



Original Reports

An exploratory data-driven approach to classify subgroups of patients with temporomandibular disorders based on pain mechanisms[☆]

Giacomo Asquini^{a,b}, Valter Devecchi^a, Domenico Viscuso^{b,d}, Rosaria Bucci^c, Ambra Michelotti^c, Bernard X.W. Liew^e, Deborah Falla^{a,*}

^a Centre of Precision Rehabilitation for Spinal Pain (CPR Spine), School of Sport, Exercise and Rehabilitation Sciences, College of Life and Environmental Sciences, University of Birmingham, Birmingham B15 2TT, United Kingdom

^b Italian Stomatologic Institute, Craniomandibular Physiotherapy Service, Via Pace 21, 20122 Milan, Italy

^c Department of Neurosciences, Reproductive Sciences and Oral Sciences, School of Orthodontics, University of Naples Federico II, Naples, Italy

^d University of Cagliari, Department of Surgical Sciences, Dental Service, Via Università 40, Cagliari, Italy

^e School of Sport, Rehabilitation and Exercise Sciences, University of Essex, Colchester, Essex, United Kingdom



ARTICLE INFO

Keywords:

Temporomandibular disorders
Network analysis
Pain phenotypes
Nociplastic
Nociceptive

ABSTRACT

Temporomandibular disorders (TMDs) are a common musculoskeletal condition, presenting treatment challenges due to their non-specific nature. Categorizing patients with TMDs into clusters based on neurobiological pain mechanisms could provide a promising approach to facilitate targeted treatments. This observational study (1) used a network analysis (NA) to explore the complexity of TMDs by investigating relationships among biopsychosocial variables, and (2) validated potential TMD subgroups based on mechanism-specific pain categories. One hundred and two patients with TMD were included. Biopsychosocial variables covered: general health, psychosocial features, TMD pain, and TMD characteristics. A NA evaluated the associations between variables and determined the role of each feature within the network. Hierarchical clustering was used to identify TMD subgroups. The NA revealed significant correlations primarily within the same feature domains, indicating a strong interplay between symptoms and psychological factors. Cluster analysis identified two subgroups driven by nociceptive and nociplastic pain mechanisms; the nociplastic group exhibited higher levels of anxiety, depression, pain catastrophization, central sensitization, pain duration, and more pain locations, along with poorer sleep quality, quality of life, and health status. In contrast, the nociceptive group exhibited restricted maximal mouth opening (MMO), heightened pain during TMJ palpation and mouth opening, and a greater positive response to manual therapy. Across all features, psychological factors, pain locations, and MMO primarily contributed to the separation of subgroups. By adopting a data-driven approach, these results support the significant role of considering the neurobiological basis of pain to improve patient classification. This knowledge may facilitate clinical reasoning and personalized treatments.

Perspective: This study used a network analysis to explore the complex biopsychosocial interactions present in people with TMDs, identifying important variables such as the Central Sensitization Inventory and pain-free maximal mouth opening. The findings distinguish potential nociceptive and nociplastic pain subgroups, offering important insights for targeted therapeutic strategies.

Introduction

Temporomandibular disorders (TMDs) are a global health challenge contributing to a high number of years lived with disability.¹ Principal symptoms are pain, with possible restricted jaw mobility and joint sounds.^{2,3} Notwithstanding the research effort in this field, TMDs

remain a challenge and are often described as nonspecific since a clear cause is not identified, or traditional classification systems are adopted which define each disorder based on anatomical structures (e.g., TMD Arthralgia versus Myalgia), without giving sufficient attention to non-anatomical and etiological factors.⁴ Additionally, treatments are often guided by pathoanatomical classifications, which may not fully

[☆] Trial registration number: NCT03990662.

* Corresponding author.

