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# Phenotypic characteristics of patients with chronic widespread pain and fibromyalgia: a cross-sectional cluster analysis

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**Objective:** This study aimed to explore whether phenotypic characteristics of patients with chronic widespread pain (CWP) and fibromyalgia (FM) can be aggregated into definable clusters that may help to tailor treatments.

**Method:** Baseline variables (sex, age, education, marital/employment status, pain duration, prior CWP/FM diagnosis, concomitant rheumatic disease, analgesics, tender point count, and disease variables derived from standardized questionnaires) collected from 1099 patients (93.4% females, mean age 44.6 years) with a confirmed CWP or FM diagnosis were evaluated by hierarchical cluster analysis. The number of clusters was based on coefficients in the agglomeration schedule, supported by dendrograms and silhouette plots. Simple and multiple regression analyses using all variables as independent predictors were used to assess the likelihood of cluster assignment, reported as odds ratios (ORs) with 95% confidence intervals (CIs).

**Results:** Only one cluster emerged (Cluster 1: 455 patients). Participants in this cluster were characterized as working (OR 66.67, 95% CI 7.14 to 500.00), with a medium-term/higher education (OR 16.80, 95% CI 1.94 to 145.41), married/cohabiting (OR 14.29, 95% CI 1.26 to 166.67), and using mild analgesics (OR 25.64, 95% CI 0.58 to > 999.99). The odds of being an individual in Cluster 1 were lower when having a worse score on the PDQ (score ≥ 18) (OR < 0.001, 95% CI < 0.001 to 0.02).

**Conclusion:** We identified one cluster, where participants were characterized by a potentially favourable clinical profile. More studies are needed to evaluate whether these characteristics could be used to guide the management of patients with CWP and FM.

Chronic widespread pain (CWP) and other fibromyalgia (FM)-defining features are common among patients referred to rheumatology outpatient clinics (1). A review of population-based studies from 2020 found the median incidence of CWP to be 12.5 per 1000 person-years (2). Although prevalent, CWP represents a clinical challenge owing to the complexity of the disorder (2, 3). According to the upcoming International Classification of Diseases 11th Revision (ICD-11), CWP can be used as a standalone diagnosis and FM will be classified as a primary pain disorder, a subtype of CWP (4). CWP is, however, also an integral core symptom in the most widely used rheumatological FM criteria, stipulating a high level of associated non-pain symptoms or multiple tender points (TPs) in addition to CWP, possibly causing the FM subtype of CWP to represent the upper end of a pain severity spectrum (5, 6). Defining non-pain symptoms include fatigue, non-refreshing sleep, cognitive impairments, and mood disturbances (7, 8). CWP and FM are reported to have a negative impact on the daily functioning of the individual and to be strongly associated with incapacity for ordinary employment and social participation (9, 10). Owing to an often high disease burden, patients with FM are at higher risk of work disability and unemployment compared to the general population (7).

In 2017, Fitzcharles et al (11) performed a study based on the James Lind Alliance Priority Setting Partnership (JLAPSP) methodology to propel clinically relevant research (11). They identified the need for

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research supporting advancement of personalized targeted treatment to improve patient outcomes (11). Personalized treatment means that different symptoms have a different influence on each patient with FM (11). Fitzcharles et al proposed that dividing this heterogenic group of patients into different subgroups would help to tailor treatments and lead to more effective care (11).

Existing guidelines for the management of FM all agree on recommending a prompt diagnosis and provision of non-pharmacological and pharmacological therapy according to the patient's needs (12–14). However, a Danish Health Technology Assessment found that, in reality, patients with chronic pain experience a substantial diagnostic delay due to prolonged and incoherent healthcare pathways, and receive insufficient support that does not match their complex personal, social, and work-related needs (15). These findings correlate with those of Wilson et al (16) from a UK population of patients with FM. Through surveys of healthcare professionals and patients diagnosed with FM, they found a delay in diagnosing patients, with subsequent delays in treatment, and inconsistent use of evidence-based management strategies focusing on the patient's needs (16).

Although evidence substantiates the notion of a disease severity spectrum and considerable heterogeneity within CWP populations, including the FM subtype, studies using preidentified subgroups to direct interventions and predict outcomes are still missing.

The aim of this study was to identify different subgroups or phenotypes in patients with CWP and FM based on several aspects of their contextual, cognitive, psychological, and symptom characteristics by performing a cluster analysis. The identification of different phenotypes may help healthcare professionals to tailor treatments and lead to more efficient management.

