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# Disease Phenotypes in Refractory Musculoskeletal Pain Syndromes Identified by Unsupervised Machine Learning

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**Objective.** Overlapping chronic pain syndromes, including fibromyalgia, are heterogeneous and often treatment-resistant entities carrying significant socioeconomic burdens. Individualized treatment approaches from both a somatic and psychological side are necessary to improve patient care. The objective of this study was to identify and visualize patient clusters in refractory musculoskeletal pain syndromes through an extensive set of clinical variables, including immunologic, psychosomatic, wearable, and sleep biomarkers.

**Methods.** Data were collected during a multimodal pain program involving 202 patients. Seventy-eight percent of the patients fulfilled the criteria for fibromyalgia, 77% had a concomitant psychiatric-mediated disorder, and 22% a concomitant rheumatic immune-mediated disorder. Five patient phenotypes were identified by hierarchical agglomerative clustering as a form of unsupervised learning, and a predictive model for the Brief Pain Inventory (BPI) response was generated. Based on the clustering data, digital personas were created with DALL-E (OpenAI).

**Results.** The most relevant distinguishing factors among clusters were living alone, body mass index, peripheral joint pain, alexithymia, psychiatric comorbidity, childhood pain, neuroleptic or benzodiazepine medication, and response to virtual reality. Having an immune-mediated disorder was not discriminatory. Three of five clusters responded to the multimodal treatment in terms of pain (BPI intensity), one cluster responded in terms of functional improvement (BPI interference), and one cluster notably responded to the virtual reality intervention. The independent predictive model confirmed strong opioids, trazodone, neuroleptic treatment, and living alone as the most important negative predictive factors for reduced pain after the program.

**Conclusion.** Our model identified and visualized clinically relevant chronic musculoskeletal pain subtypes and predicted their response to multimodal treatment. Such digital personas and avatars may play a future role in the design of personalized therapeutic modalities and clinical trials.

## INTRODUCTION

Chronic refractory pain syndromes, such as fibromyalgia and chronic low back pain, are a common and heterogeneous entity, often requiring intensive and multimodal treatment approaches.[1] Pain medication usually has a limited effect, and patients often absorb substantial clinical resources, including repetitive primary care and emergency department visits.[2]

Concomitant fibromyalgia occurs in up to 40% of the patients with inflammatory rheumatic diseases, leading to a reduced response to current treatments.[3] Depression and other psychiatric comorbidities, such as posttraumatic stress syndromes, are also associated with chronic pain syndromes and work incapacity.[4] Patients with chronic pain share a plethora of symptoms, notably pain generalization, fatigue, mood disturbances, and autonomic dysfunction.[5] In clinical practice, the interdisciplinary communication among generalists, pain specialist, rheumatologist, psychiatrists, and other health care professionals often is insufficient. Multimodal treatment programs with improved interdisciplinary care have been shown to be among the most potent treatment modalities for fibromyalgia and are recommended in different guidelines.[6] However, the effects of these expensive and time-consuming multimodal programs remain highly variable, likely because of the heterogeneous nature of patients with chronic pain.

The ability to better predict a positive or negative response could enable more effective allocation of resources.

In our center, we have set up a multimodal pain program for patients with chronic musculoskeletal pain syndromes, including primary and secondary fibromyalgia. Patients undergo a full physical and psychiatric assessment by a broad range of questionnaires and evaluation by psychiatrists, pain specialists, and rheumatologists. Sleep and mobility are assessed by wearables. Various interventions are performed, such as intensive physiotherapy, ergotherapy, chiropractic treatments, gym exercises, water therapy, and virtual reality (VR) sessions, and patients are followed up after the program via a smartphone application and phone calls.

Previous work on fibromyalgia clustering has suggested that problem- and emotion-focused coping strategies and an anti-inflammatory cytokine pattern are positive predictive factors for the disease course.[7] Additional positive predictive factors were low anxiety, ability of acceptance, and persistence, which further support a resilient phenotype. In another study, four fibromyalgia clusters were identified; of those, one had particularly high levels of pain and severe physical and mental impairment and low social support.[8] The Widespread Pain Index was predicted in a previous study on neural networks using a combination of sleep, stress, and cytokine pattern.[9]

This indicates that psychological factors, including psychosocial models, remain a major component in defining fibromyalgia phenotypes and finally predicting the choice treatment. In this study we created such a model in patients with chronic pain, for the first time from a rheumatology perspective, using a large panel of parallelly assessed somatic and psychosomatic data combined with wearables and a consensus work capacity.

## PATIENTS AND METHODS

**Data set.** Data were collected between November 2018 and November 2021 from patients with refractory musculoskeletal pain syndromes who participated in a rheumatology-led two-week multimodal pain management program at the University Hospital Lausanne in Switzerland. The study was approved by the local ethical commission, and informed consent was obtained by all patients.

