factors is necessary to aid diagnosis and reduce the disease burden. Identification of traits for which endometriosis is a risk factor is important for holistic treatment and counselling of the patient. The use of genomic data to disentangle the overlap of endometriosis with other traits has provided insights into the aetiology of endometriosis.

### <u>Genetic Variations in TrkB.T1 Isoform and their Association with Somatic and</u> <u>Psychological Symptoms in Individuals with IBS.</u>

Hong H, Mocci E, Kamp K, Zhu S, Cain KC, Burr RL, Perry J, Heitkemper MM, Weaver-Toedtman KR, Dorsey SG.

medRxiv [Preprint]. 2023 Sep 14:2023.09.14.23295434. doi: 10.1101/2023.09.14.23295434. PMID: 37745409; PMCID: PMC10516087.

Irritable bowel syndrome (IBS), a disorder of gut-brain interaction, is often comorbid with somatic pain and psychological disorders. Dysregulated signaling of brain-derived neurotrophic factor (BDNF) and its receptor, tropomyosin-related kinase B (TrkB), has been

implicated in somatic-psychological symptoms in individuals with IBS. Thus, we investigated the association of 10 single nucleotide polymorphisms (SNPs) in the regulatory 3' untranslated region (UTR) of NTRK2 (TrkB) kinase domain-deficient truncated isoform (TrkB.T1) and the *BDNF* Val66Met SNP with somatic and psychological symptoms and quality of life in a U.S. cohort (IBS n=464; healthy controls n=156). We found that the homozygous recessive genotype (G/G) of rs2013566 in individuals with IBS is associated with worsened somatic symptoms, including headache, back pain, joint pain, muscle pain, and somatization as well as diminished sleep quality, energy level and overall quality of life. Validation using U.K. BioBank (UKBB) data confirmed the association of rs2013566 with increased likelihood of headache. Several SNPs (rs1627784, rs1624327, rs1147198) showed significant associations with muscle pain in our U.S. cohort. Notably, these SNPs are predominantly located in H3K4Me1-enriched regions, suggesting their enhancer and/or transcription regulation potential. Together, our findings suggest that genetic variation within the 3'UTR region of the TrkB.T1 isoform may contribute to comorbid conditions in individuals with IBS, resulting in a spectrum of somatic and psychological symptoms that may influence their quality of life. These findings advance our understanding of the genetic interaction between BDNF/TrkB pathways and somatic-psychological symptoms in IBS, highlighting the importance of further exploring this interaction for potential clinical applications.

#### <u>Cumulative Effect of AOC1 Gene Variants on Symptoms and Pathological Conditions</u> <u>in Adult Women with Fibromyalgia: A Pilot Study.</u>

Okutan G, Perucho Alcalde T, Ruiz Casares E, Penadés BF, Sánchez Niño GM, Terrén Lora A, López Oliva S, Torrente Estríngana L, Duelo A, San Mauro Martín I. Front Genet. 2023 Jun 9;14:1180777. doi: 10.3389/fgene.2023.1180777. PMID: 37359379; PMCID: PMC10288193.

Introduction: The amine oxidase copper-containing 1 (AOC1) gene encodes for the diamine oxidase (DAO) enzyme. DAO is an enzyme that catabolizes some molecules, including histamine, and is the degradative enzyme in the polyamine catabolic pathway that is active in intestinal mucosal cells. Variants of AOC1 are associated with reduced DAO activity. resulting in accumulation of high levels of histamine and causing a wide range of neurological, gastrointestinal, and epidermal disorders, which are present in people with fibromyalgia. This study aimed to evaluate the impact of four AOC1 gene variants, namely, rs10156191, rs1049742, rs1049793, and rs2052129, on fibromyalgia symptoms measured by the Fibromyalgia Impact Questionnaire (FIQ), such as sleep disorders, atopic dermatitis, migraine, gastrointestinal (GI) disorders, allergies, and intolerances, in adult women with fibromyalgia. Methods: The sample consisted of 100 unrelated women with fibromyalgia between 33 and 60 years of age (48.48 years  $\pm 7.35$ ), whose were diagnosed by a rheumatologist based on symptoms such as pain, stiffness, and fatigue. Single-nucleotide polymorphisms (SNPs) of AOC1 were identified using oral mucosa samples collected following a standard hygiene protocol. DNA was extracted, and gene variants of interest were analyzed using multiplex single-nucleotide primer extension (SNPE). Clinical data were collected using the FIQ and a series of variables that guantified the intensity and frequency of the symptoms. Results: The minor allele frequencies of rs10156191, rs1049742, rs1049793, and rs2052129 were 31.5, 10, 32.5, and 27%, respectively. Each variant was found to be in Hardy-Weinberg equilibrium, but partial linkage disequilibrium between AOC1 SNPs is suspected. The results show that fibromyalgia symptoms measured using the FIQ tend to increase with the number of risk alleles and that the intensity of dry skin and low stool consistency may be associated with an increase in the number of these alleles. Conclusion: This study constitutes the first step in investigating associations between fibromyalgia symptoms and candidate variants of the AOC1 gene in DAO enzyme activity. Identification of reduced DAO activity may improve the quality of life and treatment of symptoms in fibromyalgia patients.

#### Sex Differences in the Serum Proteomic Profile During Acute Low Back Pain - A Preliminary Study of the Relationship to Future Low Back Pain.

Jenkins LC, Chang WJ, Humburg P, Wasinger VC, Stone LS, Dorsey SG, Renn C, Starkweather A, Schabrun SM. J Pain. 2023 Nov 19:S1526-5900(23)00621-1. doi: 10.1016/j.jpain.2023.11.009. Epub ahead

of print. PMID: 37989405.

The molecular processes driving the transition from acute to chronic low back pain (LBP) remain poorly understood and are likely to be sexually dimorphic. This study aimed to explore sex-differences in the serum proteomic profile of people experiencing an acute LBP episode and determine if serum protein concentrations were associated with three-month outcome. Serum samples were collected through venepuncture from 30 female and 29 male participants experiencing an acute LBP episode. Serum samples underwent trypsin digestion and fractionation using hydrophobic interaction chromatography and were then analysed using mass-spectrometry (MS). MS spectra were searched in the Swissprot database for protein identification. Sex differences in protein abundance changes were evident upon inspection of fold changes. Multivariable data analysis identified 21 serum proteins during the acute episode that correctly classified 93% of males and 23 serum proteins that correctly classified 90% of females with ongoing LBP at three months. Pathway analysis suggested the differentially expressed proteins during acute LBP were frequently involved in immune, inflammatory, complement or coagulation responses. This data provides preliminary evidence that biological processes during an acute LBP episode may contribute to resolution, or persistence, of LBP symptoms at three months, however, these processes differ between males and females. PERSPECTIVE: Differential expression of serum proteins was observed between male and female participants during an acute LBP episode. This preliminary work provides a foundation for future research targeting distinct immune system processes in males and females that may interfere with the transition from acute to chronic LBP.

# Interleukin-10-Producing Monocytes Contribute to Sex Differences in Pain Resolution in Mice and Humans.

Sim J, O'Guin E, Monahan K, Sugimoto C, McLean SA, Albertorio-Sáez L, Zhao Y, Laumet S, Dagenais A, Bernard MP, Folger JK, Robison AJ, Linnstaedt SD, Laumet G. bioRxiv [Preprint]. 2023 Nov 5:2023.11.03.565129. doi: 10.1101/2023.11.03.565129. PMID: 37961295; PMCID: PMC10635095.

Pain is closely associated with the immune system, which exhibits sexual dimorphism. For these reasons, neuro-immune interactions are suggested to drive sex differences in pain pathophysiology. However, our understanding of peripheral neuro-immune interactions on sex differences in pain resolution remains limited. Here, we have shown, in both a mouse model of inflammatory pain and in humans following traumatic pain, that males had higher levels of interleukin (IL)-10 than females, which were correlated with faster pain resolution. Following injury, we identified monocytes (CD11b+Ly6C+Ly6G-F4/80<sup>mid</sup>) as the primary source of IL-10, with IL-10-producing monocytes being more abundant in males than females. In a mouse model, neutralizing IL-10 signaling through antibodies, genetically ablating IL-10R1 in sensory neurons, or depleting monocytes with clodronate all impaired the resolution of pain hypersensitivity in both sexes. Furthermore, manipulating androgen levels in mice reversed the sexual dimorphism of pain resolution and the levels of IL-10-producing monocytes. These results highlight a novel role for androgen-driven peripheral IL-10producing monocytes in the sexual dimorphism of pain resolution. These findings add to the growing concept that immune cells play a critical role in resolving pain and preventing the transition into chronic pain.

### Increased Gut Permeability and Bacterial Translocation are Associated with Fibromyalgia and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Implications for Disease-Related Biomarker Discovery.

Martín F, Blanco-Suárez M, Zambrano P, Cáceres O, Almirall M, Alegre-Martín J, Lobo B, González-Castro AM, Santos J, Domingo JC, Jurek J, Castro-Marrero J. Front Immunol. 2023 Sep 7;14:1253121. doi: 10.3389/fimmu.2023.1253121. PMID: 37744357; PMCID: PMC10512706.

Background: There is growing evidence of the significance of gastrointestinal complaints in the impairment of the intestinal mucosal barrier function and inflammation in fibromyalgia (FM) and in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). However, data on intestinal permeability and gut barrier dysfunction in FM and ME/CFS are still limited with conflicting results. This study aimed to assess circulating biomarkers potentially related to intestinal barrier dysfunction and bacterial translocation and their association with selfreported symptoms in these conditions. Methods: A pilot multicenter, cross-sectional cohort study with consecutive enrolment of 22 patients with FM, 30 with ME/CFS and 26 matched healthy controls. Plasma levels of anti-beta-lactoglobulin antibodies (IgG anti- $\beta$ -LGB). zonulin-1 (ZO-1), lipopolysaccharides (LPS), soluble CD14 (sCD14) and interleukin-1-beta (IL-1β) were assayed using ELISA. Demographic and clinical characteristics of the participants were recorded using validated self-reported outcome measures. The diagnostic accuracy of each biomarker was assessed using the receiver operating characteristic (ROC) curve analysis. Results: FM patients had significantly higher levels of anti-β-LGB, ZO-1, LPS, and sCD14 than healthy controls (all P < 0.0001). In ME/CFS patients, levels of anti- $\beta$ -LGB, ZO-1, LPS, and sCD14 were significantly higher than controls, but lower than in FM (all P < 0.01), while there was no significant difference in IL-1 $\beta$  level. In the FM and ME/CFS cohorts, both anti- $\beta$ -LGB and ZO-1 correlated significantly with LPS and sCD14 (*P* < 0.001 for both). In the FM group, both anti- $\beta$ -LGB and ZO-1 were correlated significantly with physical and mental health components on the SF-36 scale (P < 0.05); whereas IL-1 $\beta$  negatively correlated with the COMPASS-31 score (P < 0.05). In the ME/CFS cohort, ZO-1 was positively correlated with the COMPASS-31 score (P < 0.05). The ROC curve analysis indicated a strong ability of anti- $\beta$ -LGB, ZO-1, LPS and sCD14 to predictively distinguish between FM and ME/CFS from healthy controls (P < 0.0001). Conclusion: Biomarkers of intestinal barrier function and inflammation were associated with autonomic dysfunction assessed by COMPASS-31 scores in FM and ME/CFS respectively. Anti- $\beta$ -LGB antibodies, ZO-1. LPS, and sCD14 may be putative predictors of intestinal barrier dysfunction in these cohorts. Further studies are needed to assess whether these findings are causal and can therefore be applied in clinical practice.

# Imaging of the Peripheral Nervous System in Nociplastic Pain: An Ultrasound Study in Patients with Fibromyalgia.

Di Carlo M, Bianchi B, Cipolletta E, Farah S, Filippucci E, Salaffi F. J Neuroimaging. 2023 Jul-Aug;33(4):558-565. doi: 10.1111/jon.13104. Epub 2023 Mar 29. PMID: 36991556.

Background and purpose: Although fibromyalgia (FM) is considered a central sensitization syndrome, studies investigating peripheral nerves in this condition are not available. The primary objective of this study is to investigate the sonographic changes (ie, increased cross-sectional area [CSA]), of peripheral nerves in patients with FM compared to healthy controls. The secondary objective is to identify potential clinical correlations associated with increased CSA in patients with FM. Methods: In this cross-sectional observational study, consecutive female patients with FM underwent sonographic assessment using a standardized scanning protocol. The CSA of seven nerves was measured bilaterally at 11 anatomic sites by an experienced sonographer. Differences in CSA of nerves were compared with those of healthy subjects by one-way analysis of variance. Patients underwent clinimetric evaluation aimed at investigating disease severity, neuropathic pain features, depression, anxiety,

fatigue, and autonomic symptoms to explore the possible correlation between CSA and clinical features. Results: Forty-seven patients and 20 healthy controls were enrolled. Differences in terms of increased CSA between patients and healthy controls were identified at multiple levels, mainly at the level of the sural nerve, vagus nerve, and sixth cervical nerve root (for all, p < .001). Sonographic findings, however, did not correlate with the clinical features explored. Conclusions: Patients with FM show higher CSA of nerves than healthy subjects. The increased CSA is most evident at the sural nerve, vagus nerve, and sixth cervical nerve root. Ultrasound, a relatively easy-to-use technique, could identify morphological changes, in peripheral nervous structures in patients with FM.