## Method

### Study design

The study was designed as an exploratory cross-sectional study, applying cluster analysis based on clinical data collected from a single hospital (Frederiksberg Hospital). Frederiksberg Hospital is the only hospital in Denmark with a designated Fibromyalgia Unit offering a diagnostic work-up and a group-based rehabilitation programme specifically tailored for patients diagnosed with CWP and FM. The Fibromyalgia Unit only receives patients residing in the Capital Region of Denmark, and has a patient turnover of about 700 patients per year. The Capital Region covers approximately one-fifth of the Danish population (17). Patients are referred from general practitioners, other departments of rheumatology, or practising specialists in rheumatology or anaesthesiology. Thus, the Fibromyalgia Unit at Frederiksberg Hospital both diagnoses patients with CWP/FM and receives patients who have already been diagnosed. All patients referred to the Fibromyalgia Unit fill in electronic questionnaires via touchscreens in the clinic. Only data on patients with a confirmed diagnosis of CWP or FM are exported into the Danish Fibromyalgia Registry (DANFIB). DANFIB was established on 1 January 2018 as a clinical research registry collecting clinical data to be used in the longitudinal monitoring and evaluation of patients with CWP and FM. The content and objectives of the DANFIB registry have been outlined in a protocol with online access (18). Exclusion criteria for registration in DANFIB were age under 18 years at baseline and an inability to understand and read Danish. All participants have provided written consent for data to be retrieved from the DANFIB registry.

### Setting

Baseline data were collected from 1 January 2018 to 1 January 2022 in the specialized clinical care setting at the Fibromyalgia Unit at Department of Rheumatology, Frederiksberg Hospital. The baseline data formed the basis for the analyses and were collected before the patients received any rehabilitation. The data were collected electronically through touchscreens and kept in the DANFIB registry. Data extracted from electronic patient files, including findings at clinical examination (manual TP count), were also integrated into the DANFIB registry.

### Participants

Eligible participants were individuals diagnosed with either CWP according to the American College of Rheumatology (ACR) 1990 definition, or FM if fulfilling the ACR 1990 classification criteria and/or the ACR 2016 diagnostic criteria (5, 6). The participants were diagnosed either at the Fibromyalgia Unit, or at other departments of rheumatology, or by a practising specialist in rheumatology in the Capital Region. The first consecutively included patients in the DANFIB registry diagnosed with CWP as a standalone diagnosis or FM and either 'employed and working' or 'not working' were enrolled in the present analysis. Participants receiving a pension, whether that be a public, early retirement, disability, or retirement pension, were excluded from the present study, because their work status has been resolved and a stepped care intervention would not bring them back on the labour market.

### Data source

The DANFIB registry provided all data regarding baseline demographics, clinical characteristics, and employment status (i.e. labour market affiliation). The variables

included in the cluster analysis were sex, age, labour market affiliation, duration of pain, already diagnosed with FM/CWP, level of education, marital status, concomitant inflammatory rheumatic disease, baseline analgesics, TP count, Pain Self-Efficacy Questionnaire (PSEQ), Fibromyalgia Impact Questionnaire – Revised (FIQR), painDETECT Questionnaire (PDQ), Symptom Severity Scale (SSS), and Widespread Pain Index (WPI). Arguments for the different variables are presented in our Statistical Analysis Plan (SAP), which has been attached as Supplementary file 1. After the cluster analysis had been completed, we explored how single selected items on the FIQR performed in the analysis, as specified in Measurements, below. Validated 'summarized scales' were used as a source to deliver the individual items, since we did not want to explore whether the summarized scales were informative per se; rather, we wanted to go back to the 'latent constructs' across all the measures that were collected (19).

## Measurements

Numerous baseline characteristics were collected. A linear combination of all of the original variables was created, since the primary goal of our analyses was to reduce the dimensionality of a large data set while preserving as much variance as possible. Thus, the analyses operate on the entire data set (and not just the summarized validated scales) to create an innovative set of new variables that are linear combinations of the original data (19).

*Contextual factors.* The Danish Civil Registration (CPR) number given at birth is unique to each Danish citizen, and provided the sex and age of the participants. Labour market affiliation, level of education, and marital status were based on patient-reported outcomes (PROs).

The labour market affiliation was divided into those 'employed and working' and those 'not working'. The group 'employed and working' covered participants who are employed, self-employed, in a 'flexjob' (a subsidized job for people with limited work capacity assigned from a rehabilitation team in each municipality), or on part-time sick leave (still employed and working part time) (20). Participants undergoing formal education or training were also considered as employed (presumed able to work) (20). Participants 'not working' included those receiving transfer payment benefits, including unemployment benefits, social assistance, full sick leave, ad interdisciplinary rehabilitation programme, support by a spouse, and home makers (20).