Underlying diagnoses were mostly fibromyalgia and chronic back pain, with or without concomitant inflammatory rheumatic disorder. Patient characteristics are seen in Table 1, and more detailed socioeconomic and clinical variables are shown in Supplementary Data S1. The multimodal pain program involved evaluation by health care professionals from more than seven specialties, including rheumatology, anesthesiology, physiotherapy, ergotherapy, psychiatry, chiropractic, and osteopathy. In total, data were collected from 202 patients before and directly after the program; of those, 123 had full data sets. Around half

**Table 1.** Patient characteristics[*]

| Demographic variables | All (N = 202) |
|---|---|
| Female, % | 73 |
| Age, mean (SD) | 47 (±10) |
| BMI, mean; min–max | 27.9; 23–74 |
| Living in a couple, % | 59.9 |
| Pain in childhood, % | 45.3 |
| Pain in adolescence, % | 68.2 |
| Work disability, % | |
| Pursued | 45 |
| Received | 13.4 |
| Refused | 8.4 |
| Nociplastic pain, % | 75 |
| Hyperlaxity, % | 27.1 |
| Immune-mediated disease, % | 21.8 |
| Active arthritis, % | 5.9 |
| Sleep obstructive apnea, % | 9.4 |
| Fibromyalgia criteria fulfilled (ACR 2010), % | 78 |
| FiRST criteria >4, % | 81 |
| Increased CRP (>10 mg/L), % | 5.9 |
| HLA–B27 positive, % | 14 |
| Rheumatic factor, % | 0.7 |
| Anti-CCP, % | 1.9 |
| Decreased sleep efficacy, % | 50.2 |
| Fragmented sleep (SFI), % | 78.4 |
| Psychiatric disorder, % | 73.8 |
| Depression, % | 56.4 |
| Anxiety, % | 30.7 |
| Posttraumatic stress disorder, % | 9.9 |
| Alexithymia, % | 34.2 |
| Multioperated patients, % | 14 |

*ACR, American College of Rheumatology; anti-CCP, anti–cyclic citrullinated peptide; BMI, body mass index; CRP, C-reactive protein; FiRST, Fibromyalgia Rapid Screening Tool; SFI, Sleep Fragmentation Index.

of the patients had a Swiss or probably Swiss origin. Forty percent were European; of those, 17% were from Portugal and 14% were from the Balkan region. Ten percent of the patients had a non-European origin, and 12% had lived in a war or conflict zone.

**Features.** Variables of interest for understanding fibromyalgia and patient response to treatment were selected by consensus opinion of three experienced rheumatologists and chronic pain specialists. These variables spanned demographics, physical characteristics, clinical information (comorbidities, types of pain), medications, and laboratory test results as well as response to treatment. All diagnosis, including psychiatric diagnoses were performed or confirmed during the program by rheumatologists or psychiatrists.

Patients responded to various questionnaires at days 0 and 14, including the Brief Pain Inventory (BPI), measuring both the intensity of pain on a sensory dimension and the interference of pain in the patient's life. Pain relief, quality, and the patient perception of the cause of pain were also assessed.[11] To define fibromyalgia, the Fibromyalgia Rapid Screening Tool[11] and the American College of Rheumatology (ACR) 2010 criteria[12] were applied.

The Sleep Fragmentation Index was assessed by actigraphy,[13] with a threshold of 20. It is defined as the sum of the movement index (total of scored epochs with one or more activity counts divided by total time in bed in hours × 100) and the fragmentation index (percentage of one-minute periods of sleep vs all periods of sleep in the sleep period).

**Data preprocessing.** Variables were standardized using min–max normalization, as per the following equation:

$$\overline{X} = \frac{X - X_{min}}{(X_{max} - X_{min})},$$

where X denotes the original value of the feature of interest, whereas $X_{max}$ and $X_{min}$ denote their maximum and minimum values, respectively. Min-max normalization was used because it scales all values to within the same range (which is important when performing clustering) and because it maintains sparsity (as zero values remain zero, unlike in other normalization approaches). Categorical variables with multiple entries were converted into one-hot encodings to support analysis. One-hot encoding involves converting a variable with n categorical options into n number of variables, each of which is a binary yes or no for being in that respective category.

Patients for whom any input variables were missing were excluded from the analysis. No imputation was performed on missing data. Of the 202 patients in the data set, there were 123 for whom all variables were available and were thus used for subsequent modeling. Variables most commonly missing were the erythrocyte sedimentation rate value (25 patients), questionnaires at the end of the two-week program (22 patients), hyperlaxity (20 patients), and the C-reactive protein (CRP) value (15 patients).

**Phenotypic clustering.** Figure 1 shows an overview of the algorithms. Clusters were generated using the features described in Table 2. We generated hierarchical agglomerative clustering using the Ward variance minimization algorithm with euclidean pairwise distances. With this method, the new entry d(u, v) is computed as follows:

$$d(u,v) = \sqrt{\frac{|v| + |s|}{T}d(v,s)^2 + \frac{|v| + |t|}{T}d(v,t)^2 - \frac{|v|}{T}d(s,t)^2},$$

where u is the newly joined cluster consisting of clusters s and t, v is an unused cluster in the forest, $T = |v|+|s|+|t|$, and |*| is the cardinality of its argument.[10] The analysis was performed using the SciPy cluster library. Cluster visualization was performed using the matplotlib and seaborn libraries. Principal components analysis (PCA) was performed on clusters using the sci-kit learn library, and the two components with maximum explained variance were visualized on a two-dimensional scatterplot. All analysis was performed using Python 3.10. The appropriate number of five clusters was determined by both examining visualizations (which included the dendrogram and the two-dimensional PCA plot) and considering the clinical interpretability and utility of different numbers of clusters.