# Habituation to Pain in Patients with Chronic Pain: Clinical Implications and Future Directions.

van der Miesen MM, Vossen CJ, Joosten EA.

J Clin Med. 2023 Jun 27;12(13):4305. doi: 10.3390/jcm12134305. PMID: 37445339; PMCID: PMC10342770.

In this review, the latest insights into habituation to pain in chronic pain are summarized. Using a systematic search, results of studies on the evidence of habituation to (experimental) pain in migraine, chronic low back pain, fibromyalgia, and a variety of chronic pain indications are presented. In migraine, reduced habituation based on self-report and the EEG-based N1 and N2-P2 amplitude is reported, but the presence of contradictory results demands further replication in larger, well-designed studies. Habituation to pain in chronic low back pain seems not to differ from controls, with the exception of EEG measures. In fibromyalgia patients, there is some evidence for reduced habituation to pain are still not fully understood and likely involve several pathways, it is now too early to conclude that habituation to pain is related to clinical outcomes and can be used as a diagnostic marker. The review ends with a discussion on future directions for research including the use of standard outcome measures to improve comparisons of habituation to pain in patients and controls, as well as a focus on individual differences.

# Gut Instinct: Sex Differences in the Gut Microbiome are Associated with Changes in Adolescent Nociception Following Maternal Separation in Rats.

Salberg S, Macowan M, Yamakawa GR, Beveridge JK, Noel M, Marsland BJ, Mychasiuk R. Dev Neurobiol. 2023 Jul 24. doi: 10.1002/dneu.22925. Epub ahead of print. PMID: 37488954.

Adolescent chronic pain is a growing public health epidemic. Our understanding of its etiology is limited; however, several factors can increase susceptibility, often developing in response to an acute pain trigger such as a surgical procedure or mild traumatic brain injury (mTBI), or an adverse childhood experience (ACE). Additionally, the prevalence and manifestation of chronic pain is sexually dimorphic, with double the rates in females than males. Despite this, the majority of pre-clinical pain research focuses on males, leaving a gap in mechanistic understanding for females. Given that emerging evidence has linked the gut microbiome and the brain-gut-immune axis to various pain disorders, we aimed to investigate sex-dependent changes in taxonomic and functional gut microbiome features following an ACE and acute injury as chronic pain triggers. Male and female Sprague Dawley rat pups were randomly assigned to either a maternal separation (MS) or no stress paradigm, then further into a sham, mTBI, or surgery condition. Chronically, the von Frey test was used to measure mechanical nociception, and fecal samples were collected for 16S rRNA sequencing. Animals in the surgery group had an increase in pain sensitivity when compared to mTBI and sham groups, and this was complemented by changes to the gut microbiome. In addition, significant sex differences were identified in gut microbiome composition, which were exacerbated in response to MS. Overall, we provide preliminary

evidence for sex differences and ACE-induced changes in bacterial composition that, when combined, may be contributing to heterogeneity in pain outcomes.

## Formalin-Evoked Pain Triggers Sex-Specific Behavior and Spinal Immune Response.

Pepino L, Malapert P, Saurin AJ, Moqrich A, Reynders A. Sci Rep. 2023 Jun 12;13(1):9515. doi: 10.1038/s41598-023-36245-7. PMID: 37308519; PMCID: PMC10261048.

Mounting evidence shows sex-related differences in the experience of pain with women suffering more from chronic pain than men. Yet, our understanding of the biological basis underlying those differences remains incomplete. Using an adapted model of formalininduced chemical/inflammatory pain, we report here that in contrast to male mice, females distinctly display two types of nocifensive responses to formalin, distinguishable by the duration of the interphase. Females in proestrus and in metestrus exhibited respectively a short-lasting and a long-lasting interphase, underscoring the influence of the estrus cycle on the duration of the interphase, rather than the transcriptional content of the dorsal horn of the spinal cord (DHSC). Additionally, deep RNA-sequencing of DHSC showed that formalinevoked pain was accompanied by a male-preponderant enrichment in genes associated with the immune modulation of pain, revealing an unanticipated contribution of neutrophils. Taking advantage of the male-enriched transcript encoding the neutrophil associated protein Lipocalin 2 (Lcn2) and using flow cytometry, we confirmed that formalin triggered the recruitment of LCN2-expressing neutrophils in the pia mater of spinal meninges. preferentially in males. Our data consolidate the contribution of female estrus cycle to pain perception and provide evidence supporting a sex-specific immune regulation of formalinevoked pain.

# Brain-Predicted Age Difference Estimated Using DeepBrainNet is Significantly Associated with Pain and Function-A Multi-Institutional and Multiscanner Study.

Valdes-Hernandez PA, Laffitte Nodarse C, Johnson AJ, Montesino-Goicolea S, Bashyam V, Davatzikos C, Peraza JA, Cole JH, Huo Z, Fillingim RB, Cruz-Almeida Y. Pain. 2023 Jul 24. doi: 10.1097/j.pain.0000000000002984. Epub ahead of print. PMID: 37490099.

Brain age predicted differences (brain-PAD: predicted brain age minus chronological age) have been reported to be significantly larger for individuals with chronic pain compared with those without. However, a debate remains after one article showed no significant differences. Using Gaussian Process Regression, an article provides evidence that these negative results might owe to the use of mixed samples by reporting a differential effect of chronic pain on brain-PAD across pain types. However, some remaining methodological issues regarding training sample size and sex-specific effects should be tackled before settling this controversy. Here, we explored differences in brain-PAD between musculoskeletal pain types and controls using a novel convolutional neural network for predicting brain-PADs, ie, DeepBrainNet. Based on a very large, multi-institutional, and heterogeneous training sample and requiring less magnetic resonance imaging preprocessing than other methods for brain age prediction, DeepBrainNet offers robust and reproducible brain-PADs, possibly highly sensitive to neuropathology. Controlling for scanner-related variability, we used a large sample (n = 660) with different scanners, ages (19-83 years), and musculoskeletal pain types (chronic low back [CBP] and osteoarthritis [OA] pain). Irrespective of sex, brain-PAD of OA pain participants was  $\sim$ 3 to 4.7 years higher than that of CBP and controls, whereas brain-PAD did not significantly differ among controls and CBP. Moreover, brain-PAD was significantly related to multiple variables underlying the multidimensional pain experience. This comprehensive work adds evidence of pain type-specific effects of chronic pain on brain age. This could help in the clarification of the debate around possible relationships between brain aging mechanisms and pain.

## Sex Differences in Visceral Sensitivity and Brain Activity in a Rat Model of Comorbid Pain: A Longitudinal Study.

Da Silva JT, Hernandez-Rojas LG, Mekonen HK, Hanson S, Melemedjian O, Scott AJ, Ernst RK, Seminowicz DA, Traub RJ.

Pain. 2023 Sep 27. doi: 10.1097/j.pain.00000000000003074. Epub ahead of print. PMID: 37756658.

Temporomandibular disorder (TMD) and irritable bowel syndrome (IBS) are 2 chronic overlapping pain conditions (COPCs) that present with significant comorbidity. Both conditions are more prevalent in women and are exacerbated by stress. While peripheral mechanisms might contribute to pain hypersensitivity for each individual condition, mechanisms underlying the comorbidity are poorly understood, complicating pain management when multiple conditions are involved. In this study, longitudinal behavioral and functional MRI-based brain changes have been identified in an animal model of TMD-like pain (masseter muscle inflammation followed by stress) that induces de novo IBS-like comorbid visceral pain hypersensitivity in rats. In particular, data indicate that increased activity in the insula and regions of the reward and limbic systems are associated with more pronounced and longer-lasting visceral pain behaviors in female rats, while the faster pain resolution in male rats may be due to increased activity in descending pain inhibitory pathways. These findings suggest the critical role of brain mechanisms in chronic pain conditions and that sex may be a risk factor of developing COPCs.

## Stem Cells Therapeutic Effect in a Reserpine-Induced Fibromyalgia Rat Model: A Possible NLRP3 Inflammasome Modulation with Neurogenesis Promotion in the Cerebral Cortex.

Mokhemer SA, Desouky MK, Abdelghany AK, Ibrahim MFG. Life Sci. 2023 Jul 15;325:121784. doi: 10.1016/j.lfs.2023.121784. Epub 2023 May 15. PMID: 37196857.

Fibromyalgia is a chronic pain syndrome with a multifactorial pathophysiology affecting 2-8 % of the population. Aims: To investigate the therapeutic effects of bone marrow mesenchymal stem cells (BMSCs) against fibromyalgia-related cerebral cortex damage and the possible underlying mechanisms of action. Materials and methods: Rats were randomly allocated into three groups; control, fibromyalgia and fibromyalgia treated with BMSCs groups. Physical and behavioural assessments were performed. Cerebral cortices were collected for biochemical and histological assessment. Key findings: Fibromvalgia group showed behavioural changes indicating presence of pain, fatigue, depression, and sleep disturbances. Moreover, biochemical biomarkers alterations were demonstrated by a significant decrease in brain monoamines and GSH levels, but MDA, NO, TNF-alpha, HMGB-1, NLRP3, and caspase-1 levels significantly increased. Furthermore, histological assessment revealed structural and ultrastructural alterations indicating neuronal and neuroglial degeneration with microglia activation, an increase in mast cell number and IL-18 immune-expression. Additionally, a significant decrease in Beclin-1 immune-expression, and blood brain barrier disruption were noticed. Interestingly, BMSCs administration significantly improved behavioural alterations, restored the reduced brain monoamines and oxidative stress markers, and reduced TNF-alpha, HMGB-1, NLRP3, and caspase-1 levels. Profoundly, cerebral cortices demonstrated improved histological structure, significant decrease in mast cell number and IL-1 $\beta$  immune-expression, besides a significant increase in Beclin-1 and DCX immune-expression. Significance: For the best of our knowledge, this is the first study showing ameliorative effects for BMSCs treatment in fibromyalgia-related cerebral cortical damage. The neurotherapeutic effects of BMSCs could be attributed to NLRP3 inflammasome signaling pathway inhibition, mast cell deactivation, and stimulation of neurogenesis and autophagy.

## A Female-Specific Role for Trigeminal Dynorphin in Orofacial Pain Comorbidity.

Shu H, Liu S, Crawford J, Tao F. Pain. 2023 Jul 13. doi: 10.1097/j.pain.0000000000002980. Epub ahead of print. PMID: 37463238.

Migraine is commonly reported in patients with temporomandibular disorders (TMDs), but little is known about the mechanisms underlying the comorbid condition. Here, we prepared a mouse model to investigate this comorbidity, in which masseter muscle tendon ligation (MMTL) was performed to induce a myogenic TMD, and the pre-existing TMD enabled a subthreshold dose of nitroglycerin (NTG) to produce migraine-like pain in mice. RNA sequencing followed by real-time quantitative polymerase chain reaction confirmation showed that MMTL plus NTG treatment increased prodynorphin (Pdyn) mRNA expression in the spinal trigeminal nucleus caudalis (Sp5C) of female mice but not in male mice. Chemogenetic inhibition of Pdyn-expressing neurons or microinjection of antidynorphin antiserum in the Sp5C alleviated MMTL-induced masseter hypersensitivity and diminished the MMTL-enabled migraine-like pain in female mice but not in male mice. Moreover, chemogenetic activation of Pdyn-expressing neurons or microinjection of dynorphin A(1-17) peptide in the Sp5C enabled a subthreshold dose of NTG to induce migraine-like pain in female mice but not in male mice.

### Antimicrobial Therapies for Chronic Pain (Part 1): Analgesic Mechanisms.

Wang EJ, Karri J, Tontisirin N, Cohen SP. Korean J Pain. 2023 Jul 1;36(3):281-298. doi: 10.3344/kjp.23129. PMID: 37394272; PMCID: PMC10322662.