*Cognitive factors.* Information on the participants' pain-related cognitive coping was provided by the PSEQ. After the cluster analysis had been performed, we looked at item 17 (level of memory problems) on the symptom subscale of the FIQR. Both the PSEQ and FIQR have been validated in a Danish population of patients with FM (21, 22).

*Psychological factors.* Regarding psychological factors, we selected two items from the symptom subscale of the FIQR: items 16 (level of depression) and 18 (level of anxiety).

*Symptom and pain characteristics.* Data were collected using the following standardized questionnaires: FIQR, PDQ, SSS, and WPI. Additional items from the symptom subscale of the FIQR were singled out after the analysis: items 12 (level of pain), 13 (level of energy), 15 (quality of sleep), 19 (level of tenderness to touch), and 21 (level of sensitivity to loud noises, bright lights, odours, and cold). Information about symptom duration, diagnosis of CWP and FM, concomitant inflammatory rheumatic disease (i.e. primary or secondary CWP), and baseline analgesics were collected as PROs. A clinical examination of each participant provided the manually obtained TP count according to 1990 ACR guidelines (6).

## Sample size and power considerations

Since this cross-sectional study was designed for exploratory purposes only, the following power considerations are presented for merely pragmatic reasons. For a comparison of two independent binomial proportions (comparing prognostic factor exposed vs unexposed) using Pearson's chi-squared statistics with a chi-squared approximation and a two-sided significance level of 0.05, assuming a sample size of 388 participants per cluster (splitting the sample into two independent samples of approximately the same size; 776 participants in total), the corresponding power is at least 80%, when comparing proportions of 50% versus 40% (20).

## Statistical analyses

After standardization of the data set (to means and standard deviations), we applied a hierarchical cluster analysis (Ward's method) to assign specific clusters to each participant. Selection of the number of clusters was based on coefficients in the agglomeration schedule, supported by dendrograms and silhouette plots to assess the overall fit for the clustering assignments. The clusters were subsequently used as the novel phenotype grouping variable used to assess whether there were significant cluster differences (in their data distributions) within the potential prognostic factors given at baseline.

The baseline variables were described for all participants. Continuous data and ordinal scales were reported

descriptively, using means and standard deviations to estimate the standardized mean differences. Dichotomous data were reported as an absolute number as well as the relative number (%) and subsequently converted into standardized differences. The term balance diagnostics was used to describe the methods used to assess whether the distribution of baseline covariates was similar between the two clusters. The present study was designed to compare the mean of continuous variables or the prevalence of dichotomous baseline covariates between the clusters. The means of continuous variables and the distribution of categorical variables were reported for each group. Using the Kruskal–Wallis test, analyses were conducted to test the clusters. The Kruskal–Wallis test determined whether there was a statistically significant difference between the samples.

Using standardized differences allows for the comparison of the relative balance of variables measured in different units. Unlike t-tests and other two-sample statistical tests of hypothesis, standardized differences are not influenced by sample size. Thus, standardized differences were used to compare balance in measured variables between the clusters. Standardized differences are increasingly being used to compare balance in baseline covariates between groups in propensity-score matched samples (23). A limitation to their use is a lack of consensus on what value of a standardized mean difference (SMD) denotes an important residual imbalance between treated and untreated subjects in the matched sample. While there is no clear consensus on this issue, an SMD of ≥ 0.2 was applied to indicate that there may be a meaningful imbalance in the baseline covariate, whereas an SMD ≥ 0.8 was considered as definitive incomparability (i.e. clinically important difference). Finally, logistic regression models were used to create a propensity score (i.e. the likelihood of being assigned to a cluster). Both simple and multiple (using all available variables as independent predictors) regression analyses were performed. Multicollinearity is a risk when applying many variables that are correlated, and this was assessed by evaluating the size and stability of the regression coefficients. Results from the logistic regressions are reported as odds ratios (ORs) with 95% confidence intervals (95% CIs). All analyses were performed using SAS version 9.4 (SAS Studio; SAS, Cary, NC, USA).

## Results

### Study population

This study comprised 1099 patients from the DANFIB registry. Of these 1099 patients, 28 were registered as diagnosed with CWP (i.e. not fulfilling additional criteria for FM). Most of the study population were women (93.4%), with a mean age of 44.6 years (Table 1).

### Cluster analysis

Based on the change between coefficients in the agglomeration schedule from the hierarchical cluster analysis and associated dendrogram and silhouette plot (Supplementary file 1), we found a solution of two clusters to be optimal. Cluster 1 (n = 455) was defined as participants being significantly different from the rest, meaning that participants in this group had many similar characteristics and were a more homogeneous group. The remaining participants (Cluster 2) were a heterogeneous group that could not be assigned one specific cluster; therefore, they were defined as ‘Other patients’ (n = 644). Cluster 1 contained all of the participants with CWP except for two, who were included in ‘Other patients’. The cluster split of the sample is presented in Figure 1.