**Statistical analysis.** Statistical analyses were performed using Python 3.10.8. Python packages used were pandas (1.4.2), NumPy (1.22), SciPy (1.7.3), matplotlib (3.5.1), seaborn (0.11.2), sklearn (1.0.2), and statsmodels (0.13.2). For all statistical analyses, P values of <0.05 were considered to be statistically significant.

**Internal correlation and comparison of clusters.** Variables were grouped into continuous variables and categorical variables. Variables were compared using appropriate tests: two-sample proportion tests for binary outcomes and chi-square tests for categorical outcomes. Correlations were calculated using point biserial correlations for correlations between binary and continuous variables. Accordingly, clusters were compared using a one-way analysis of variance for continuous variables, as listed in Table 2. A Bonferroni adjustment was applied to a significance level of 0.05 for P values to identify variables with statistically significant variation among clusters. Two experienced rheumatologists performed the clinical interpretation of clusters.

**Creation of "digital personas.".** "Personas" is a term for fictitious, representative identities used for various purposes. Here we use the term "digital personas" to describe the five
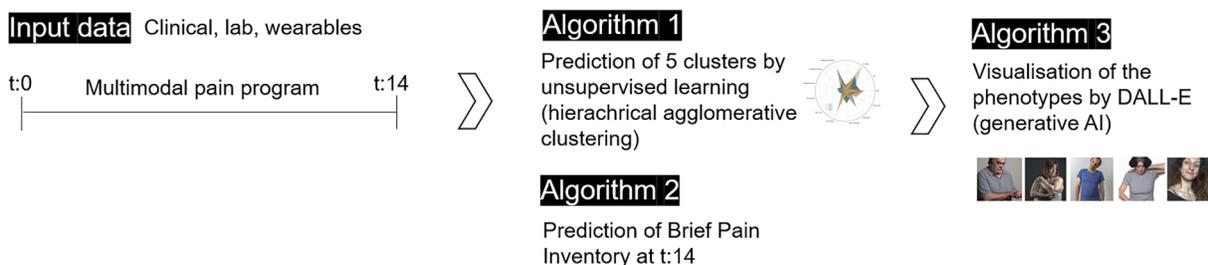


**Figure 1.** Algorithm overview.

**Table 2.** Clinical variables and phenotypic domains used for the clustering model*

| Phenotypic domain | Clinical variables |
| --- | --- |
| Demographics | Age, sex, relationship status, no. of children, disability insurance status (demanded vs received vs refused), time taken off work |
| Physical characteristics | BMI (<18.5 vs 18.5–25 vs 25–30 vs >30), menopausal status, hyperlaxity, disturbed sleep[a] |
| Comorbidities | Immune-mediated rheumatic disease, airway comorbidities (any of the following: OSA, COPD, asthma), back pain, metabolic disease (any of the following: diabetes, gout), depression or anxiety, posttraumatic stress disorder, other psychiatric conditions (any of the following: bipolar disorder, personality disorder, alexithymia, enduring personality change after catastrophic experience[b]) |
| Pain | Back pain, peripheral pain (any of the following: peripheral neuropathy, significant peripheric arthrosis, enthesopathy, bursitis, tendinopathy, shoulder pain), neuropathic pain (any of the following: radiculopathy, peripheral neuropathy), nociplastic pain, nociceptive pain, chronic pain as child or adolescent |
| Medications | Opiates (weak vs strong), Antidepressive treatment (tricyclics vs mirtazepine vs dual antidepressant therapy vs trazodone vs sympathomimetics), neuroleptics, benzodiazepines, Z-drugs, NSAIDs, prednisolone, biologics (bDMARDs) |
| Laboratory | CRP, ESR |
| Response | Response to VR treatment (subjectively positive vs subjectively negative, reduction in pain, reduction in anxiety), change in BPI intensity score, change in BPI impact score |

*Z-drugs are nonbenzodiazepine hypnotics for the treatment of sleep disorders (eg, zolpidem or zopiclone). bDMARD, biologic disease-modifying antirheumatic drug; BMI, body mass index; BPI, Brief Pain Inventory; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; NSAID, nonsteroidal anti-inflammatory drug; OSA, obstructive sleep apnea; PTSD, posttraumatic stress disorder; VR, virtual reality.
[a]Defined as a Sleep Fragmentation Index of >20 or sleep efficiency less than 85%, as measured using a MotionWatch 8.
[b]As described by *International Classification of Diseases, 10th Revision* code F62.0.

different patient clusters as representative phenotypes according to previous clustering studies.[14] As a new approach, we illustrate those personas by generative artificial intelligence (AI) by prompting key elements of each phenotype in DALL-E (labs.openai.com) as follows: "Show an image of a person with the following characteristics…." An age range of the persona was provided according to the results from supervised learning and clinical estimation.