There is increasing evidence that the relationship between chronic pain and infections is complex and intertwined. Bacterial and viral infections can cause pain through numerous mechanisms such as direct tissue damage and inflammation, the induction of excessive immunologic activity, and the development of peripheral or central sensitization. Treating infections might relieve pain by attenuating these processes, but a growing body of literature suggests that some antimicrobial therapies confer analgesic effects, including for nociceptive and neuropathic pain symptoms, and affective components of pain. The analgesic mechanisms of antimicrobials are indirect, but might be conceptualized into two broad categories: 1) the reduction of the infectious burden and associated pro-inflammatory processes; and 2) the inhibition of signaling processes (e.g., enzymatic and cytokine activity) necessary for nociception and maladaptive neuroplastic changes via off-target effects (unintended binding sites). For the former, there is evidence that symptoms of chronic low back pain (when associated with Modic type 1 changes), irritable bowel syndrome, inflammatory bowel disease, chronic pelvic pain, and functional dyspepsia might be improved after antibiotic treatment, though significant questions remain regarding specific regimens and dose, and which subpopulations are most likely to benefit. For the latter, there is evidence that several antimicrobial classes and medications exert analgesic effects independent of their reduction of infectious burden, and these include cephalosporins, ribavirin, chloroguine derivatives, rapalogues, minocycline, dapsone, and piscidin-1. This article aims to comprehensively review the existing literature for antimicrobial agents that have demonstrated analgesic efficacy in preclinical or clinical studies.

# Antimicrobial Therapies for Chronic Pain (Part 2): The Prevention and Treatment of Chronic Pain.

Wang EJ, Dolomisiewicz E, Karri J, Tontisirin N, Cohen SP. Korean J Pain. 2023 Jul 1;36(3):299-315. doi: 10.3344/kjp.23130. PMID: 37394273; PMCID: PMC10322666.

The discovery and development of antimicrobial therapies represents one of the most significant advancements in modern medicine. Although the primary therapeutic intent of

antimicrobials is to eliminate their target pathogens, several antimicrobials have been shown to provide analgesia as a secondary benefit. Antimicrobials have demonstrated analgesic effects in conditions that involve dysbiosis or potential subclinical infection (e.g., chronic low back pain with Modic type 1 changes; chronic prostatitis/chronic pelvic pain; irritable bowel syndrome; inflammatory bowel disease; functional gastrointestinal disorders/dyspepsia; myalgic encephalomyelitis/chronic fatigue syndrome), and might even prevent the chronification of pain after acute infections that are associated with excessive systemic inflammation (e.g., post COVID-19 condition/long Covid, rheumatic fever). Clinical studies often assess the analgesic effects of antimicrobial therapies in an observational manner, without the ability to identify causative relationships, and significant gaps in the understanding remain regarding the analgesic potential of antimicrobials. Numerous interrelated patient-specific, antimicrobial-specific, and disease-specific factors altogether contribute to the perception and experience of pain, and each of these requires further study. Given worldwide concerns regarding antimicrobial resistance, antimicrobials must continue to be used judiciously and are unlikely to be repurposed as primary analgesic medications. However, when equipoise exists among several antimicrobial treatment options, the potential analgesic benefits of certain antimicrobial agents might be a valuable aspect to consider in clinical decision-making. This article (the second in a two-part series) aims to comprehensively review the evidence on the prevention and treatment of chronic pain using antimicrobial therapies and suggest a framework for future studies on this topic.

# How can Experimental Endotoxemia Contribute to our Understanding of Pain? A Narrative Review.

### Benson S, Karshikoff B.

Neuroimmunomodulation. 2023 Oct 5;30(1):250–67. doi: 10.1159/000534467. Epub ahead of print. PMID: 37797598; PMCID: PMC10619593.

Background: The immune system and the central nervous system exchange information continuously. This communication is a prerequisite for adaptive responses to physiological and psychological stressors. While the implicate relationship between inflammation and pain is increasingly recognized in clinical cohorts, the underlying mechanisms and the possibilities for pharmacological and psychological approaches aimed at neuro-immune communication in pain are not fully understood yet. This calls for preclinical models which build a bridge from clinical research to laboratory research. Summary: Experimental models of systemic inflammation (experimental endotoxemia) in humans have been increasingly recognized as an approach to study the direct and causal effects of inflammation on pain perception. This narrative review provides an overview of what experimental endotoxemia studies on pain have been able to clarify so far. We report that experimental endotoxemia results in a reproducible increase in pain sensitivity, particularly for pressure and visceral pain (deep pain), which is reflected in responses of brain areas involved in pain processing. Increased levels of blood inflammatory cytokines are required for this effect, but cytokine levels do not always predict pain intensity. We address sex-dependent differences in immunological responses to endotoxin, and discuss why these differences do not necessarily translate to differences in behavioral measures. We summarize psychological and cognitive factors that may moderate pain sensitization driven by immune activation. Key messages: Together, studying the immune-driven changes in pain during endotoxemia offers a deeper mechanistic understanding of the role of inflammation in chronic pain. Experimental endotoxemia models can specifically help to tease out inflammatory mechanisms underlying individual differences, vulnerabilities, and comorbid psychological problems in pain syndromes. The model offers the opportunity to test the efficacy of interventions, increasing their translational applicability for personalized medical approaches.

### TRPA1 Rare Variants in Chronic Neuropathic and Nociplastic Pain Patients.

Marchi M, Salvi E, Andelic M, Mehmeti E, D'Amato I, Cazzato D, Chiappori F, Lombardi R, Cartelli D, Devigili G, Dalla Bella E, Gerrits M, Almomani R, Malik RA, Ślęczkowska M,

Mazzeo A, Gentile L, Dib-Hajj S, Waxman SG, Faber CG, Vecchio E, de Tommaso M, Lauria G.

Pain. 2023 Sep 1;164(9):2048-2059. doi: 10.1097/j.pain.000000000002905. Epub 2023 Apr 19. PMID: 37079850; PMCID: PMC10443199.

Missing aspects of the heritability of chronic neuropathic pain, as a complex adult-onset trait, may be hidden within rare variants with low effect on disease risk, unlikely to be resolved by a single-variant approach. To identify new risk genes, we performed a next-generation sequencing of 107 pain genes and collapsed the rare variants through gene-wise aggregation analysis. The optimal unified sequence kernel association test was applied to 169 patients with painful neuropathy, 223 patients with nociplastic pain (82 diagnosed with chronic widespread pain and 141 with fibromyalgia), and 216 healthy controls. Frequency and features of variants in TRPA1, which was the most significant gene, were further validated in 2 independent cohorts of 140 patients with chronic pain (90 with painful neuropathy and 50 with chronic widespread pain) and 34 with painless neuropathy. The effect of aminoacidic changes were modeled in silico according to physicochemical characteristics. TRPA1 was significantly enriched of rare variants which significantly discriminated chronic pain patients from healthy controls after Bonferroni correction (P = 6.7 × 10<sup>-4</sup>,  $\rho$  = 1), giving a risk of 4.8-fold higher based on the simple burden test (P = 0.0015, OR = 4.8). Among the 32 patients harboring *TRPA1* variants, 24 (75%) were diagnosed with nociplastic pain, either fibromyalgia (12; 37.5%) or chronic widespread pain (12; 37.5%), whereas 8 (25%) with painful neuropathy. Irrespective of the clinical diagnosis, 12 patients (38%) complained of itch and 10 (31.3%) of cold-induced or cold-accentuated pain, mostly episodic. Our study widens the spectrum of channelopathy-related chronic pain disorders and contributes to bridging the gap between phenotype and targeted therapies based on patients' molecular profile.

# Sex Differences in Peripheral Immune Cell Activation: Implications for Pain and Pain Resolution.

Friedman TN, La Caprara O, Zhang C, Lee K, May J, Faig CA, Baldwin T, Plemel JR, Taylor AMW, Kerr BJ.

Brain Behav Immun. 2023 Nov;114:80-93. doi: 10.1016/j.bbi.2023.07.029. Epub 2023 Aug 6. PMID: 37544463.

Decades of research into chronic pain has deepened our understanding of the cellular mechanisms behind this process. However, a failure to consider the biological variable of sex has limited the application of these breakthroughs into clinical application. In the present study, we investigate fundamental differences in chronic pain between male and female mice resulting from inflammatory activation of the innate immune system. We provide evidence that female mice are more sensitive to the effects of macrophages. Injecting small volumes of media conditioned by either unstimulated macrophages or macrophages stimulated by the inflammatory molecule TNF $\alpha$  lead to increased pain sensitivity only in females. Interestingly, we find that TNFα conditioned media leads to a more rapid resolution of mechanical hypersensitivity and altered immune cell recruitment to sites of injury. Furthermore, male and female macrophages exhibit differential polarization characteristics and motility after TNF $\alpha$ stimulation, as well as a different profile of cytokine secretions. Finally, we find that the Xlinked gene TIr7 is critical in the facilitating the adaptive resolution of pain in models of acute and chronic inflammation in both sexes. Altogether, these findings suggest that although the cellular mechanisms of pain resolution may differ between the sexes, the study of these differences may yield more targeted approaches with clinical applications.

## Sexual Dimorphism in the Mechanism of Pain Central Sensitization.

Barcelon E, Chung S, Lee J, Lee SJ. Cells. 2023 Aug 9;12(16):2028. doi: 10.3390/cells12162028. PMID: 37626838; PMCID: PMC10453375. It has long been recognized that men and women have different degrees of susceptibility to chronic pain. Greater recognition of the sexual dimorphism in chronic pain has resulted in increasing numbers of both clinical and preclinical studies that have identified factors and mechanisms underlying sex differences in pain sensitization. Here, we review sexually dimorphic pain phenotypes in various research animal models and factors involved in the sex difference in pain phenotypes. We further discuss putative mechanisms for the sexual dimorphism in pain sensitization, which involves sex hormones, spinal cord microglia, and peripheral immune cells. Elucidating the sexually dimorphic mechanism of pain sensitization may provide important clinical implications and aid the development of sex-specific therapeutic strategies to treat chronic pain.

### The Potent Analgesia of Intrathecal 2R, 6R-HNK via TRPA1 Inhibition in LF-PENS-Induced Chronic Primary Pain Model.

Liu AR, Lin ZJ, Wei M, Tang Y, Zhang H, Peng XG, Li Y, Zheng YF, Tan Z, Zhou LJ, Feng X. J Headache Pain. 2023 Oct 19;24(1):141. doi: 10.1186/s10194-023-01667-1. PMID: 37858040; PMCID: PMC10585932.

Background: Chronic primary pain (CPP) is an intractable pain of unknown cause with significant emotional distress and/or dysfunction that is a leading factor of disability globally. The lack of a suitable animal model that mimic CPP in humans has frustrated efforts to curb disease progression. 2R, 6R-hydroxynorketamine (2R, 6R-HNK) is the major antidepressant metabolite of ketamine and also exerts antinociceptive action. However, the analgesic mechanism and whether it is effective for CPP are still unknown. Methods: Based on nociplastic pain is evoked by long-term potentiation (LTP)-inducible high- or low-frequency electrical stimulation (HFS/LFS), we wanted to develop a novel CPP mouse model with mood and cognitive comorbidities by noninvasive low-frequency percutaneous electrical nerve stimulation (LF-PENS). Single/repeated 2R, 6R-HNK or other drug was intraperitoneally (i.p.) or intrathecally (i.t.) injected into naïve or CPP mice to investigate their analgesic effect in CPP model. A variety of behavioral tests were used to detect the changes in pain, mood and memory. Immunofluorescent staining, western blot, reverse transcriptionquantitative real-time polymerase chain reaction (RT-gPCR) and calcium imaging of in cultured dorsal root ganglia (DRG) neurons by Fluo-8-AM were used to elucidate the role and mechanisms of 2R, 6R-HNK in vivo or in vitro. Results: Intrathecal 2R, 6R-HNK, rather than intraperitoneal 2R, 6R-HNK or intrathecal S-Ketamine, successfully mitigated HFSinduced pain. Importantly, intrathecal 2R, 6R-HNK displayed effective relief of bilateral pain hypersensitivity and depressive and cognitive comorbidities in a dose-dependent manner in LF-PENS-induced CPP model. Mechanically, 2R, 6R-HNK markedly attenuated neuronal hyperexcitability and the upregulation of calcitonin gene-related peptide (CGRP), transient receptor potential ankyrin 1 (TRPA1) or vanilloid-1 (TRPV1), and vesicular glutamate transporter-2 (VGLUT2) in peripheral nociceptive pathway. In addition, 2R, 6R-HNK suppressed calcium responses and CGRP overexpression in cultured DRG neurons elicited by the agonists of TRPA1 or/and TRPV1. Strikingly, the inhibitory effects of 2R, 6R-HNK on these pain-related molecules and mechanical allodynia were substantially occluded by TRPA1 antagonist menthol. Conclusions: In the newly designed CPP model, our findings highlighted the potential utility of intrathecal 2R, 6R-HNK for preventing and therapeutic modality of CPP. TRPA1-mediated upregulation of CGRP and neuronal hyperexcitability in nociceptive pathways may undertake both unique characteristics and solving process of CPP.

# **Clinical Studies**

The Chronic Overlapping Pain Condition Screener.