### Contextual factors

No significant differences were found in age or sex (Table 1). Most participants in Cluster 1 were employed and working (72.1%), had a medium-term or long-term higher education (67.0%), and were married or cohabiting (72.8%). All SMD values were above 0.2 (Table 1).

### Cognitive factors

The participants in Cluster 1 revealed fewer problems in the FIQR, item 17 (level of memory problems), scoring on average 4.3, in contrast to the group of ‘Other patients’, scoring on average 7. Participants in Cluster 1 had a significantly higher score on the PSEQ (31.3) compared to ‘Other patients’ (17.4).

### Psychological factors

The participants in Cluster 1 reported depression and anxiety to a lesser degree; on average 3.2 and 1.5, respectively, whereas the ‘Other patients’ scored higher, with 6.5 and 4.9, respectively (Table 1).

### Symptom and pain characteristics

The participants identified as corresponding to Cluster 1 had better scores than the ‘Other patients’ on all of the standardized questionnaires (Table 1). The participants in Cluster 1 had a significantly lower symptom burden (FIQR symptom subscale 24.3) and higher level of functional ability (FIQR function subscale 13.1) than participants in ‘Other patients’ (FIQR symptom subscale 37.5, function subscale 21.8). They reported

Table 1. Balance between Cluster 1 and all of the remaining participants.

| | Total (n = 1099) | Cluster 1 (n = 455) | Other patients (n = 644) | SMD | p Kruskal–Wallis |
|---|---|---|---|---|---|
| Baseline demographics | | | | | |
| Female, n (%) | 1027 (93.4%) | 420 (92.3%) | 607 (94.3%) | –0.08 | 0.1990 |
| Age (years) | 44.6 (10.4) | 45.6 (11.2) | 43.9 (9.7) | 0.17 | 0.0011 |
| Labour market affiliation, n (%) | | | | | |
| Employed and working | 529 (48.1%) | 328 (72.1%) | 201 (31.2%) | 0.90 | < 0.0001 |
| Not working | 570 (51.9%) | 127 (27.9%) | 443 (68.8%) | –0.90 | |
| Duration of pain (weeks) | 253.7 (145.2) | 250.5 (146.1) | 255.9 (144.5) | –0.04 | 0.5121 |
| Already diagnosed with FM/CWP, n (%) | 489 (44.5%) | 183 (40.2%) | 306 (47.5%) | –0.15 | 0.0166 |
| Level of education, n (%) | | | | | |
| Primary or high school | 489 (44.5%) | 150 (33.0%) | 339 (52.6%) | –0.41 | < 0.0001 |
| Medium-term or long-term higher education | 610 (55.5%) | 305 (67.0%) | 305 (47.4%) | 0.41 | |
| Marital status, n (%) | | | | | |
| Married/cohabiting | 709 (64.5%) | 331 (72.8%) | 378 (58.7%) | 0.30 | < 0.0001 |
| Single/widowed/separated or divorced | 390 (35.5%) | 124 (27.3%) | 266 (41.3%) | –0.30 | |
| Concomitant inflammatory rheumatic disease, n (%) | 441 (40.1%) | 165 (36.3%) | 276 (42.9%) | –0.14 | 0.0281 |
| Baseline analgesics, n (%) | | | | | |
| Strong analgesics (opioids), including tramadol | 240 (21.8%) | 63 (13.9%) | 177 (27.5%) | –0.34 | < 0.0001 |
| Mild analgesics, including NSAIDs | 940 (85.5%) | 405 (89.0%) | 535 (83.1%) | 0.17 | 0.0059 |
| Neuropathic medication | 243 (22.1%) | 72 (15.8%) | 171 (26.6%) | –0.26 | < 0.0001 |
| Muscle relaxants | 142 (12.9%) | 42 (9.2%) | 100 (15.5%) | –0.19 | 0.0022 |
| Low-dose naltrexone | 93 (8.5%) | 34 (7.5%) | 59 (9.2%) | –0.06 | 0.3220 |
| Cannabinoids | 46 (4.2%) | 12 (2.6%) | 34 (5.3%) | –0.14 | 0.0313 |
| Clinical examination | | | | | |
| Tender point count (0–18) | 15.0 (3.4) | 14.0 (3.7) | 15.8 (2.9) | –0.55 | < 0.0001 |
| Standardized questionnaires | | | | | |
| FIQR subtotal score function | 18.0 (6.7) | 13.1 (5.6) | 21.8 (4.8) | –1.66 | < 0.0001 |
| FIQR subtotal score impact | 14.0 (4.7) | 10.3 (4.4) | 16.6 (2.9) | –1.69 | < 0.0001 |
| FIQR subtotal score symptom | 32.0 (8.5) | 24.3 (5.5) | 37.5 (5.4) | –2.43 | < 0.0001 |
| FIQR 'Level of pain' | 7.3 (1.8) | 6.1 (1.7) | 8.2 (1.3) | –1.44 | < 0.0001 |
| FIQR 'Level of energy' | 7.6 (2.1) | 6.3 (2.1) | 8.5 (1.5) | –1.20 | < 0.0001 |
| FIQR 'Quality of sleep' | 8.2 (2.2) | 7.1 (2.4) | 9.0 (1.5) | –0.97 | < 0.0001 |
| FIQR 'Level of depression' | 5.1 (3.1) | 3.2 (2.6) | 6.5 (2.7) | –1.24 | < 0.0001 |
| FIQR 'Level of memory problems' | 6.1 (2.8) | 4.3 (2.6) | 7.4 (2.1) | –1.34 | < 0.0001 |
| FIQR 'Level of anxiety' | 3.5 (3.4) | 1.5 (2.1) | 4.9 (3.4) | –1.18 | < 0.0001 |
| FIQR 'Level of tenderness to touch' | 6.8 (2.9) | 5.0 (3.0) | 8.1 (2.0) | –1.25 | < 0.0001 |
| FIQR 'Level of sensitivity' | 7.3 (2.8) | 5.7 (3.0) | 8.4 (1.9) | –1.05 | < 0.0001 |
| PSEQ | 23.2 (12.0) | 31.3 (10.4) | 17.4 (9.6) | 1.39 | < 0.0001 |
| PDQ score | 21.7 (7.3) | 16.6 (6.2) | 25.3 (5.7) | –1.46 | < 0.0001 |
| PDQ ≥ 18, n (%) | 778 (70.8%) | 194 (42.6%) | 584 (90.7%) | –1.18 | < 0.0001 |
| SSS | 8.9 (2.0) | 7.4 (1.7) | 9.9 (1.5) | –1.53 | < 0.0001 |
| WPI | 13.4 (3.8) | 11.9 (3.8) | 14.4 (3.5) | –0.69 | < 0.0001 |