**Predictive model.** A regression model was fitted to predict the response to the pain management program. The outcome variables were either change in the value of the BPI impact score or change in the BPI intensity score. Features were selected using stepwise backward feature selection. Both linear and polynomial regression models were fitted. Performance was assessed using mean square error (MSE), root mean square error (RMSE), and $R^2$ scores as well as visualizations such as residual versus fitted values and a Q-Q plot. The coefficients and statistical significance were examined for each model variable.

## RESULTS

**Cluster analysis.** A model of three and five clusters was developed. We decided to proceed with the five-cluster model because it was clinically judged as more appropriate. Figure 2 shows the deviation of 30 clinical variables from the mean for each cluster. The following variables significantly varied among clusters: nociplastic pain, chronic or recurrent pain during childhood or adolescence (mostly recurrent "growing pains," sprains and musculoskeletal injuries, abdominal pain, cephalea, back pain, and incapacitating dysmenorrhea), living in a couple, normal body mass index (BMI), alexithymia, psychiatric comorbidity, combined

psychological factors (alexithymia, bipolar, personality disorder, lasting personality change after disaster experience), and positive response to VR. *P* values are shown in Supplementary Data S2. Interestingly, the presence or absence of an immune-mediated rheumatic disorder (secondary fibromyalgia) was not a differentiating factor. The model of three clusters using the same variables is shown in Supplementary Data S3. Here we confirm that there is one chronic pain cluster that is characterized by living in couples, no psychiatric comorbidity, and nociceptive pain. VR was effective in another cluster that is characterized by nociplastic pain and psychiatric comorbidity. Figure 3 shows radar plots for the five different clusters focusing on different variables (A-C).

**Cluster summary.** Cluster 1 (n = 43, 27 female patients, 16 male patients) comprised mainly overweight individuals with persisting peripheral articular pain with or without an underlying inflammatory rheumatic disorder (eg, diagnosed as psoriasis arthritis, microcrystal arthritis, or erosive osteoarthritis [OA]) without measurable inflammation. The pain character was nociceptive and peripheral. There were no signs of depression in this cluster. Patients had low scores throughout psychological assessment. A positive response to the BPI intensity score was achieved after the two-week program.

Our clinical interpretation of this cluster is that this cluster is associated with individuals with an undifferentiated underlying inflammatory disorder or sometimes OA. Often patients have physically demanding work. Despite low scores throughout psychological assessment, occult depression or stress-related symptoms seem possible in this cluster.

Cluster 2 (n = 21, 18 female patients, 3 male patients) comprised individuals with obesity with a metabolic comorbidity living alone with severe sleep impairment receiving antidepressant
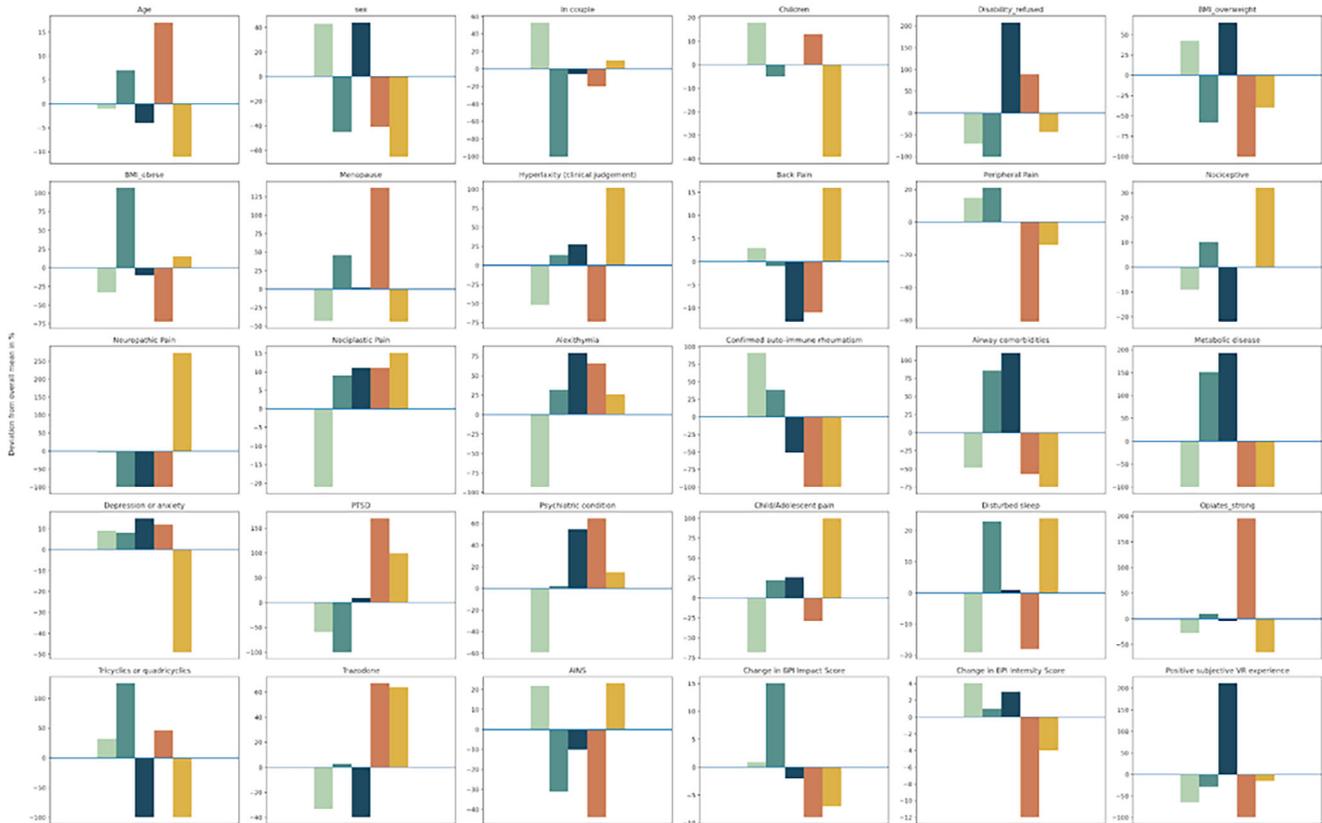
**Figure 2.** Cluster deviation from the mean. Clusters 1 through 5 are shown as bars with different colors. AINS, anti-inflammatory non-steroidal drugs; BMI, body mass index; BPI, Brief Pain Inventory; PTSD, post-traumatic stress disorder.