Schrepf A, Maixner W, Fillingim R, Veasley C, Ohrbach R, Smith S, Williams DA. J Pain. 2023 Aug 24:S1526-5900(23)00511-4. doi: 10.1016/j.jpain.2023.08.009. Epub ahead of print. PMID: 37633574.

Ten Chronic Overlapping Pain Conditions (COPCs) are currently recognized by the National Institutes of Health Pain Consortium (eg, irritable bowel syndrome, chronic migraine headache, and chronic low back pain). These conditions affect millions of Americans: however, assessing these conditions, their co-occurrence, and their relationship to treatment has proven challenging due to time constraints and a lack of standardized measures. We present a Chronic Overlapping Pain Condition-Screener (COPC-S) that is logic-driven, efficient, and freely available in electronic format to nonprofit entities. Thirty experts were convened to identify and modify self-report criteria for each COPC as well as criteria that trigger the administration of the diagnostic criteria from a body map and a brief series of questions. Their recommendations were then programmed into the Research Electronic Data Capture platform and refined for comprehensibility and ease of use by patient focus groups. The electronic screener and physician-administered criteria were both administered to patients with known COPCs in a counter-balanced fashion to determine the level of agreement between methods. The expert panel identified screening items/body map regions and diagnostic criteria for all 10 COPCs. Patients found the content comprehensible and the platform easy to use. Cohen's Kappa statistics suggested good agreement between the electronic COPC-S and criteria administered by a physician ( $\kappa$  = .813). The COPC-S is an efficient tool for screening multiple COPCs and has applicability to research studies, clinical trials, and clinical practice. PERSPECTIVE: Assessing COPCs remains a challenge for researchers and clinicians. The COPC-S is an efficient and logic-driven electronic tool that allows for the rapid screening assessment of 10 COPCs. The instrument may have utility in research and clinical settings.

### Characterization and Burden of Localized Back Pain Versus Back Pain with Chronic Overlapping Pain Conditions.

### Terkawi AS, Popat RA, Mackey S.

Pain Pract. 2023 Jul 1. doi: 10.1111/papr.13267. Epub ahead of print. PMID: 37392043.

Background: Chronic low back pain (cLBP) is the most common cause of years lived with disability (YLD). Chronic overlapping pain conditions (COPCs) is a relatively new taxonomy for widespread pain. Researchers have postulated that patients with COPCs have more pain-related impact than those with isolated pain conditions. We know little about the combination of COPCs with cLBP. This study aims to characterize patients with isolated cLBP compared to those with cLBP and associated COPCs across multiple domains of physical, psychological, and social functioning. Methods: Using Stanford's CHOIR registrybased learning health system, we performed a cross-sectional study on patients with localized cLBP (group L) versus cLBP with COPCs (group W). We used demographic, PROMIS (Patient-Reported Outcomes Measurement Information System), and legacy survey data to characterize the physical, psychological, social, and global health outcomes. We further subdivided the COPCs into intermediate and severe based on the number of body regions involved. We used descriptive statistics and generalized linear regression models to characterize and compare the pain groups. Results: Among 8783 patients with cLBP, 485 (5.5%) had localized cLBP (Group L) without widespread pain. Compared to Group L. patients in Group W were more likely to be females, younger, and reported longer duration of pain. Although the mean pain scores were significantly higher in group W, this difference did not appear clinically significant (average pain scores MD -0.73, 95% CI [-0.91 to -0.55]). Group W had significantly worse outcomes in all PROMIS outcomes. However, outcomes with large clinical differences (Cohen's d > 0.5) were fatigue (MD = -7.0, 95% CI [-8.0 to -6.1]); sleep impairment (MD = -6.2, 95% CI [-7.1 to -5.3]); sleep disturbance (MD = -5.3, 95% CI [-6.2 to -4.5]); pain behavior (MD = -2.2, 95% CI [-2.5 to -1.8]); physical function (MD = 4.0, 95% CI [3.2-5.0]); pain interference (MD = -3.4, 95% CI [-4.0 to -2.8]); and anxiety (MD = -4.9, 95% CI [-5.7 to -4.0]). Adjusted analysis controlling for age, gender, BMI category, and duration of pain confirmed worsening of all outcomes with more widespread pain. Conclusion: COPCs are a common presentation with cLBP. The combination of COPCs with cLBP is associated with significantly worse physical, psychological, social, and global health outcomes. This information may identify patients with COPCs and cLBP to optimally risk and treatment stratify their care and individualize their management.

## Does the Number of Comorbidities Predict Pain and Disability in Older Adults with Chronic Low Back Pain? A Longitudinal Study With 6- and 12-Month Follow-ups.

Lemes ÍR, Morelhão PK, Verhagen A, Gobbi C, Oliveira CB, Silva NS, Lustosa LP, Franco MR, Pinto RZ.

J Geriatr Phys Ther. 2023 Nov 8. doi: 10.1519/JPT.0000000000000400. Epub ahead of print. PMID: 37937986.

Background and purpose: People who live longer often live with multimorbidity. Nevertheless, whether the presence of multimorbidity affects pain and disability in older adults with chronic low back pain (LBP) remains unclear. The aim of this study was to investigate whether multimorbidity predicts pain intensity and disability at 6- and 12-month follow-ups in older adults with chronic LBP. Methods: This was a prospective, longitudinal study with 6- and 12month follow-ups. Participants with chronic LBP (age  $\geq$  60 years) were recruited and interviewed at baseline, 6 months, and 12 months. Self-reported measures included the number of comorbidities, assessed through the Self-Administered Comorbidity Questionnaire, pain intensity, assessed with the 11-point Numerical Rating Scale, and disability, assessed with the Roland-Morris Disability Questionnaire. Data were analyzed using univariate and multivariate regression models. Results and discussion: A total of 220 participants were included. The number of comorbidities predicted pain intensity at 6-month  $(\beta = 0.31 [95\% Cl: 0.12 to 0.50])$  and 12-month  $(\beta = 0.29 [95\% Cl: 0.08 to 0.50])$  follow-ups. The number of comorbidities predicted disability at 6-month ( $\beta$ = 0.55 [95% CI: 0.20 to 0.90]) and 12-month ( $\beta$ = 0.40 [95% CI: 0.03 to 0.77]) follow-ups. Conclusion: The number of comorbidities at baseline predicted pain and disability at 6-month and 12-month follow-ups in older adults with chronic LBP. These results highlight the role of comorbidities as a predictive factor of pain and disability in patients with chronic LBP, emphasizing the need for timely and continuous interventions in older adults with multimorbidity to mitigate LBP-related pain and disability.

#### Fibromyalgia and Irritable Bowel Syndrome Interaction: A Possible Role for Gut Microbiota and Gut-Brain Axis.

Garofalo C, Cristiani CM, Ilari S, Passacatini LC, Malafoglia V, Viglietto G, Maiuolo J, Oppedisano F, Palma E, Tomino C, Raffaeli W, Mollace V, Muscoli C. Biomedicines. 2023 Jun 13;11(6):1701. doi: 10.3390/biomedicines11061701. PMID: 37371796; PMCID: PMC10296515.

Fibromyalgia (FM) is a serious chronic pain syndrome, characterised by muscle and joint stiffness, insomnia, fatigue, mood disorders, cognitive dysfunction, anxiety, depression and intestinal irritability. Irritable Bowel Syndrome (IBS) shares many of these symptoms, and FM and IBS frequently co-exist, which suggests a common aetiology for the two diseases. The exact physiopathological mechanisms underlying both FM and IBS onset are unknown. Researchers have investigated many possible causes, including alterations in gut microbiota, which contain billions of microorganisms in the human digestive tract. The gut-brain axis has been proven to be the link between the gut microbiota and the central nervous system, which can then control the gut microbiota composition. In this review, we will discuss the similarities between FM and IBS as well as the similarities in microbiota composition between FM and IBS as well as the similarities in microbiota composition between FM and IBS patients. We will also briefly discuss the potential therapeutic approaches based on microbiota manipulations that are successfully used in IBS and could be employed also in

FM patients to relieve pain, ameliorate the rehabilitation outcome, psychological distress and intestinal symptoms.

#### Applications of Botulinum Toxin to the Female Pelvic Floor: Botulinum Toxin for Genito-Pelvic Pain Penetration Disorder and Chronic Pelvic Pain in Women. Karp BI, Stratton P.

Toxicon. 2023 Jul;230:107162. doi: 10.1016/j.toxicon.2023.107162. Epub 2023 May 16. PMID: 37201800; PMCID: PMC10330736.

Chronic pain conditions like genito-pelvic pain penetration disorder and chronic pelvic pain cause significant morbidity in women worldwide and yet are underdiagnosed and undertreated. While the use of botulinum toxin for pain conditions has expanded, there are few randomized controlled studies of botulinum toxin for pelvic pain conditions in women. This paper provides an update on the current status and context for considering botulinum toxin treatment for these conditions to complement and expand currently available approaches. High quality clinical trials to evaluate safety and efficacy and to determine optimal doses and approaches to injection are urgently needed.

# The Multi-Generational Familial Aggregation of Interstitial Cystitis, Other Chronic Nociplastic Pain Disorders, Depression, and Panic Disorder.

Allen-Brady K, Fyer AJ, Weissman M.

Psychol Med. 2023 Jul 17:1-10. doi: 10.1017/S0033291723001885. Epub ahead of print. PMID: 37458197.

Background: Interstitial cystitis/painful bladder syndrome (IC) is a chronic pelvic pain condition which has high comorbidity with other nociplastic, or unexplained, pain disorders [e.g. fibromyalgia (FM), irritable bowel syndrome (IBS), and myalgic encephalomyelitis/chronic fatigue (ME/CFS)] and some psychiatric conditions [major depressive disorder (MDD) and panic disorder (PD)]. Here we investigated the shared familiality of IC and these other nociplastic and psychiatric conditions. Methods: Subjects were identified in the Utah Population Database, which links genealogy data back to the 1800s to medical record diagnosis billing code data back to 1995. We computed the relative risk of each of these disorders among first (FDR), second (SDR), and third-degree relatives (TDR) of six proband groups: IC, FM, IBS, ME/CFS, PD, and MDD. Given the known familial aggregation of each of these disorders, we conducted our analyses to test for heritable interrelationships using proband subgroups whose members did not have the diagnosis assessed in their relatives. Results: We observed strong evidence for heritable interrelationships among all six disorders. Most analyses indicated significantly increased risk for each of the six disorders in FDR, SDR, and TDR of all or most proband groups. Out of 30 possible bidirectional disorder interrelationships, 26 were significant among FDR, 23 were significant among SDR, and 7 were significant among TDR. Clustering was observed in both close and distant relatives. Conclusions: Our results support a common, heritable component to IC and other nociplastic and psychiatric conditions.

Are Pelvic Pain and Increased Pelvic Floor Muscle Tone Associated in Women with Persistent Noncancer Pelvic Pain? A Systematic Review and Meta-Analysis. Kadah S, Soh SE, Morin M, Schneider M, Ang WC, McPhate L, Frawley H. J Sex Med. 2023 Jul 28:qdad089. doi: 10.1093/jsxmed/qdad089. Epub ahead of print. PMID: 37507352.

Background: The association between pelvic pain and pelvic floor muscle (PFM) tone in women with persistent noncancer pelvic pain (PNCPP) is unclear. Aim: To synthesize the evidence of the association between pelvic pain and PFM tone in women with PNCPP. Methods: A systematic review was conducted via MEDLINE, Emcare, Embase, CINAHL, PsycINFO, and Scopus to identify relevant studies. Studies were eligible if pelvic pain and

PFM tone outcome measures were reported among women aged >18 years. The National Heart, Lung, and Blood Institute's Quality Assessment Tool for Observational Cohort and Cross-sectional Studies was used to assess study quality. Studies were pooled by assessment of PFM tone via a random effects model. Associations between the presence of pelvic pain and PFM tone were assessed with odds ratio (OR), while linear associations were assessed with Pearson or Spearman correlation. Outcomes: Pelvic pain measures (intensity, threshold, and frequency) and resting PFM tone in women with PNCPP, as evaluated by any clinical assessment method or tool. Results: Twenty-four studies were included in this review. The presence of pelvic pain was significantly associated with increased PFM tone as assessed by digital palpation (OR, 2.85; 95% CI, 1.66-4.89). Pelvic pain intensity was inversely but weakly associated with PFM flexibility when evaluated through dynamometry (r = -0.29; 95% CI, -0.42 to -0.17). However, no significant associations were found between pelvic pain and PFM tone when measured with other objective assessment methods. Clinical implications: Pelvic pain and increased PFM tone may not be directly associated; alternatively, a nonlinear association may exist. A range of biopsychosocial factors may mediate or moderate the association, and clinicians may need to consider these factors when assessing women with PNCPP. Strengths and limitations: This review was reported according to the PRISMA guidelines. All possible findings from relevant theses and conference abstracts were considered in our search. However, nonlinear associations between pelvic pain and increased PFM tone were not assessed as part of this review. Conclusion: Pelvic pain may be linearly associated with increased PFM tone and decreased PFM flexibility when measured with digital palpation or dynamometry; however, this association was not observed when other aspects of PFM tone were assessed through objective methods. Future studies are required using robust assessment methods to measure PFM tone and analyses that account for other biopsychosocial factors that may influence the association.