Data are shown as mean (SMD) unless otherwise stated.
CWP, chronic widespread pain; FIQR, Fibromyalgia Impact Questionnaire – Revised; FM, fibromyalgia; M/F, male/female; NSAID, non-steroidal anti-inflammatory drug; PDQ, painDETECT Questionnaire (range from 0 to 38); PSEQ, Pain Self-Efficacy Questionnaire; SMD, standardized mean difference; SSS, Symptom Severity Scale; WPI, Widespread Pain Index.

a significantly lower level of pain (FIQR item 12: 6.1) and polysensory hypersensitivity (FIQR item 21: 5.7) and had fewer TPs (14.0), and fewer had a PDQ score above 18 (42.6%) compared to the 'Other patients' (FIQR item 12: 8.2 and item 21: 8.4, TP 15.8; and 90.7% had a PDQ ≥ 18). Also, participants in Cluster 1 were less likely to have self-reported comorbid inflammatory or degenerative rheumatic diseases (36.3%). Participants among 'Other patients' had a higher consumption of strong analgesics (opioids) (27.5%), which included tramadol. The proportion of patients already diagnosed with CWP or FM before being referred to the Fibromyalgia Unit was smaller in Cluster 1 (40.2%) than in the group of 'Other patients' (47.5%). No significant difference was found in duration of pain (Table 1).

## Logistic regression modelling

The results of our logistic models are shown in Table 2. Multicollinearity was deemed to be ignorable as the regression coefficients were stable. The results showed that being employed and working (OR 66.67, 95% CI 7.14 to 500.00), having a medium-term or long-term higher education (OR 16.80, 95% CI 1.94 to 145.41), being married or cohabiting (OR 14.29, 95% CI 1.26 to 166.67), and using mild analgesics (OR 25.64, 95% C:

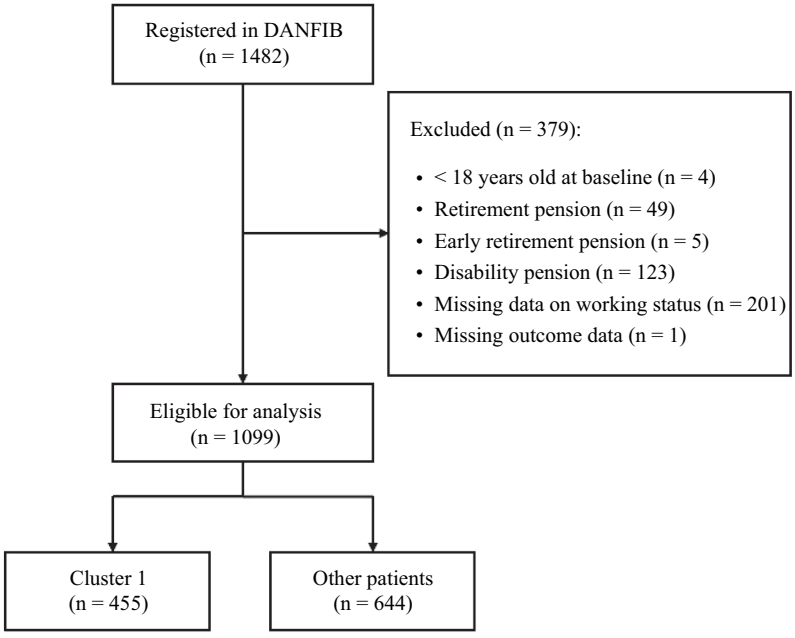


Figure 1. Overview of cross-sectional research flow among the eligible participants (at baseline).

0.58 to > 999.99) increased the odds of being in Cluster 1. The logistic regression in Table 2 also showed that scoring worse on the FIQR, PDQ, SSS, or WPI, or having a higher TP count, reduced the odds of being in Cluster 1. A PDQ score ≥ 18 (OR < 0.001, 95% CI < 0.001 to 0.02) significantly increased the odds of being an individual in the 'Other patients' cluster.

## Discussion

In this exploratory cross-sectional cluster analysis, conducted in a large sample of patients with a confirmed diagnosis of CWP or FM referred for specialized treatment, we identified a group of participants who were significantly different from all the others (Cluster 1). These participants were relatively homogeneous and characterized by having a lower overall symptom burden, a higher level of functioning, also in terms of being employed and working, and a high level of pain self-efficacy. They were further characterized by being married or cohabitating, and having a medium-term or long-term higher education, and by using mild analgesics. Therefore, it may be hypothesized that Cluster 1 contains participants with a more favourable pain profile and prognosis.

Most clinical guidelines for the management of CWP and FM are based on a stepped care model approach (12, 14). The stepped care model is characterized by patients starting out on similar treatment pathways, which are intensified and specialized stepwise as the disease severity progresses (15, 24). We found a large group of patients that was more homogeneous and perhaps had a more adaptive phenotype that may not need scaling of treatment intensity despite being diagnosed with CWP and FM. Thus, our results could potentially, with support from more studies, be translated into clinical practice with the identification of those patients in less need of specialized care.

Contextual factors, such as employment status, are known to be influenced by pain, and evidence shows that pain-related psychological and cognitive factors, such as pain self-efficacy, pain catastrophizing, and fear-avoidance behaviour, are determinants of work disability (25). In patients with FM, pain self-efficacy has been identified as a stable predictor of depression, pain, and functional ability over time (26). In support of this, our study found that participants with a low score on the PSEQ were most likely to be in the 'Other patients' group, which was characterized by a low level of employment. Correspondingly, we found that individuals with a medium-term or long-term higher education were employed and working, and had the highest odds of being in Cluster 1. Also, there is evidence that treatment of pain with opioids or cannabinoids can extend the period of work disability rather than shorten it (25). This is in accordance with our cluster analysis, which found that most participants who were not working had a higher consumption of strong analgesics.

Predicting individuals at risk of being expelled from the labour market by prognostic factors may help to retain them in employment and prevent progressive health inequities and societal costs. The challenge is to identify the phenotypic characteristics of people at risk. Although chronic pain is largely responsible for people not working (25), research shows that reduction in pain-related psychological factors is a stronger predictor of return to work than reduction in pain severity (25). The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations

Table 2. Results of logistic regression models showing the associations between measured covariates and Cluster 1 membership as the dependent variable (odds ratios for being a member of Cluster 1).