therapy. Women were mostly in a perimenopausal or postmenopausal status. Some patients of this cluster had low-grade inflammation with increased CRP values (data not shown in Figure 2) but without confirmed immune-mediated disease. Some received prednisone but no biologics. This was the only cluster with a clear improvement of BPI impact during the multimodal program.

Our clinical interpretation of this cluster is that obesity, muscular deconditioning metabolic syndrome, exhaustion and loneliness, and low-grade inflammation overlap with perimenopausal symptoms (pain, sleep impairment, and mood disturbance) and potentially calcifying tendinitis, bursitis, or inflammatory OA (partly due to obesity combined with the loss of anti-inflammatory effect of estrogens). These patients had the greatest benefit from the multimodal treatment that focused on physical reconditioning, group therapies, group effect, and "environectomy" (taking patients out of their familar surroundings). Potentially, this cluster was particularly affected by the isolation during the pandemic, leading to psychological stress, increased kinesiophobia, and weight gain (despite some of the patients being included before the pandemic).

Cluster 3 (n = 24, 15 female patients, 9 male patients) comprised younger individuals with low BMI, alexithymia, and a psychiatric condition (mostly depression and/or anxiety). A metabolic or lung comorbidity, such as asthma, could be present. The pain character was rather nociplastic, often existing since

childhood or adolescence. This patient cluster responded best to VR.

This cluster is characterized by somatoform pain disorders occuring in younger patients, mostly starting at childhood and often with substantial psychiatric comorbidity. In our observations, male patients in this cluster typically work in the information technology (IT) field or spend a lot time with gaming. There is relatively good response to the BPI intensity score during the program.

Cluster 4 (n = 13, 11 female patients, 2 male patients) comprised older individuals than in the other clusters with strong opioid, benzodiazepine, or trazodone treatment. Sometimes the individuals experienced failed back surgery or poor outcome of multimodal treatment. Their blood sedimentation rate could be elevated.

Our interpretation of this cluster is that these individuals experience medication overtreatment, often with a combination of opioids and psychotropic medication. Treatment of this cluster is complex and includes opioid weaning and posttraumatic stress disorder (PTSD) therapy.