#### Laser Treatment for Patients with Vulvodynia and Interstitial Cystitis/Bladder Pain Syndrome: A Case Series (The UNICORN-3 Study).

Okui N, Okui MA, Kouno Y, Nakano K.

Cureus. 2023 Jul 12;15(7):e41786. doi: 10.7759/cureus.41786. PMID: 37449291; PMCID: PMC10338019.

Introduction: Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic pain disorder characterized by urgency, frequency of urination, and pelvic pain. Women with IC/BPS often experience sexual dysfunction, vulvodynia, and vaginal health issues. Combined erbium and neodymium yttrium aluminum garnet (YAG) laser treatments targeting the vagina and vulva have shown promise in improving symptoms. Our study aims to investigate the effectiveness of these combined laser treatments in women with IC/BPS and vulvodynia. Methods Women diagnosed with vulvodynia and IC/BPS underwent combined laser treatment using vaginal erbium:YAG laser (VEL) and neodymium:YAG laser (Nd:YAG). Various parameters were evaluated, including the vulvodynia test, numeric rating scale (NRS-11) for pain, interstitial cystitis symptom index and problem index (ICSI and ICPI), pelvic pain and urgency/frequency symptom score (PUF), and mean urination volume/daily urination frequency in a three-day urination diary. Treatment was administered three times, with intervals of one month between each session, and follow-up evaluations were conducted at six and 12 months. All statistical analyses were designed and programmed by the Al chatbot GPT-4 (chatGPT-4). Results Fifteen female patients diagnosed with vulvodynia and IC/BPS were treated with three sessions of VEL + Nd:YAG. Significant improvements were observed in the vulvodynia test, NRS-11 scores, PUF, ICSI scores, ICPI scores, mean urination volume, and daily urination frequency at six and 12 months (p<0.01). Short-term improvements in IC/BPS pain scores correlated with improvements in the vulvodynia test (p=0.007), suggesting a synergistic effect. However, no significant correlations were found at 12 months. Conclusion Combined laser treatments targeting the vagina and vulva showed significant therapeutic effects in women with IC/BPS and vulvodynia. The addition of Nd:YAG to the VEL treatment enhanced outcomes. Short-term improvements in IC/BPS pain scores correlated with improvements in the vulvodynia test, indicating a synergistic effect. Long-term improvements in both vulvodynia and IC/BPS symptoms may occur independently. These findings highlight the importance of comprehensive approaches for treating coexisting vulvodynia and IC/BPS.

# Low Dose Naltrexone's Utility for Non-Cancer Centralized Pain Conditions - A Scoping Review.

Rupp A, Young E, Chadwick AL.

Pain Med. 2023 Jun 11:pnad074. doi: 10.1093/pm/pnad074. Epub ahead of print. PMID: 37302106.

Background: At low doses, naltrexone (LDN) has been shown to modulate inflammation through the interruption of microglial cell activation within the central nervous system. One of the most likely contributors to centralized pain is changes in microglial cell processing, therefore, it has been postulated that LDN can be used to manage patients with pain resulting from central sensitization due to this relationship. This scoping review aims to synthesize the relevant study data for LDN as a novel treatment strategy for various centralized pain conditions. Methods: A comprehensive literature search was conducted using PubMed, Embase, and Google Scholar guided by the Scale for Assessment of Narrative Review Articles (SANRA) criteria. Results: 47 studies related to centralized pain conditions were identified. Many of the studies were case reports/series and narrative reviews, however a few RCTs have been conducted. Overall, the body of evidence revealed improvement in patient-reported pain severity as well outcomes related to hyperalgesia, physical function, quality of life, and sleep. Variability in dosing paradigms and the time to patient response was present in the reviewed studies. Conclusions: Evidence synthesized for this scoping review supports the ongoing use of LDN for the treatment of refractory pain in various centralized chronic pain conditions. Upon review of the current available published studies, it is apparent that further high-quality, well-powered RCTs need to be conducted in order to establish efficacy, standardization for dosing, and determine response times. In summary, LDN continues to offer promising results in the management of pain and other distressing symptoms in patients with chronic centralized pain conditions.

### What Do We Know about Nociplastic Pain?

Bułdyś K, Górnicki T, Kałka D, Szuster E, Biernikiewicz M, Markuszewski L, Sobieszczańska M.

Healthcare (Basel). 2023 Jun 17;11(12):1794. doi: 10.3390/healthcare11121794. PMID: 37372912; PMCID: PMC10298569.

Nociplastic pain is a recently distinguished type of pain, distinct from neuropathic and nociceptive pain, and is well described in the literature. It is often mistaken for central sensitization. Pathophysiology has not been clearly established with regard to alteration of the concentration of spinal fluid elements, the structure of the white and gray matter of the brain, and psychological aspects. Many different diagnostic tools, i.e., the painDETECT and Douleur Neuropathique 4 questionnaires, have been developed to diagnose neuropathic pain, but they can also be applied for nociplastic pain; however, more standardized instruments are still needed in order to assess its occurrence and clinical presentation. Numerous studies have shown that nociplastic pain is present in many different diseases such as fibromyalgia, complex regional pain syndrome type 1, and irritable bowel syndrome. Current pharmacological and nonpharmacological treatments for nociceptive and neuropathic pain are not entirely suitable for treating nociplastic pain. There is an ongoing effort to establish the most efficient way to manage it. The significance of this field has led to several clinical trials being carried out in a short time. The aim of this narrative review was to discuss the currently available evidence on pathophysiology, associated diseases, treatment possibilities, and clinical trials. It is important that physicians widely discuss and

acknowledge this relatively new concept in order to provide optimized pain control for patients.

Noziplastischer Schmerz in Forschung und Praxis : Übersicht über biopsychosoziale Grundlagen, Möglichkeiten und Schwierigkeiten [Nociplastic Pain in Research and Practice : Overview of Biopsychosocial Principles, Possibilities and Difficulties]. Schmidt H, Blechschmidt V.

Schmerz. 2023 Aug;37(4):242-249. German. doi: 10.1007/s00482-023-00734-5. Epub 2023 Jul 11. PMID: 37432482.

Traditionally, two mechanistic pain categories were distinguished: nociceptive and neuropathic pain. After the definitions of these two mechanistic descriptors were refined more precisely in the International Association for the Study of Pain (IASP) taxonomy in 2011, a large group of patients remained whose pain could not be assigned to either of the two categories. Nociplastic pain was therefore proposed as a third mechanistic descriptor in 2016. This review article presents the current state of the integration of nociplastic pain into research and clinical practice. In particular, the possibilities and difficulties of applying this concept are addressed from a human and animal experimental research perspective.

#### Craniofacial Disorders and Headaches. A Narrative Review.

Piekartz HV, van der Meer H, Olivo SA. Musculoskelet Sci Pract. 2023 Jul 1:102815. doi: 10.1016/j.msksp.2023.102815. Epub ahead of print. PMID: 37419842.

Objectives: Craniofacial- and headache disorders are common co-morbid disorders. The aim of this review is to provide an overview of the research discussing craniofacial pain, especially temporomandibular disorders, and its relationship and impact on headaches, as well as suggestions for diagnostic assessment tools and physical therapeutic management strategies. Method: A narrative structured review was performed. A search was conducted in MEDLINE using terms related to craniofacial pain and headaches. Additionally, papers regarding this topic were also extracted from the authors' personal libraries. Any study design (i.e., RCT, observational studies, systematic review, narrative review) that reported the concepts of interest was included, using Covidence. Results were narratively synthesized and described. Results: From an epidemiological perspective, craniofacial pain and headaches are strongly related and often co-existing. This may be due to the neuroanatomical connection with the trigeminal cervical complex, or due to shared predisposing factors such as age, gender, and psychosocial factors. Pain drawings, questionnaires, and physical tests can be used to determine the cause of pain, as well as other perpetuating factors in patients with headaches and craniofacial pain. The evidence supports different forms of exercise and a combination of hands-on and hands-off strategies aimed at both the craniofacial pain as well as the headache. Conclusion: Headaches may be caused or aggravated by different disorders in the craniofacial region. Proper use of terminology and classification may help in understanding these complaints. Future research should look into the specific craniofacial areas and how headaches may arise from problems from those regions. (249 words).

# Endometriosis and the Diagnosis of Different Forms of Migraine: An Association with Dysmenorrhoea.

Pasquini B, Seravalli V, Vannuccini S, La Torre F, Geppetti P, Iannone L, Benemei S, Petraglia F.

Reprod Biomed Online. 2023 Jul;47(1):71-76. doi: 10.1016/j.rbmo.2023.03.020. Epub 2023 Apr 7. PMID: 37202318.

Research question: Women with endometriosis are frequently affected by headache. How many of these have a clear diagnosis of migraine? Are the different forms of migraine related

to the phenotypes and/or characteristics of endometriosis? Design: This was a prospective nested case-control study. A consecutive series of 131 women with endometriosis who attended the endometriosis clinic were enrolled and examined for the presence of headache. A headache guestionnaire was used to determine the characteristics of the headaches, and the diagnosis of migraine was confirmed by a specialist. The case group included women with endometriosis and a diagnosis of migraine, while the control group included women with only endometriosis. History, symptoms and other comorbidities were collected. A pelvic pain score and associated symptoms were assessed using a visual analogue scale. Results: A diagnosis of migraine was made in 53.4% (70/131) of participants. Pure menstrual migraine was reported by 18.6% (13/70), menstrually related migraine by 45.7% (32/70) and nonmenstrual migraine by 35.7% (25/70). Dysmenorrhoea and dysuria were significantly more frequent in patients with endometriosis and migraine than in those without migraine (P = 0.03) and P = 0.01). No difference was found for other variables, including age at diagnosis and duration of endometriosis, endometriosis phenotype, the presence of other autoimmune comorbidities or heavy menstrual bleeding. In most patients with migraine (85.7%) the headache symptoms had started years before the diagnosis of endometriosis. Conclusion: The occurrence of headache in many patients with endometriosis is associated with the presence of different forms of migraine, is related to pain symptoms and often precedes the diagnosis of endometriosis.

## Debate: Differences and Similarities between Tension-Type Headache and Migraine.

Onan D, Younis S, Wellsgatnik WD, Farham F, Andruškevičius S, Abashidze A, Jusupova A, Romanenko Y, Grosu O, Moldokulova MZ, Mursalova U, Saidkhodjaeva S, Martelletti P, Ashina S.

J Headache Pain. 2023 Jul 21;24(1):92. doi: 10.1186/s10194-023-01614-0. PMID: 37474899; PMCID: PMC10360340.

Tension-type headache (TTH) and migraine are two common primary headaches distinguished by clinical characteristics according to the third edition of the International Classification of Headache Disorders. Migraine is identified by specific features such as being more prevalent in females, being aggravated by physical activity, certain genetic factors, having photophobia, phonophobia, nausea, vomiting, or aura, and responding to specific drugs. Nonetheless, TTH and migraine share some common characteristics, such as onset occurring in the 20 s, and being triggered by psychological factors like stress. moderate pain severity, and mild nausea in chronic TTH. Both conditions involve the trigeminovascular system in their pathophysiology. However, distinguishing between TTH and migraine in clinical practice, research, and epidemiological studies can be challenging, as there is a lack of specific diagnostic tests and biomarkers. Moreover, both conditions may coexist, further complicating the diagnostic process. This review aims to explore the similarities and differences in the pathophysiology, epidemiology, burden and disability, comorbidities, and responses to pharmacological and non-pharmacological treatments of TTH and migraine. The review also discusses future research directions to address the diagnostic challenges and improve the understanding and management of these conditions.

# Yoga Versus Education for Veterans with Chronic Low Back Pain: A Randomized Controlled Trial.

Roseen EJ, Pinheiro A, Lemaster CM, Plumb D, Wang S, Elwy AR, Streeter CC, Lynch S, Groessl E, Sherman KJ, Weinberg J, Saper RB.

J Gen Intern Med. 2023 Jul;38(9):2113-2122. doi: 10.1007/s11606-023-08037-2. Epub 2023 Jan 17. PMID: 36650329; PMCID: PMC10361953.