E-mail address: d.falla@bham.ac.uk (D. Falla).

consider the complexity of such disorders.^{5,6} A promising approach to overcome this challenge is the categorization of patients into clusters based on the neurobiological mechanisms underlying their pain.⁷⁻¹² This approach could enhance the understanding of a patient's specific clinical condition, thereby guiding the selection of more effective treatment strategies by looking at multiple domains and delivering more personalized treatments.⁶⁻¹¹ In this regard, previous research on patients with TMDs identified different clusters of individuals by studying numerous biopsychosocial variables.¹¹ Patients were predominantly distributed in two clusters termed 'pain-sensitive' and 'global-symptoms'.¹¹ The pain-sensitive cluster was characterized by increased sensitivity to experimental pain, while the global-symptoms cluster showed both higher pain sensitivity and psychological distress.¹¹ Furthermore, additional research has identified a heightened risk of developing a painful TMD among individuals exhibiting a multisystem phenotype characterized by the triad of bodily pain, psychological distress, and sleep disturbance.¹³ These findings suggest that pain and related treatments should not be viewed in isolation but rather as part of a more comprehensive context, integrated into a complete "distress monitoring system" focusing on overall individual health.¹³ In a narrative review reporting on clinical reasoning for the management of patients with TMDs, potential subgroups of patients with TMDs have been described based on the dominant type of sensitization present (i.e., central versus peripheral).¹⁴ Tissue-based interventions are suggested for those with peripheral sensitization, while strategies targeting the central nervous system are proposed for those with central sensitization.¹⁴ Nevertheless, empirical evidence confirming the existence of such subgroups within a cohort of patients with TMDs is currently lacking.

Previous studies examining mechanism-based classifications of musculoskeletal pain have highlighted the distinct characteristics of nociceptive and nociplastic pain.^{9,10,12} Nociceptive pain is typically elicited by physical stimuli, well localized, and is associated with minimal psychosocial impairment.¹² Conversely, nociplastic pain often manifests as generalized, unpredictable pain accompanied by significant psychosocial distress.¹² Therefore, different treatments are required depending on the mechanism-base category of pain.^{4,12}

In addition to identifying patient clusters, it is necessary to understand the interactions among features that define the observed clusters, as the features themselves – such as central sensitization or joint mobility – are the actual targets of treatment, not the clusters. To this end, a network analysis (NA) is an effective approach commonly used to examine complex systems since it gives the possibility of evaluating and graphically illustrating multiple relations between features.¹⁵ This approach can identify key features that are highly interconnected with others, which may highlight potential targets for treatment. Thus, a better understanding of the interactions across biopsychosocial variables can help to characterize TMD subgroups and ultimately guide treatment decisions. Similar advancements have occurred for neck pain, with different studies employing a NA to reveal interactions and factors contributing to chronic pain after trauma, exemplifying its potential in unravelling complex conditions.^{16,17}

In a cohort of patients with TMDs, this observational study aimed to: (1) unravel the complexity of TMDs by exploring the relationships and conditional dependencies across biopsychosocial variables (e.g., general health variables, psychosocial features, TMD characteristics and related clinical tests), and by identifying the most relevant variables; (2) verify potential TMD subgroups by differentiating mechanism-based categories of pain.¹² Although estimating a network is an exploratory approach, we hypothesized that stronger dependencies will be present across variables belonging to the same domain (e.g., general health domain, psychological domain) with some presenting interdomain connections. Moreover, we hypothesized that this analysis would reveal subgroups of TMD patients according to dominant pain mechanisms i.e., nociceptive versus nociplastic pain mechanisms.

Methods

The data for the current study were obtained from a prospective observational study that identified predictors of good outcomes following manual therapy in a cohort of patients with TMDs.^{18,19} The study was conducted in Italy (Milan) at the TMJ-Unit of the Italian Stomatological Institute. The Ethics Committee of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico approved the study (acceptance no. "534_2019bis"). Written informed consent was obtained from all participants who received a full explanation of the study. The study was conducted according to the Declaration of Helsinki and was prospectively registered (NCT03990662). The report of this study complies with the "Strengthening The Reporting of Observation studies in Epidemiology" (STROBE checklist) and adequate standards for network analyses.^{20,21}