| | Simple regression OR (95% CI) | Multiple regression OR (95% CI) |
|---|---|---|
| Demographics | | |
| Female sex (vs male) | 0.73 (0.45 to 1.18) | 0.73 (0.04 to 14.49) |
| Age (years) | 1.02 (1.01 to 1.03) | 1.03 (0.92 to 1.14) |
| Labour market affiliation | | |
| Employed and working (vs not working) | 5.68 (4.37 to 7.41) | 66.67 (7.14 to 500.00) |
| Duration of pain (weeks) | 1.00 (1.00 to 1.00) | 1.00 (0.99 to 1.01) |
| Already diagnosed with FM/CWP (vs no existing diagnosis) | 0.74 (0.58 to 0.95) | 0.29 (0.05 to 1.84) |
| Level of education | | |
| Medium/long education (vs primary or high school) | 2.26 (1.76 to 2.90) | 16.80 (1.94 to 145.41) |
| Marital status | | |
| Married/cohabitating (vs single/widowed/separated/divorced) | 1.88 (1.45 to 2.43) | 14.29 (1.26 to 166.67) |
| Concomitant inflammatory rheumatic disease (vs no other rheumatic disease) | 0.76 (0.59 to 0.97) | 0.26 (0.04 to 1.64) |
| Analgesics | | |
| Strong analgesics (opioids) including tramadol (vs no use) | 0.42 (0.31 to 0.58) | 0.08 (0.00 to 1.61) |
| Mild analgesics, including NSAIDs (vs no use) | 1.65 (1.15 to 2.36) | 25.64 (0.58 to > 999.99) |
| Neuropathic medication (vs no use) | 0.52 (0.38 to 0.71) | 0.09 (0.01 to 0.75) |
| Muscle relaxants (vs no use) | 0.55 (0.38 to 0.81) | 0.36 (0.03 to 4.31) |
| Low-dose naltrexone (vs no use) | 0.80 (0.52 to 1.24) | 0.23 (0.01 to 10.00) |
| Cannabinoids (vs no use) | 0.49 (0.25 to 0.95) | 0.04 (< 0.001 to 4.52) |
| Clinical examination | | |
| Tender point count (0–18) | 0.84 (0.81 to 0.88) | 0.67 (0.49 to 0.91) |
| Standardized questionnaires | | |
| FIQR subtotal score function | 0.74 (0.72 to 0.77) | 0.57 (0.42 to 0.77) |
| FIQR subtotal score impact | 0.63 (0.60 to 0.67) | 0.50 (0.34 to 0.74) |
| FIQR subtotal score symptom | 0.58 (0.54 to 0.62) | 0.60 (0.30 to 1.22) |
| FIQR 'Level of pain' | 0.36 (0.32 to 0.41) | 0.11 (0.03 to 0.35) |
| FIQR 'Level of energy' | 0.49 (0.45 to 0.54) | 0.23 (0.10 to 0.52) |
| FIQR 'Quality of sleep' | 0.59 (0.54 to 0.64) | 0.27 (0.12 to 0.60) |
| FIQR 'Level of depression' | 0.66 (0.63 to 0.70) | 0.35 (0.18 to 0.70) |
| FIQR 'Level of memory problems' | 0.59 (0.56 to 0.63) | 0.33 (0.15 to 0.69) |
| FIQR 'Level of anxiety' | 0.68 (0.65 to 0.72) | 0.31 (0.16 to 0.63) |
| FIQR 'Level of tenderness to touch' | 0.62 (0.58 to 0.66) | 0.21 (0.09 to 0.51) |
| FIQR 'Level of sensitivity' | 0.65 (0.61 to 0.69) | 0.33 (0.16 to 0.69) |
| PSEQ | 1.14 (1.12 to 1.16) | 1.35 (1.15 to 1.59) |
| PDQ score | 0.79 (0.77 to 0.81) | 0.77 (0.59 to 1.02) |
| PDQ ≥ 18 (vs < 18) | 0.08 (0.06 to 0.11) | < 0.001 (< 0.001 to 0.02) |
| SSS | 0.39 (0.34 to 0.43) | 0.14 (0.06 to 0.35) |
| WPI | 0.83 (0.80 to 0.86) | 0.57 (0.41 to 0.79) |

CWP, chronic widespread pain; FIQR, Fibromyalgia Impact Questionnaire – Revised; FM, fibromyalgia; NSAID, non-steroidal anti-inflammatory drug; OR, odds ratio; PDQ, painDETECT Questionnaire (range from 0 to 38); PSEQ, Pain Self-Efficacy Questionnaire; SSS, Symptom Severity Scale; WPI, Widespread Pain Index.

regarding patient phenotyping substantiates that chronic painful conditions carry an increased risk of also having a mood disorder (27). The association between CWP and depression is also well established, and the available evidence suggests that the coexistence of depressive symptoms in patients with FM is associated with increased pain intensity, more functional disability, and poorer health-related quality of life (28). In line with a study by Terol Cantero et al (29), who found that anxiety and depression were significant features separating two profiles – a 'maladaptive' and an 'adaptive' profile – our study found that participants in Cluster 1 who were retained in work also had significantly lower scores for depression and anxiety compared to participants in the 'Other patients' cluster, and therefore may have an 'adaptive' profile. Still, the anxiety scores were generally low, with a total mean of 3.5 among the study sample.