Background: Yoga is effective for chronic low back pain (cLBP) in civilians but understudied among Veterans. Objective: Determine whether yoga is more effective than an educational book for improving disability and pain among Veterans with cLBP. Design, setting, and participants: Veterans diagnosed with cLBP at a VA medical center enrolled in a randomized

controlled trial from March to December of 2015. Interventions: Twelve weekly hatha yoga classes or education using The Back Pain Helpbook. Measures: Co-primary outcomes were changes from baseline at 12 weeks in back-related disability on the modified Roland Morris Disability Questionnaire and pain on the Defense & Veterans Pain Rating Scale. Secondary outcomes were global improvement, patient satisfaction, pain medication use, and posttraumatic stress symptoms. An intention-to-treat approach was used in primary analyses. Results: One hundred twenty Veterans (mean age, 55.5 [SD = 16.9]; 11 [9%] women; mean number of chronic conditions, 5.5) were randomized to yoga (n = 62) and education (n = 58). At 12 weeks, reductions in back-related disability in yoga (mean difference [MD] = - 3.50, 95% CI: - 5.03, - 1.97) were not significantly different than education (MD = - 2.55, 95% CI: -4.10, - 0.99; between-group difference: - 0.95 [95% CI: - 3.14, 1.23], p = 0.39). For pain, there was no significant difference between yoga (MD = - 1.01, 95% CI: - 1.67, - 0.35) and education (MD = - 0.81, 95% CI: - 1.36, - 0.27; between-group difference: - 0.20, 95% CI: -1.06, 0.66, p = 0.65). More yoga than education participants reported being very much or extremely improved (39% vs 19%, OR = 3.71, 95% CI: 1.37, 10.02, p = 0.01) and very satisfied with treatment (60% vs 31%, OR = 4.28, 95% CI: 1.70, 10.77, p = 0.002). No differences in pain medication use or post-traumatic stress symptoms were observed at 12 weeks. No serious adverse events were reported in either group. Conclusion: Twelve weekly yoga classes were not more effective than an education intervention for improving pain or disability outcomes among mostly older male Veterans with cLBP and multiple comorbid health conditions.

A Novel Classification of Endometriosis Based on Clusters of Comorbidities.

Sarria-Santamera A, Yemenkhan Y, Terzic M, Ortega MA, Asunsolo Del Barco A. Biomedicines. 2023 Sep 2;11(9):2448. doi: 10.3390/biomedicines11092448. PMID: 37760889; PMCID: PMC10525703.

Endometriosis is a heterogeneous, complex, and still challenging disease, due to its epidemiological, etiological and pathogenic, diagnostic, therapeutic, and prognosis characteristics. The classification of endometriosis is contentious, and existing therapies show significant variability in their effectiveness. This study aims to capture and describe clusters of women with endometriosis based on their comorbidity. With data extracted from electronic records of primary care, this study performs a hierarchical clustering with the Ward method of women with endometriosis with a subsequent analysis of the distribution of comorbidities. Data were available for 4055 women with endometriosis, and six clusters of women were identified: cluster 1 (less comorbidity), cluster 2 (anxiety and musculoskeletal disorders), cluster 3 (type 1 allergy or immediate hypersensitivity); cluster 4 (multiple morbidities); cluster 5 (anemia and infertility); and cluster 6 (headache and migraine). Clustering aggregates similar units into similar clusters, partitioning dissimilar objects into other clusters at a progressively finer granularity-in this case, groups of women with similarities in their comorbidities. Clusters may provide a deeper insight into the multidimensionality of endometriosis and may represent diverse "endometriosis trajectories" which may be associated with specific molecular and biochemical mechanisms. Comorbiditybased clusters may be important to the scientific study of endometriosis, contributing to the clarification of its clinical complexity and variability. An awareness of those comorbidities may help elucidate the etiopathogenesis and facilitate the accurate earlier diagnosis and initiation of treatments targeted toward particular subgroups.

## Typing Myalgic Encephalomyelitis by Infection at Onset: A DecodeME Study.

Bretherick AD, McGrath SJ, Devereux-Cooke A, Leary S, Northwood E, Redshaw A, Stacey P, Tripp C, Wilson J, Chowdhury S, Lewis I, Almelid Ø, Baby SV, Baker T, Becher H, Boutin T, Clyde M, Garcia D, Ireland J, Kerr SM, McDowall E, Perry D, Samms GL, Vitart V, Wolfe JC, Ponting CP.

NIHR Open Res. 2023 Aug 21;3:20. doi: 10.3310/nihropenres.13421.4. PMID: 37881452; PMCID: PMC10593357.

Background: People with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) experience core symptoms of post-exertional malaise, unrefreshing sleep, and cognitive impairment. Despite numbering 0.2-0.4% of the population, no laboratory test is available for their diagnosis, no effective therapy exists for their treatment, and no scientific breakthrough regarding pathogenesis has been made. It remains unknown, despite decades of small-scale studies, whether individuals experience different types of ME/CFS separated by onset-type. sex or age. Methods: DecodeME is a large population-based study of ME/CFS that recruited 17,074 participants in the first 3 months following full launch. Detailed guestionnaire responses from UK-based participants who all reported being diagnosed with ME/CFS by a health professional provided an unparalleled opportunity to investigate, using logistic regression, whether ME/CFS severity or onset type is significantly associated with sex, age, illness duration, comorbid conditions or symptoms. Results: The well-established sex-bias among ME/CFS patients is evident in the initial DecodeME cohort: 83.5% of participants were females. What was not known previously was that females tend to have more comorbidities than males. Moreover, being female, being older and being over 10 years from ME/CFS onset are significantly associated with greater severity. Five different ME/CFS onset types were examined in the self-reported data; those with ME/CFS onset (i) after glandular fever (infectious mononucleosis); (ii) after COVID-19 infection; (iii) after other infections; (iv) without an infection at onset; and, (v) where the occurrence of an infection at or preceding onset is not known. Among other findings, ME/CFS onset with unknown infection status was significantly associated with active fibromyalgia. Conclusions: DecodeME participants differ in symptoms, comorbid conditions and/or illness severity when stratified by their sex-at-birth and/or infection around the time of ME/CFS onset.

Hierarchical Cluster Analysis Based on Clinical and Neuropsychological Symptoms <u>Reveals Distinct Subgroups in Fibromyalgia: A Population-Based Cohort Study.</u> Maurel S, Giménez-Llort L, Alegre-Martin J, Castro-Marrero J. Biomedicines. 2023 Oct 23;11(10):2867. doi: 10.3390/biomedicines11102867. PMID: 37893239; PMCID: PMC10604090.

Fibromyalgia (FM) is a condition characterized by musculoskeletal pain and multiple comorbidities. Our study aimed to identify four clusters of FM patients according to their core clinical symptoms and neuropsychological comorbidities to identify possible therapeutic targets in the condition. We performed a population-based cohort study on 251 adult FM patients referred to primary care according to the 2010 ACR case criteria. Patients were aggregated in clusters by a K-medians hierarchical cluster analysis based on physical and emotional symptoms and neuropsychological variables. Four different clusters were identified in the FM population. Global cluster analysis reported a four-cluster profile (cluster 1: pain, fatigue, poorer sleep quality, stiffness, anxiety/depression and disability at work; cluster 2: injustice, catastrophizing, positive affect and negative affect; cluster 3: mindfulness and acceptance; and cluster 4: surrender). The second analysis on clinical symptoms revealed three distinct subgroups (cluster 1: fatigue, poorer sleep quality, stiffness and difficulties at work; cluster 2: pain; and cluster 3: anxiety and depression). The third analysis of neuropsychological variables provided two opposed subgroups (cluster 1: those with high scores in surrender, injustice, catastrophizing and negative affect, and cluster 2: those with high scores in acceptance, positive affect and mindfulness). These empirical results support models that assume an interaction between neurobiological, psychological and social factors beyond the classical biomedical model. A detailed assessment of such risk and protective factors is critical to differentiate FM subtypes, allowing for further identification of their specific needs and designing tailored personalized therapeutic interventions.

#### <u>Clinical Features of Chronic Primary Pain in Individuals Presenting Painful</u> <u>Temporomandibular Disorder and Comorbidities.</u>

Dos Santos Proença J, Baad-Hansen L, do Vale Braido GV, Campi LB, de Godoi Gonçalves DA.

J Oral Rehabil. 2023 Sep 19. doi: 10.1111/joor.13598. Epub ahead of print. PMID: 37727030.

Background: The diagnosis of chronic primary pain (CPP), according to the recently released International Classification of Disease (ICD-11) criteria, refers to conditions with complex aetiologies. CPP is characterized by specific clinical features such as generalized sensory hypersensitivity and widespread pain, and is associated with functional disability and emotional distress. Objective: This study investigated clinical features of CPP in individuals with painful temporomandibular disorders (TMD) and comorbidities (fibromyalgia, migraine and/or tension-type headache). Methods: This cross-sectional study was conducted with a sample of 129 individuals. Painful TMD, fibromyalgia and primary headaches were evaluated based on well-established international criteria. Generalized sensory hypersensitivity was assessed using psychophysical tests. Symptoms of anxiety and depression were assessed by the Generalized Anxiety Disorder-7 and Patient Health Questionnaire-9. The Central Sensitization Inventory was applied to assess central sensitization-related symptoms and the Pittsburg Sleep Quality Index to evaluate the quality of sleep. The presence of widespread pain was assessed using a body map. The sample was stratified into three groups: control (n = 25), TMD-painful TMD only (n = 35) and TMD + Cm-painful TMD and comorbidities (n = 69). Statistical analysis was performed using one-way ANOVA, chi-squared test and ANCOVA, considering gender as a covariate ( $\alpha = .05$ ). Results: Compared to controls, individuals presenting painful TMD and comorbidities showed lower pressure pain thresholds in all evaluated areas ( $p \le .012$ ) and a higher number of painful areas in the body (p = .001). They presented more symptoms of anxiety (p = .040) and depression (p = .018), and a higher score in the Central Sensitization Inventory ( $p \le .006$ ) than the other groups. Conclusion: Individuals with painful TMD and comorbidities presented more clinical features of CPP compared to those affected by TMD only.

### <u>Characteristics of Temporomandibular Disorders and Orofacial Pain in Individuals</u> with Rheumatoid Arthritis.

Mesic VF, Laskarin AM, Kehler T, Spalj S, Dozet M, Pavicic DK. Int J Prosthodont. 2023 Nov 1;36(5):630-636. doi: 10.11607/ijp.8145. PMID: 36484668.

Purpose: To compare characteristics of temporomandibular disorders (TMDs) in patients with rheumatoid arthritis (RA) to patients without RA. Materials and methods: The sample included 80 patients (aged 33 to 73 years; 88% women and 22% men) with 40 in each group. An international diagnostic protocol for TMDs was followed. Results: Arthralgia was the most prevalent TMD in the RA group. Orofacial pain was more common in the RA group than in the controls (42.5% vs 15%, P = .031), with higher chronic pain grade and pain intensity (P ≤ .005). Somatization and depression were also increased (P < .001). In multiple logistic regression analysis, arthralgia (OR: 6.4; 95% CI: 1.1 to 37.1; P = .038) and age ≥ 55 years were predictors of RA (OR: 3.9; 95% CI: 1.4 to 10.8; P = .009) when controlling for the effects of biological sex and pain intensity. TMDs were related to 7.4 times higher odds for presence of orofacial pain, while RA was related to 3.4 times higher odds for pain. Conclusions: RA patients experienced more orofacial pain and higher pain intensity, somatization, and depression compared to healthy individuals. Pain is more influenced by TMDs than by RA.

## Symptoms of Complex Pelvic Pain: A Survey in Three Cohorts of Women.

Hagemann CT, Spetalen S, Saga S, Bratlie I, Dons V, Stafne SN. Acta Obstet Gynecol Scand. 2023 Oct;102(10):1396-1408. doi: 10.1111/aogs.14678. Epub 2023 Sep 12. PMID: 37698177; PMCID: PMC10540926.

Introduction: There has been increased interest in addressing chronic pelvic pain and its complexity in women. The often multifactorial etiology of chronic pelvic pain and its heterogeneous presentation, however, make the condition challenging to manage. Overlap with other pain-related conditions is frequently reported, and chronic pelvic pain may impact sexual function. Nevertheless, little is known about the symptom burden of chronic pelvic pain and more complex pelvic pain in different groups of women. Thus, the aim of our study was to use a newly validated Norwegian version of the Amsterdam Complex Pelvic Pain Symptom Scale (ACPPS) to describe and compare the symptom severity of complex pelvic pain in three cohorts of women and to assess associations between demographic and gynecological characteristics and the severity of the condition. Material and methods: In our cross-sectional study, we collected self-reported data from patients referred to gynecological outpatient clinics, members of vulvodynia or endometriosis patient associations, and healthy volunteers. The 397 participants (47% response rate) completed an online survey about their demographic and gynecological characteristics and symptoms related to complex pelvic pain, including the Norwegian ACPPS. Score means on guestionnaires, with standard deviations and 95% confidence intervals, were recorded. We used Pearson's chi-square test, Analysis of variance and multivariable linear regression were used to assess associations of demographic and gynecological characteristics with ACPPS scores, Results; Members of the patient associations had significantly higher self-reported symptom burden than patients and volunteers. Symptom burden was lower among older and postmenopausal women, and unemployed women scored higher than employed ones. Especially high scores on the ACPPS were found among women with complaints of chronic pelvic pain, at least moderate pelvic pain intensity, and/or chronic vulvar pain. Women who had experienced sexual assault and/or reported low sexual function also reported high scores. In multivariable regression, fibromvalgia, low mental health and past sexual assault were found to be associated with high scores on the ACPPS. Conclusion: Many women in our study reported complex pelvic pain, and overlap with other pain-related conditions, low mental health and past sexual assault was associated with high symptom burden. Those findings support taking a biopsychosocial approach to treating women who present with such complaints.