Participants, recruitment and procedure

All patients attending the TMJ-Unit of the Italian Stomatological Institute (Italy) from July 2019 to May 2021 were screened for inclusion by a dentist with more than ten years of experience in TMD and orofacial pain assessment and management. After the screening, the dentist excluded other forms of pain in the orofacial area (e.g. odontogenic pain, neuropathic pain) referring to the International Classification of Orofacial Pain²² and confirmed the TMD diagnosis using the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD).^{23,24} From 131 patients with potential TMD screened for eligibility, 102 were recruited. Inclusion Criteria were: (1) adults (≥ 18 years); (2) presenting with one or multiple pain-related TMD diagnoses according to DC/TMD²³; (3) had not received any interventions for the TMD in the past six months including physical therapy, oral appliance, anti-inflammatory drugs or surgical interventions (only self-care was allowed such as thermotherapy and massage); (4) capable of speaking and understanding Italian; (5) able to provide written informed consent. Exclusion criteria were: (1) TMD pain associated with a history of systemic rheumatoid/inflammatory arthritis; (2) presenting with any physical (e.g. facial paralysis, odontogenic pain, neurological disorders, neuropathic pain, head or neck cancer) or mental status (e.g. cognitive deficit, mental illness and/or disorders) that could influence the study outcomes. After participants provided written consent, they were assessed by a physiotherapist with more than five years of experience in TMD management to obtain data of the outcome measures described below.

Outcome measures

Outcome measures were chosen based on previous research investigating altered pain modulation and features related to different mechanism-based categories of pain in musculoskeletal disorders and, in particular in patients with TMDs.^{10,11,25} All outcomes are summarized in Table 1 (a full description is reported in the supplementary file S1 of the previous publication¹⁹), and are structured in four domains to better understand and describe the relationships between variables. These domains consisted of general health, psychosocial, pain characteristics, and TMJ mechanosensitivity domain, and they were selected to cover features for the identification of nociceptive and nociplastic subgroups.

General health variables

Sleep quality and health-related quality of life were investigated for their role in chronic pain and treatment outcomes in TMD patients.²⁶⁻²⁸ Sleep quality was evaluated via an 11-point Numerical Rating Scale (NRS), where 0 is 'the best possible sleep' and 10 is 'the worst possible sleep' related to the preceding 6 months.^{18,19} This scale holds moderate psychometric properties in fibromyalgia patients to evaluate sleep quality.²⁹

Current health-related quality of life was measured using the Italian version of the EQ-5D-5L [www.euroqol.org], and through the patient's

Table 1

Summary of the biopsychosocial variables of interest grouped for different domains. Node labels used in the NA and outcome measures are also reported.

| Variables | Node labels | Outcome measures |
|--------------------------------------|-------------|--|
| General health domain | | |
| Quality of life | QoL | EQ5D ²⁷ |
| Health status | HS | EuroQol VAS ²⁷ |
| Sleep quality | Sleep | 11-point [0–10] NRS relating to current pain, from 0 indicating ‘worst possible sleep’ to 10 indicating ‘best possible sleep’ ²⁹ |
| Oral Behaviours | OBC | Oral Behaviours Checklist ³⁶ |
| Psychosocial domain | | |
| Pain catastrophizing | CSQ-C | Catastrophizing domain score from the Coping Strategies Questionnaire 27 ⁴⁶ |
| Anxiety | Anxiety | Hospital Anxiety Scales (HADS-A) ⁴⁴ |
| Depression | Depression | Hospital Depression Scales (HADS-D) ⁴⁴ |
| Central sensitization | CSI | Central Sensitization Inventory ⁴⁶ |
| Pain characteristics domain | | |
| Pain duration | Pain Dur | Number of days experiencing pain |
| Pain intensity | Pain Int | VAS: current rest pain, average pain and worst pain in the past week ⁵⁵ |
| Number of pain locations | Pain Locs | Body chart (as described in the protocol of DC/TMD ²³) |
| Graded Chronic Pain Scale | GCPS | RDC/TMD Axis II Graded Chronic Pain Scale version 2.0 scores (Characteristic Pain Intensity (CPI) and disability points based on disability score and disability days) using the Italian version of the RDC/TMD questionnaire [Italian version - www.rdc-tmdinternational.org] |
| TMJ mechanosensitivity domain | | |
| Mechanical Pain – mouth opening | Pain MO | VRS: pain during the maximal opening of the mouth; |
| Mechanical Pain – clenching | Pain Clen | VSR: pain during maximal clenching |
| TMJ range of motion - pain-free | MMO | Maximal Mouth Opening (MMO) without pain measured in mm through a ruler as described in the DC/TMD protocol ²³ |
| Pain TMJ palpation | Pain TMJ | Dynamic TMJ lateral pole palpation (1 kg of palpation pressure) in according to DC/TMD protocol ²³ |
| Pain muscle palpation | Pain M | Score range: 0–1 (no pain = 0; pain = 1) Palpation in the following 6 bilateral points: lateral pterygoid area (0.5 kg intraoral palpation), temporalis tendon (0.5 kg intraoral palpation), masseter muscle (1 kg extraoral palpation) as described in the DC/TMD protocol. ²³ Score range: 0–1 (< 3 sites with familiar pain = 0; ≥ 3 sites with familiar pain = 1) |
| Immediate response to MT | MT response | JAw test ¹⁹ : Immediate effects of brief intraoral manual therapy (MT) techniques on pain (VRS) and TMJ range of motion (MMO) ¹⁹ Score range 0–2: (0 = no change; 1 = pain improvement or MMO improvement; 2 = improvement of both) |