The PDQ has been widely used to evaluate patterns of somatosensory symptoms and subtype not just in patients with neuropathic pain, but also in individuals with various musculoskeletal pain conditions (27). The PDQ is recommended by the IMMPACT group for screening for neuropathic pain phenotypes and for characterizing/subgrouping based on somatosensory profiles (27). The PDQ has also proven to be a helpful instrument when identifying somatosensory profiles in patients with CWP (30–33), and the total score on PDQ has been found to correlate with TP count and pressure–pain thresholds assessed by cuff algometry in

patients with FM, supporting the ability of the PDQ to identify individuals characterized by widespread pain hypersensitivity (30). Our study found that a PDQ score ≥ 18 significantly reduced the odds of being in Cluster 1, and participants with a high PDQ score belonging to the 'Other patients' cluster also had a significantly higher TP count and WPI, signifying that this group could represent the upper end of a pain severity spectrum with more pronounced pain hypersensitivity.

The FIQR is the recommended disease-specific self-rating instrument for evaluating disease burden and the impact of disease in patients with FM (34). A study by Palstam et al (35) proposed that the total score on the Fibromyalgia Impact Questionnaire (FIQ) could be used to predict work disability. However, the Danish validation of the FIQR found that the total FIQR score should be interpreted with caution (22); that is, the FIQR should be considered as an instrument consisting of three separate subscales: 'function', 'overall impact', and 'symptoms' (22). We found symptom severity and impact of disease to be lower in Cluster 1, and those with a more pronounced disease burden belonged to the group of 'Other patients' (also illustrated by a high TP count, PDQ score, and WPI). Surprisingly, there was no difference in pain duration between the patients in Cluster 1 and 'Other patients'. However, the proportion of patients already diagnosed with CWP and FM by a rheumatologist before referral to the clinic was larger in the group 'Other patients'. Evidence from prospective studies indicates that psychosocial as well as other risk factors (e.g. concomitant diseases) for chronicity and disability in patients with CWP and FM are often present in the early stages rather than gradually appearing over time (2). Patients in the clinical setting often present with multimorbidity, and all comorbidities can potentially influence the disease burden and outcome of the disease. In our study, 40.1% of the total study population had a self-reported concomitant inflammatory rheumatic disease, with the proportion being lower among the participants in Cluster 1. Unhelpful responses to pain, such as activity avoidance, may be harder to alter when they have been present for a long time, thereby increasing the risk of prolonged disability and delays in dealing with workplace factors, resulting in greater risk of long-term absenteeism, unemployment, and marginalization or exclusion from the labour market. An early and targeted treatment strategy may prevent this and should be a high priority.

The strengths of this study included the large sample of consecutively enrolled patients from a clinical setting with a confirmed diagnosis of CWP or FM, as well as the large variety of collected baseline characteristics, adding to the robustness of the results. The study also had limitations that need to be considered. One limitation may be that the data primarily consisted of patient-reported outcomes and may have been influenced by recall bias. Also, the DANFIB registry is not a national registry, but mainly covers patients referred from the Capital Region, which may limit generalizability. Furthermore, all participants were recruited from a specialized care setting and may therefore not be representative of the overall referral population but come from the more severe end of the disease spectrum. Finally, the study was cross-sectional. To enhance the clinical relevance of the study findings, we have planned a longitudinal study on this cohort [the protocol has been published in BMJ Open (20)]. The longitudinal study will clarify whether those individuals in Cluster 1 have better employment prospects over time and whether those in the 'Other patients' group are at risk of being excluded from the Danish labour market. Furthermore, we will be able to test whether the possible prognostic factors that we have identified in this exploratory cross-sectional cluster analysis are valid in a prospective study aimed at predicting work status.

## Conclusion

In this study, conducted on a large clinical sample of patients with a confirmed diagnosis of CWP or FM from a tertiary care setting, one cluster of participants who were significantly different from all the others emerged from the cluster analysis. Participants assigned to this cluster made up a homogeneous subgroup characterized by a seemingly more favourable clinical profile and by being retained in work. More studies are needed to evaluate whether the characteristics of this homogeneous subgroup could be used as a guide for the management of patients with CWP and FM.

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## Disclosure statement

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## Ethics

The DANFIB registry has been approved by the Danish Data Protection Agency and granted authorization for the period January 2018 to January 2033 (j.nr. 2012-58-0004). Additional approval for this study

was therefore not necessary according to Danish law. Sensitive personal data will be anonymized according to regulations stipulated by the Danish Data Protection Agency, and informed consent is obtained from all participants before enrolment in the DANFIB registry.

## Supplementary material

Supplemental data for this article can be accessed online at https://doi.org/10.1080/03009742.2023.2297514

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