Cluster 5 (n = 22, 20 female patients, 2 male patients) comprised younger individuals with hypermobility and back pain. They had mixed pain character, mainly neuropathic and nociceptive rather than nociplastic. Most of the patients experienced pain
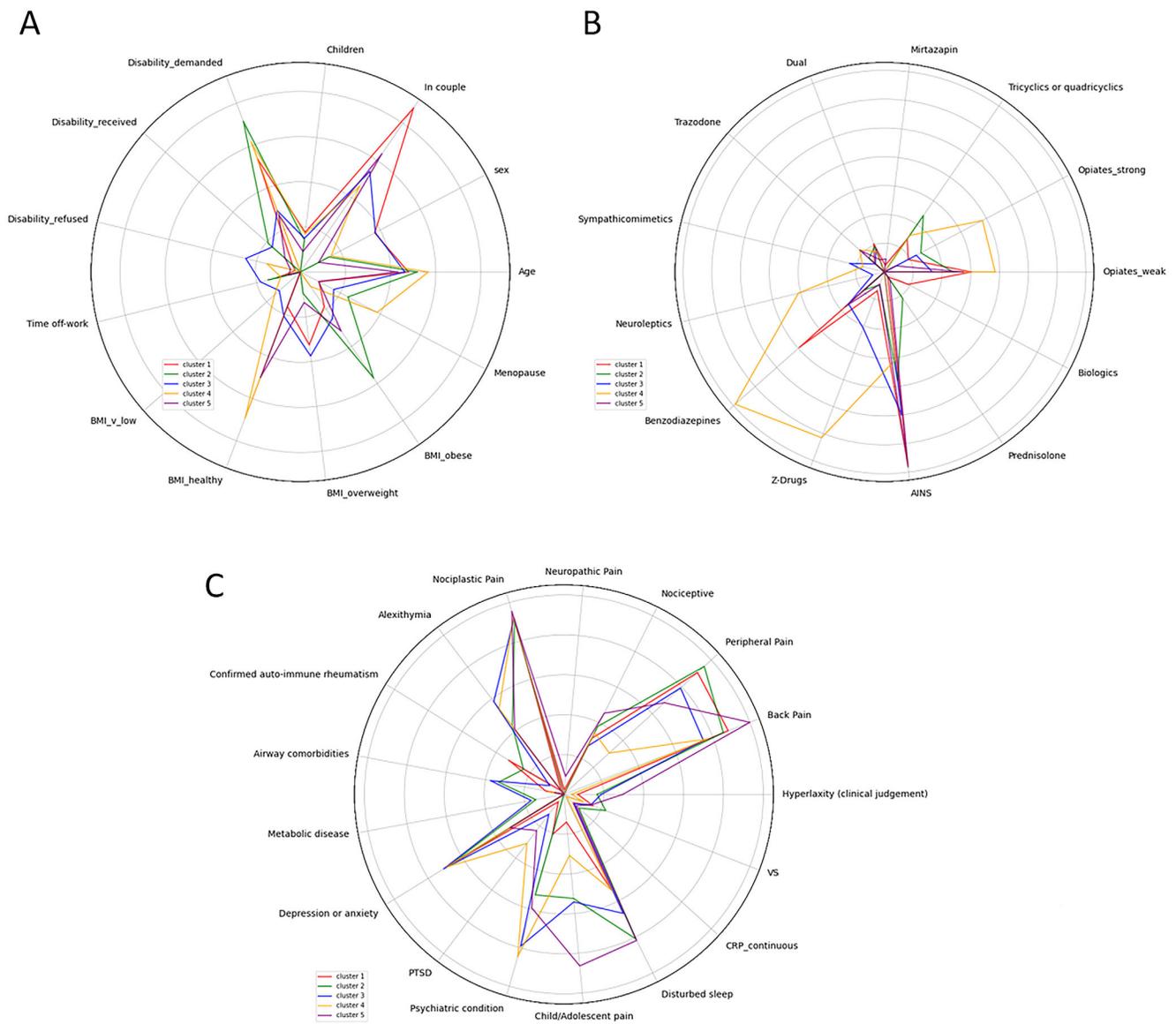
**Figure 3.** Radar plots for the five clusters. (A) Demographic and socio-economic factors, BMI. (B) Medication. (C) Type of pain, comorbidity, sleep and inflammatory markers. Each axis of the radar plot represents a different variable. Each cluster is represented by a different color within the same chart. For example, cluster 4 stands out in panel B for psychotropic medication, and cluster 3 stands out in panel D for response to VR treatment. AINS, anti-inflammatory nonsteroidal drugs; BMI, body mass index; BPI, Brief Pain Inventory; CRP, C-reactive protein; PTSD, post-traumatic stress disorder; VR, virtual reality; VS, sedimentation rate.

since their childhood or adolescence, had severe sleep impairment, and took trazodone.

Our clinical interpretation of this cluster is that this cluster includes younger hypermobile individuals, mostly women with pain dysregulation problems that occurred in childhood or adolescence. Some of them have PTSD, which complicates or causes childhood pain.

**Digital personas created by generative AI.** DALL-E-generated personas for clusters 1 through 5 are shown in Figure 4. DALL-E refused several prompts containing psychiatric variables because they were not in line with their policy, but these

still could be included by paraphrasing. The cluster 1 persona, an elderly man, has a visual emphasis on peripheral arthralgia. The cluster 2 persona is female and obese and has a suffering mimic. The cluster 3 persona is a younger male patient with alexithymia and has a stare. The cluster 4 persona is a woman with back pain. In contrast to the other images, her hand is not realistic. Cluster persona 5 is a middle-aged woman with psychiatric comorbidity.

**Predictive model.** Independently from the clustering, a machine learning model was trained to identify variables that predict positive and negative response to the multimodal treatment
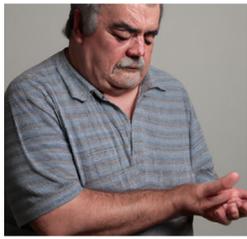
**Cluster 1**: An overweight individual of 56 years with nociceptive, peripheral pain, concomitant inflammatory rheumatic disorder. No psychiatric comorbidity. Good response of BPI intensity.