# Qualitative and Quantitative Assessment of Headaches in People with Temporomandibular Joint Disorders: A Pilot Study.

Gębska M, Frąszczak M, Dalewski B, Kołodziej Ł. Adv Clin Exp Med. 2023 Oct;32(10):1193-1199. doi: 10.17219/acem/171821. PMID: 37747439.

Background: Headaches (HAs) and temporomandibular joint dysfunction (TMD) are common comorbidities, and the presence of one of them in a patient increases the incidence of the other. The relationship between these 2 conditions may involve common pathophysiological processes. Considering the topicality of the problem, it is justified to conduct research in this field. In this study, we assessed HA type and severity in people with TMD. Objectives: The aim of the study was to conduct qualitative and quantitative assessments of HAs in people with temporomandibular joint (TMJ) disorders. Material and methods: The study group consisted of 51 subjects of both sexes with a TMD diagnosed using the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) test. A self-report questionnaire was utilized to self-assess the presence of TMD symptoms, while the standardized Short-Form of the McGill Pain Questionnaire was used to gualitatively and guantitatively assess HAs. Results: People with TMD were significantly more likely to report HA occurrences (p < p0.001). Pain intensity was statistically significantly higher among individuals with TMD compared to those without TMD symptoms (p < 0.001). Most often, the HA was associated with a pressing pain (r = 0.82) and least often, it was described as cutting (r = 0.30). Neck and shoulder girdle pain (p = 0.059; 82.9%) and clenching and/or grinding of teeth (p =0.021; 92.7%) were significantly more common among patients who declared HAs than among those without HAs. The results obtained so far may indicate a significant relationship between HA and TMD. Conclusion: We have described the relationship between the

occurrence of HAs and TMD. Headaches are more frequent and more severe in people with TMD.

# Exploring Comorbidities in Adolescent and Young Adults with Hypermobile Ehlers-Danlos Syndrome with and without a Surgical History: A Preliminary Investigation.

Gagnon H, Lunde CE, Wu Z, Novais EN, Borsook D, Sieberg CB. Children (Basel). 2023 Sep 16;10(9):1562. doi: 10.3390/children10091562. PMID: 37761523; PMCID: PMC10528958.

Ehlers-Danlos Syndrome (EDS) is a rare disease affecting the skin, joints, vasculature, and internal organs. Approximately 85% of those affected are categorized as the hypermobile type (hEDS), which is associated with numerous medical and psychiatric comorbidities, including chronic pain. Additionally, approximately 71% of patients with hEDS undergo at least one surgical procedure; however, indicators for surgery and pain outcomes after surgery are poorly understood. This preliminary study used a medical chart review to identify the frequency and nature of comorbidities in a cohort of adolescents and young adult patients with hEDS and a surgical history compared to those without a surgical history. Results showed that patients diagnosed with hEDS who underwent surgery reported significantly more comorbidities (e.g., CRPS, IBS, Fibromyalgia, POTS, hypothyroidism, etc.) than those who did not have surgery. Seventy percent of individuals who presented for surgery fell within the categories of orthopedic, gastrointestinal, or

laparoscopic/endometriosis-related surgeries. Identifying patients with hEDS who are at risk for needing surgery will help identify the mechanisms contributing to risk factors for poor surgical outcomes. The results of this study may be instructive in the management and care of hEDS patients undergoing surgery.

# Dysautonomia, Hypermobility Spectrum Disorders and Mast Cell Activation Syndrome as Migraine Comorbidities.

Blitshteyn S.

Curr Neurol Neurosci Rep. 2023 Oct 17. doi: 10.1007/s11910-023-01307-w. Epub ahead of print. PMID: 37847487.

Purpose of review: Dysautonomia refers to the dysfunction of the autonomic nervous system and encompasses a wide variety of autonomic symptoms and disorders. The most common autonomic disorders are postural orthostatic tachycardia syndrome (POTS), neurocardiogenic syncope (NCS), and orthostatic hypotension (OH), which may be encountered in clinical practice as part of a triad of dysautonomia, hypermobility spectrum disorders (HSD), and mast cell activation syndrome (MCAS). Migraine is one of the most common comorbidities of POTS, HSD, and MCAS; conversely, these conditions are also prevalent in patients with migraine, especially in those with multiple systemic symptoms, such as chronic dizziness, lightheadedness, orthostatic intolerance, joint pain, and allergic symptoms. Diagnostic criteria, pathophysiologic mechanisms, and therapeutic considerations in patients with migraine and comorbid dysautonomia, HSD, and MCAS are reviewed. Recent findings: Numerous studies indicate a significant overlap and shared pathophysiology in migraine, dysautonomia, HSD, and MCAS. In clinical setting, dysautonomia, HSD, and MCAS may present a diagnostic and therapeutic challenge in patients with migraine and require a high index of suspicion on the part of the neurologist. Diagnosis and treatment of these complex disorders in patients with migraine is essential to comprehensive patientcentric care, reduced symptom burden, and improved functional impairment secondary to both migraine and comorbidities.

# **Epidemiology Studies**

## Associations and Gastrointestinal Symptoms in Women with Endometriosis in Comparison to Women with Irritable Bowel Syndrome: A Study Based on a Population Cohort.

Junkka SS, Ohlsson B. BMC Gastroenterol. 2023 Jul 3;23(1):228. doi: 10.1186/s12876-023-02861-w. PMID: 37400789; PMCID: PMC10316551.

Background: Endometriosis and irritable bowel syndrome (IBS) have similar symptoms, pathogenesis, and risk factors. These diagnoses often coexist and are frequently misdiagnosed leading to diagnostic delays. This study of a population-based cohort aimed to investigate associations relating to endometriosis and IBS and to compare gastrointestinal symptoms between endometriosis and IBS. Method: The study cohort included women from the Malmö Offspring Study with information about endometriosis and IBS diagnoses from the National Board of Health and Welfare. The participants answered a questionnaire about lifestyle habits, medical and drug history, and self-reported IBS. The visual analog scale for IBS was used to estimate gastrointestinal symptoms the past 2 weeks. Endometriosis diagnosis and self-reported IBS were used as dependent variables to study associations with age, body mass index (BMI), education, occupation, marital status, smoking, alcohol habits, and physical activity using logistic regression. Mann-Whitney U Test or Kruskal-Wallis tests were used to calculate the differences in symptoms between groups. Results: Of the 2,200 women with information from medical records, 72 participants had endometriosis; 21 (29.2%) of these had self-reported IBS. Of the 1,915 participants who had answered the questionnaire, 436 (22.8%) had self-reported IBS. Endometriosis was associated with IBS (OR:1.86; 95%CI:1.06-3.26; p = 0.029), as well as with age 50-59 years (OR:6.92; 95%CI:1.97-24.32; p = 0.003), age ≥ 60 years (OR:6.27; 95%CI:1.56-25.17; p = 0.010), sick leave (OR:2.43; 95%CI:1.08-5.48; p = 0.033), and former smoking (OR:3.02; 95%CI:1.19-7.68; p = 0.020). There was an inverse association with BMI (OR: 0.36; 95%CI: 0.14-4.91; p = 0.031). IBS was associated with endometriosis (OR:1.77; 95%CI:1.02-3.07; p = 0.041) and sick leave (OR:1.77; 95%CI:1.14-2.73; p = 0.010), with a tendency to association with smoking (OR:1.30; 95%CI:0.98-1.72; p = 0.071). When excluding participants using drugs associated with IBS, the condition was associated with current smoking (OR:1.39; 95%Cl:1.03-1.89; p = 0.033) and inversely with age 50-59 years (OR:0.58; 95%Cl:0.38-0.90; p = 0.015). There were differences in the gastrointestinal symptoms between IBS and healthy participants, but not between endometriosis and IBS or healthy participants. Conclusion: There were associations between endometriosis and IBS, without differences in gastrointestinal symptoms. Both IBS and endometriosis were associated with smoking and sick leave. Whether the associations reflect causality or depend on common risk factors and pathogenesis remains to be determined.

# Associations between Endometriosis and Common Symptoms: Findings from the Australian Longitudinal Study on Women's Health.

Gete DG, Doust J, Mortlock S, Montgomery G, Mishra GD. Am J Obstet Gynecol. 2023 Jul 25:S0002-9378(23)00505-7. doi: 10.1016/j.ajog.2023.07.033. Epub ahead of print. PMID: 37499990.

Background: Endometriosis has been linked with higher rates of a variety of symptoms; however, the findings from longitudinal studies are scarce and inconsistent. Objectives: To examine the association between endometriosis and common symptoms in a prospective cohort study. Study design: This study included 7606 women born in 1973-78 using data from the Australian Longitudinal Study on Women's Health surveyed each 3 years from 2009 to 2018. We identified women with endometriosis using self-report from each survey and linked administrative health data. At each survey, women also completed a checklist on the presence of 24 symptoms. Generalised estimating equations for multinomial responses were used for analyses. Results: Women with endometriosis had significantly more menstrual symptoms than those without endometriosis with adjusted odds ratios (95% CIs) for severe

period pain 3.61 (3.11-4.19), heavy menstrual bleeding 2.40 (2.10-2.74), irregular bleeding 1.76 (1.52-2.03), and pre-menstrual tension 1.52 (1.32-1.76); and had higher odds of mental health problems: depression 1.67 (1.39-2.01), anxiety 1.59 (1.24-2.03); allergies and nonspecific symptoms: allergies/ hay-fever/ sinusitis 1.62 (1.40-1.89), severe tiredness 1.79 (1.56-2.05), sleep difficulty 1.56 (1.35-1.81), and palpitations 1.77 (1.37-2.18). There was also a strong association with other forms of pain: backpain 1.76 (1.53-2.04), headaches/migraines 1.50 (1.29-1.74), and stiff/ painful joints 1.65 (1.41-1.93). Women with endometriosis also had increased odds of developing bowel and urinary symptoms; constipation 1.67 (1.35-2.08), haemorrhoids/piles 1.46 (1.12-1.90), indigestion/heartburn 1.25 (1.03-1.52), urine burn/stings 2.80 (1.71-4.58), and vaginal discharge/irritation 1.37 (1.03-1.82). The association between each symptom and endometriosis was similar whether endometriosis was surgically confirmed or clinically suspected. No association was found between endometriosis and the risk of skin problems, leaking urine, or breathing difficulty. Conclusions: This study suggests that women with endometriosis are more likely to report not only menstrual symptoms, but also that there is an increased risk of mental health disorders, other pain symptoms, bowel and urinary symptoms, and non-specific symptoms such as severe tiredness and difficulty sleeping.

# Temporomandibular Disorders and Fibromyalgia Prevalence: A Systematic Review and Meta-Analysis.

Yakkaphan P, Smith JG, Chana P, Tan HL, Ravindranath PT, Lambru G, Renton T. J Oral Facial Pain Headache. 2023 Nov 17;37(3):177-193. doi: 10.11607/ofph.3260. PMID: 37975782.

Purpose: To evaluate the prevalence of chronic widespread pain (CWP) and fibromyalgia syndrome (FMS) in TMD patients and the prevalence of TMDs in patients with FMS. Method: A systematic search was performed in electronic databases. Studies published in English examining the prevalence of comorbid TMDs and CWP/FMS were included. The Newcastle-Ottawa Scale was used to assess study quality, and meta-analyses using defined diagnostic criteria were conducted to generate pooled prevalence estimates. Results: Nineteen studies of moderate to high quality met the selection criteria. Meta-analyses yielded a pooled prevalence rate (95% CI) for TMDs in FMS patients of 76.8% (69.5% to 83.3%). Myogenous TMDs were more prevalent in FMS patients (63.1%, 47.7% to 77.3%) than disc displacement disorders (24.2%, 19.4% to 39.5%), while a little over 40% of FMS patients had comorbid inflammatory degenerative TMDs (41.8%, 21.9% to 63.2%). Almost a third of individuals (32.7%, 4.5% to 71.0%) with TMDs had comorbid FMS, while estimates of comorbid CWP across studies ranged from 30% to 76%. Conclusions: Despite variable prevalence rates among the included studies, the present review suggests that TMDs and CWP/FMS frequently coexist, especially for individuals with painful myogenous TMDs. The clinical. pathophysiologic, and therapeutic aspects of this association are important for tailoring appropriate treatment strategies.