**Cluster 2:** Peri- or postmenopausal female of 53 years with obesity and metabolic comorbidity, living alone, severe sleep impairment, antidepressant therapy. Good response of BPI impact.

**Cluster 3**: Individual of 30 years with low BMI, alexithymia and a psychiatric condition. Airway or metabolic co-morbidity. Excellent response to virtual reality treatment. Good response of BPI intensity.

**Cluster 4:** A post-menopausal woman of 58 years with previous spine surgery. Strong opioid and/or trazodone use. A psychiatric condition and alexithymia. Poor response to multimodal treatment.
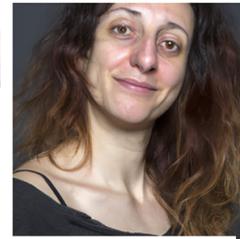
**Cluster 5:** A hypermobile women of 34 years with neuropathic and nociceptive pain, back pain, normal BMI, pain since childhood or adolescence, severe sleep impairment, sometimes PTSD. Poor response to multimodal treatment.

**Figure 4.**    "Digital personas" as virtual representatives of chronic musculoskeletal pain phenotypes (these are not real persons). Characteristic variables as well as the command to create a photograph of a person for each cluster were prompted in DALL-E (www.labs.openai.com). Sex and age were chosen arbitrarily. Images appear realistic, apart from the left hand in the persona of cluster 4. Positive response after the two-week multimodal treatment program was observed in cluster 2 on BPI interference and in clusters 2 and 3 on BPI intensity. Cluster 3 showed a positive short-term response on VR. BMI, body mass index; BPI, Brief Pain Inventory; PTSD, posttraumatic stress disorder; VR, virtual reality.

program, defined either using BPI intensity or BPI impact. Here, the best-performing final model was a polynomial regression with variables related to context (age, being in a couple, receiving disability benefits) and medications (taking weak opiates, strong opiates, tricyclic/tetracyclic antidepressants, mirtazapine, trazodone, sympathomimetics, and neuroleptics) (Supplementary Data S4) for predicting BPI impact. Linear regression showed statistical significance only for one input parameter: trazodone ($P = 0.003$), which had a negative effect on the response (delta BPI impact) after the two-week program. Several trends were shown for other input variables. Age tended toward statistical significance ($P = 0.092$) for a negative effect on response. Taking weak opiates tended toward statistical significance ($P = 0.079$) and exerted a positive effect, whereas taking strong opiates appeared to have a negative effect. The performance of the final model showed an MSE of 0.016, an RMSE of 0.127, and an $R^2$ of 0.39. The poor response to trazodone and strong opioids is in line with the poor response of clusters 4 and 5. Older age was also typical for clusters that did not respond well to the program. Distributions of BPI impact and intensity scores are shown in the Supplementary Data S5, and a Q-Q plot for the prediction model is illustrated in Supplementary Data S6.

## DISCUSSION

This study identified five phenotypes occurring in chronic, difficult-to-treat musculoskeletal pain syndromes. The underlying data set or "ground truth" of this model is a highly heterogeneous patient cohort, with around 80% of the patients fulfilling the criteria for fibromyalgia and a majority of those having a psychiatric comorbidity.

There is an increasing number of publications on machine learning for predictions and clustering in patients with chronic pain but, to our knowledge, not in the completeness and temporal integrity as shown here in the context of an inpatient multimodal assessment and not for musculoskeletal pain.[15] The high number of patients with pain since childhood or adolescence, especially occurring in cluster 5, was surprising and might contribute to pain chronicity as a vulnerability factor. Both the prevalence and importance in the clustering model of PTSD, alexithymia, and psychotropic medication were interesting, with the experience of trazodone notably higher than expected. Finally, we were surprised about the importance of living alone versus living in a couple in this model, potentially reflecting the psychosocial pain model.

We believe that the phenotypes presented here shed light on musculoskeletal pain syndromes and fibromyalgia and help to reconsider the importance of certain variables that may be underrated from a clinical view. The creation of digital personas, as visualized here by DALL-E, could be helpful to illustrate disease phenotypes and may be of educational value in creating new eHealth solutions.[16] To our knowledge, this is the first report on digital personas in fibromyalgia that might be transformed into avatars and potentially be leveraged by multimodal generative AI models. Those virtual pain patients then might be used for the development of pharmacological and nonpharmacological therapies, including self-management. The visualization of avatars via AI certainly opens up ethical discussions on stigmatism or the correct representation of racial and ethnic minority individuals.