#### Comorbidities of Rural Children and Adolescents with Migraine and without Migraine. Walter SM, Dai Z, Wang K.

Children (Basel). 2023 Jun 29;10(7):1133. doi: 10.3390/children10071133. PMID: 37508629; PMCID: PMC10378174.

Background: Migraine is associated with comorbidities that are common in the general rural pediatric population. The purpose of this study is to evaluate the differences in the occurrence of comorbidities between rural children and adolescents with and without migraine. (2) Methods: A cross-sectional, secondary data analysis using electronic medical records of 1296 patients (53.8% females, aged  $12.4 \pm 3.2$ ) was completed. Mann-Whitney U test was used to detect the difference in the number of comorbidities between the two groups. Chi-square test was used to identify the differences in the number of comorbidities, which were classified as low (0-1 comorbidities), medium (2-3 comorbidities), and high (4 or

plus comorbidities) degree of comorbidities. (3) Results: Significant differences were found between those children and adolescents with migraine vs. those without for depression (p < 0.0001), anxiety (p < 0.0001), and Ehlers-Danlos Syndrome (EDS; p = 0.0309). A marginally significant difference was found between those children and adolescents with migraine (47.2%; n = 306) vs. those without (42.1%; n = 273) for unhealthy weight (p = 0.0652). Approximately 40% of the migraineurs had 2-3 comorbidities, whereas 32% of the non-migraineurs had 2-3 comorbidities (p = 0.0003). (4) Conclusions: Findings demonstrate the importance of identifying comorbidities associated with rural pediatric migraine in order to develop effective treatment strategies that optimize patient outcomes.

#### Prevalence of Fibromyalgia and Chronic Fatigue Syndrome among Individuals with Irritable Bowel Syndrome: An Analysis of United States National Inpatient Sample Database.

Tarar ZI, Farooq U, Nawaz A, Gandhi M, Ghouri YA, Bhatt A, Cash BD. Biomedicines. 2023 Sep 22;11(10):2594. doi: 10.3390/biomedicines11102594. PMID: 37892968; PMCID: PMC10604744.

Background and Aim: Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder associated with other somatic disorders. We studied the prevalence and predictors of fibromyalgia and chronic fatigue syndrome (CFS) in IBS patients. Methods: We used the National Inpatient Sample and included hospitalization of individuals with IBS, using ICD-10 codes, from 2016-2019. The prevalence and predictors of fibromyalgia and CFS in IBS patients were studied. Univariate and multivariate patient- and hospital-level regression models were used to calculate the adjusted odds of fibromyalgia and CFS in the IBS patient population. Results: Of 1,256,325 patients with an ICD-10 code of IBS included in the study, 10.73% (134,890) also had ICD-10 codes for fibromyalgia and 0.42% (5220) for CFS. The prevalence of fibromyalgia and CFS was significantly higher in IBS patients (adjusted odds ratio (AOR) 5.33, 95% confidence interval (CI) 5.24-5.41, p < 0.001, and AOR 5.40, 95% CI 5.04-5.78, p < 0.001, respectively) compared to the general adult population without IBS. IBS-diarrhea, IBS-constipation, and IBS-mixed types were independently associated with increased odds of fibromyalgia and CFS. Increasing age (AOR 1.02, 95% CI 1.01-1.04, p 0.003; AOR 1.02, 95% CI 1.01-1.03, p 0.001), female gender (AOR 11.2, 95% CI 11.1-11.4, *p* < 0.001; AOR 1.86, 95% CI 1.78-1.93, *p* < 0.001) and white race (AOR 2.04, 95% CI 1.95-2.12, p < 0.001; AOR 1.69, 95% CI 1.34-2.13, p < 0.001) were independent predictors of increased odds of fibromyalgia and CFS, respectively. Conclusions: It appears that IBS is associated with an increased prevalence of somatic disorders such as fibromyalgia and CFS.

### The Bidirectional Association between Chronic Musculoskeletal Pain and Sleep-Related Problems: A Systematic Review and Meta-Analysis.

Santos M, Gabani FL, de Andrade SM, Bizzozero-Peroni B, Martínez-Vizcaíno V, González AD, Mesas AE.

Rheumatology (Oxford). 2023 Sep 1;62(9):2951-2962. doi: 10.1093/rheumatology/kead190. PMID: 37104741.

Objectives: This systematic review and meta-analysis synthesizes the evidence on prospective bidirectional associations between sleep-related problems (SRP) and chronic musculoskeletal pain (CMP). Methods: A literature search for cohort studies available in the PubMed, Scopus, Web of Science, PsycINFO and Cochrane Library databases as of 19 July 2022 was performed. Pooled odds ratios and effect sizes were calculated through random effects meta-analysis. Subgroup and meta-regression analyses were performed to explore differences by follow-up time, proportion of each sex and mean age. The Meta-analysis Of Observational Studies in Epidemiology guidelines were strictly followed. Results: Twenty studies with a total of 208 190 adults (aged 34.4-71.7 years) were included, with 17 of them being used in the meta-analysis. Individuals with SRP at baseline had a 1.79-fold higher

incidence (odds ratio [OR] = 1.79; 95% CI: 1.55, 2.08; I2 = 84.7%; P < 0.001) and a 2.04-fold higher persistence (OR = 2.04; 95% CI: 1.42, 2.94; I2 = 88.5%; P < 0.005) of CMP than those without SRP. In the subgroup analysis of the association between SRP and CMP, the longer the follow-up time of the studies, the higher the heterogeneity between them. In the corresponding meta-regression, no significant effect was observed for follow-up time, sex proportion or age. Individuals with CMP at baseline had a 2.02-fold higher incidence of SRP (OR = 2.02; 95% CI: 1.62, 2.53; I2 = 90.0%; P < 0.001) than those without CMP. Coonclusion: This study provides robust evidence concerning the longitudinal association between SRP and incidence-persistence of CMP in adults. In addition, the available prospective studies support the existence of a bidirectional relationship between CMP and SRP.

### <u>Hypermobility Spectrum Disorders and Irritable Bowel Syndrome: A Nationwide Study</u> of 1.6 million Adolescents.

Zloof Y, Peretz L, Braun M, Simchoni M, Tsur AM, Tzur D, Derazne E, Ben-Tov A, Pinhas-Hamiel O, Amarilyo G, Daher S, Shlaifer A, Braun-Moscovici Y. J Gastroenterol Hepatol. 2023 Sep 2. doi: 10.1111/jgh.16341. Epub ahead of print. PMID: 37658800.

Background and aim: The association between hypermobility spectrum disorders/hypermobile type Ehlers-Danlos syndrome (HDS/hEDS) and irritable bowel syndrome (IBS) is yet to be clarified. We aimed to assess this association in a national sample of adolescents. Methods: A population-based cross-sectional study included 1 627 345 Israeli adolescents (58% male; mean age 17 years) who were medically assessed before compulsory military service during 1998-2020. Diagnoses of HSD/hEDS and IBS were confirmed by board-certified specialists. The prevalence and odds ratios (ORs) for IBS in adolescents with and without HSD/hEDS were computed. Results: A total of 4686 adolescents (2553 male) with HSD/hEDS were identified, of whom 71 were diagnosed with IBS (prevalence = 1.5%). Of the 1 621 721 adolescents in the control group, 8751 were diagnosed with IBS (prevalence = 0.5%). Unadjusted logistic regression revealed a significant association between HSD/hEDS and IBS (OR = 2.16 [95% confidence interval, CI, 1.90-2.45]), which persisted in multivariable adjusted models (OR = 2.58 [95% CI, 2.02-3.24]), and in several sensitivity analyses. The association was evident in both male and female adolescents with ORs of 2.60 (95% CI, 1.87-3.49), and 2.46 (95% CI, 1.66-3.49), respectively. The association was accentuated in a sensitivity analysis accounting for other medical and psychiatric comorbidities. Conclusions: We found a significant association between HSD/hEDS and IBS in both male and female adolescents. Clinical awareness of the association can promote early diagnosis of IBS and appropriate multidisciplinary treatment. Further research is required to identify the common pathological pathways of the conditions and to develop new IBS treatment strategies for people with HSD/hEDS.

### Comorbid Conditions in Egyptian Patients with Migraine.

Magdy R, Othman AS, Elsebaie EH, Elsayed RM, Abdelrahman W, Shalaby S, Saraya M, El-Sayed Abd El-Ghani S, Ayoub YK, Elshall A, Elmazny A. Neurol Res. 2023 Dec;45(12):1100-1110. doi: 10.1080/01616412.2023.2257418. Epub 2023 Nov 1. PMID: 37748177.

Background: Identifying migraine comorbidities may guide prognosis and treatment options. This study aimed to assess the frequency of comorbid conditions among adults with migraine living in Greater Cairo. Methods: In this cross-sectional study, Egyptian migraine sufferers aged ≥ 18 years living in Greater Cairo were consecutively recruited (April 2019 - April 2021). Following The International Classification of Headache Disorders-third edition, diagnosis of migraine was confirmed, and the type of migraine was defined as whether episodic or chronic, with or without aura, with childhood/adolescence or adulthood onset. Specialist physicians from the research team assessed comorbid conditions among the respondents.

Results: The mean age of respondents (n = 1064) was  $35 \pm 7$ . Irritable bowel syndrome represented the most common comorbidity in our patients (45.5%), followed by vitamin D deficiency (41.8%). The frequency of epilepsy, stroke, multiple sclerosis, and systemic lupus erythematosus was significantly higher in patients with chronic than episodic type ( $\chi 2 =$ 4.514, P = 0.034), ( $\chi 2 = 12.302$ , P = 0.001), ( $\chi 2 = 12.302$ , P = 0.001), ( $\chi 2 = 4.806$ , P 0.028), respectively. Females with menstrual migraines had a significantly higher frequency of generalized anxiety disorder, panic attacks, and restless leg syndrome than those with nonmenstrual migraines ( $\chi 2 = 7.636$ , P 0.006), ( $\chi 2 = 9.245$ , P = 0.002), and ( $\chi 2 = 11.997$ , P =0.001), respectively. The frequency of diabetes was significantly higher in patients with migraine with aura than in those without aura ( $\chi 2 = 4.248$ , P value 0.039). Conclusion: This study provides a better understanding of the comorbidities in Egyptian patients with migraine and will provide new avenues for developing individualized therapy for migraine patients.

## Seventeen-Year National Pain Prevalence Trends Among U.S. Military Veterans.

Taylor KA, Kapos FP, Sharpe JA, Kosinski AS, Rhon DI, Goode AP. J Pain. 2023 Nov 10:S1526-5900(23)00613-2. doi: 10.1016/j.jpain.2023.11.003. Epub ahead of print. PMID: 37952861.

U.S. military veterans experience higher pain prevalence than nonveterans. However, it is unclear how the disparities in pain prevalence have changed over time because previous trend studies are limited to veterans using the Veterans Health Administration. This repeated cross-sectional study aimed to characterize pain prevalence trends in the overall population of U.S. veterans compared to nonveterans, using nationally-representative data. We analyzed 17 years of data from the National Health Interview Survey (2002-2018), with a mean annual unweighted sample of 29,802 U.S. adults (total unweighted n=506,639) and mean annual weighted population of 229.7 million noninstitutionalized adults. The weighted proportion of veterans ranged 11.48% in 2002 (highest) to 8.41% in 2017 (lowest). We found that veterans experience a similar or higher prevalence of pain than nonveterans across the study period, except for severe headache or migraine and facial pain. Pain prevalence among veterans increased over time, with a higher rate of increase compared to nonveterans for all pain variables. From 2002 to 2018 there was an absolute increase (95% CI) in pain prevalence among veterans (severe headache or migraine: 2.0% [1.6% to 2.4%]; facial pain: 1.9% [1.4% to 2.4%]; neck pain: 4.7% [4.1% to 5.2%]; joint pain: 11.4% [10.8% to 11.9%]; low back pain: 10.3% [9.5% to 11.1%]; any pain: 10.0% [9.6% to 10.4%]; and multiple pains: 9.9% [9.2% to 10.6%]. The continued pain prevalence increase among veterans may have implications for healthcare utilization, highlighting the need for improved pain prevention and care programs for this population with a disproportionate pain burden. PERSPECTIVE: This article uses routinely-collected cross-sectional data that are nationallyrepresentative of U.S. adults to present changes in pain prevalence among military veterans compared to nonveterans. The findings underscore the need for improved prevention and pain care programs for veterans, who experienced a widening disproportionate pain burden from 2002 to 2018.

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