A strength of this study is the completeness of the data set, including multimodal evaluation by different specialists, immunologic and (objective) sleep assessment, and a multimodal

consensus on physical and psychological resources and work capacity at one time point. The phenotypes were clinically reasonable and meaningful (as described in the Results sections as "interpretation" of clusters). Psychiatric comorbidity, notably psychotropic polypharmacy, and alexithymia as personality traits were among the main discriminating factors. The importance of alexithymia has recently been investigated in a machine learning model based on an alexithymia scale, in which it accurately distinguished patients from fibromyalgia controls.[17]

The negative role of living alone with potential solitude was unexpected but has been described in fibromyalgia before.[18] Polymedication, including the combination of high-dose opioids and antidepressants, was associated with a poor outcome in one cluster and has been discussed before in fibromyalgia.[19] On the other hand, we were surprised by the positive signal of VR, notably occurring in cluster 3, which is a new finding that will be pursued in further analyses. We noted more IT workers in this cluster, which might indicate a potential openness toward this treatment.

In the subsequent prediction model, we could only identify one significant negative predictor for the reduction of pain intensity after two weeks of multimodal treatment, which was the use of trazodone. Similarly, high-dose opioids showed a negative trend. The precise mechanism for the influence of trazodone is not known. It is often prescribed for insomnia in patients with associated opioid therapy[20] or in patients with associated mood disorders.[21] The use of trazodone could therefore be a marker of comorbidities impacting treatment response.

In the five clusters, we observed a positive effect in clusters 1 through 3 for BPI intensity and in cluster 2 for BPI interference (including general activity, walking, work, mood, enjoyment of life, relations with others, and sleep). This means that clusters 4 and 5 responded poorly to the program. The reasons for this may be the high opioid dose and age in cluster 4 and a strong psychosomatic component (and potentially PTSD) in cluster 5. Thus, clusters with high opioid use and higher age, as well as young, hypermobile women with pain since childhood, may be less eligible for the treatment program. The good response toward BPI impact in cluster 2 may indicate that patients with low-grade inflammation due to obesity and perimenopause, as well as muscle atrophy and perhaps sedentary behavior, seem to be good candidates for multimodal treatment in terms of function. Clearly, it must be stated, however, that pain reduction after two weeks is not necessarily an ideal outcome measure for a multimodal treatment. Other patient-reported outcomes, including an improved mental status, in fact may outperform pain as an end point of the pain program. In the literature, multimodal nonpharmacological therapies have shown efficacy in pain syndromes in various studies and meta-analyses.[22] However, most of the time, large inclusion criteria, such as ACR criteria for fibromyalgia,[12] are applied.[23] Potentially, algorithms such as those presented here may increase therapy responses of multimodal treatment or may help to identify patients for clinical trials. There are several reports

on fibromyalgia clustering analyses, but none with a focus on musculoskeletal pain. One study focused on generalized pain occurring in patients with chronic headache applied unsupervised machine learning methods by k-means.[7] Two clusters of women were identified; of those, one had (central) hypersensitization, sleep disturbance, kinesiophobia, and neuropathic pain. The characteristic of this cluster resembles that of cluster 5 in our study. In another study, four fibromyalgia clusters based on pain, physical, social, and psychological function were defined by interviews.[8]

Apart from our focus on musculoskeletal pain, the main difference in our study is the simultaneously (multimodal) obtained large spectrum of data from different medical specialties, patient-reported outcomes, and wearables at one time point. We are not aware of other unsupervised learning analyses on musculoskeletal chronic pain syndromes.

Apart from the low sample size, our study has other limitations. A mid- or long-term response to the program is not predicted yet and may better reflect outcomes from multimodal treatment. The feature importance of categorical or binary variables (such as living alone or in a couple, or medication yes or no) may be overestimated in algorithms as compared to numeric values. Unfortunately, we were not able to test our model in a similar independent data set, but the predictive model confirmed some of the key features of the clustering model. As a further limitation, the number of five clusters versus three clusters was chosen based on the clinical interpretability, without calculating a cluster validation index. We integrated several socioeconomic variables in the clustering model. The origin of the patients was not included in the model, which may be a limitation regarding pain perception. In general, we noticed a low level of education in all clusters. This could be reflected in occupations with higher physical exertion and thus an increased inability to work. However, this in turn was not decisive in the clustering model. The clinical interpretation was performed by two experienced rheumatologists and did not include an interpretation of other specialties, such as psychiatry, anesthesia, or physiotherapy. We acknowledge a possible sex skew in this study. However, the male sample size seemed too small for a meaningful analysis. Thus, we reduced the weight on sex in the cluster description and clinical interpretation.

Notwithstanding, this work may help patient selection in multimodal programs for chronic musculoskeletal pain and may help to establish personalized treatments adapted to clusters. Our results may also raise awareness for the transition of adolescent patients with chronic pain and for perimenopause as two pivotal watersheds in chronic pain. Further studies are necessary to investigate the potential role of such an algorithm as a medical device and its concrete implementation in the clinical care pathway.

In conclusion, this study adds knowledge to understand the complex orchestration of disease variables in chronic pain and

fibromyalgia. It illustrates the possibilities of AI to foster personalized health care.

## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr Hügle had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study conception and design.** Hügle, Ming Azevedo.
**Acquisition of data.** Prétat, Suter, Ming Azevedo
**Analysis and interpretation of data.** Hügle, Prétat, Suter, Lovejoy, Ming Azevedo.

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