judgement about his/her health status with a visual analogue scale range 0–100, representing respectively ‘worst’ to ‘best’ imaginable health state.³⁰ This scale showed adequate statistical proprieties and validity.^{27–31}

Oral behaviour over the last month was investigated since it could considerably impact on the evolution and maintenance of TMD pain.^{32–34} The Italian version of the RDC/TMD questionnaire Axis II Oral Behaviours Checklist (OBC) [www.rdc-tmdinternational.org] was used by following the DC/TMD protocol recommendations.^{23–25} The OBC showed adequate psychometric properties, with patient behaviours corresponding to those examined.^{33–36}

Psychosocial features

Psychosocial factors (e.g., depression, anxiety), central sensitization (CS) and pain catastrophizing are known to show a strong influence on

TMD onset and chronicity.^{37,38} Psychological distress is associated with high severity and persistence of TMD pain,³⁹ and it is more common among people with chronic TMD.^{40–42} Consequently, participants were asked to complete the Italian version of the Hospital Anxiety and Depression Scale (HADS).⁴³ This scale is useful for examining current feelings of depression, anxiety and manifestations of somatic symptoms,⁴⁴ and it showed superior concurrent validity in comparison to other depression/anxiety scales.⁴⁵ HADS is divided into one subscale for anxiety (HADS-A) and another for depression (HADS-D), with more elevated levels of anxiety and depression at high values.⁴⁵

The Italian version of the 27-item Coping Strategies Questionnaire (CSQ-27) was used to measure catastrophizing during pain over the previous month.⁴⁶ The English version of the CSQ-27 demonstrated sufficient internal consistency (Cronbach’s alpha from 0.72 to 0.86) and adequate construct validity.⁴⁷ For data analysis, only the catastrophizing domain score (CSQ-CAT) was used and was separated from other scores since it differentiated from other domains by clustering with pain-related distress items.⁴⁷ Also, previous research suggests that catastrophizing in patients with TMD might not only affect symptom severity but also treatment outcome.⁴⁸

Finally, the Italian version of the Central Sensitization Inventory (CSI) was used since existing literature suggests that the CSI reflects psychological distress and hypervigilance.^{49–51} CSI test-retest reliability and internal consistency were shown to be satisfactory in individuals with and without pain.⁵² The Italian version of the CSI has an acceptable Cronbach’s alpha [0.87].⁵¹

Pain characteristics

Pain duration, pain intensity, number of pain locations, and pain-related disability were examined. The duration of pain was collected from patient hospital records and interviews.¹⁹

Current resting pain intensity, in addition to the average and worst pain intensity over the past week, was registered with a Visual Analogue Scale (VAS) (10 cm horizontal line without marks, with “no pain” written at the left extremity and “worst pain imaginable” at the right extremity).^{53–55} A verbal rating scale (VRS) was used to score pain intensity during the maximal opening of the mouth and maximal clenching.¹⁹ The VAS and the VRS are known to be reliable and valid tools for assessing pain intensity.⁵⁴

Additionally, participants were asked to complete a pain drawing as described in the DC/TMD.²³ Pain in different body regions (e.g., headache, back pain, shoulder pain, neck pain) was summarized as a count variable.

Finally, chronic facial pain severity in the last 6 months was examined via the Italian version of the Research Diagnostic Criteria for TMD (RDC/TMD) questionnaire Axis II Graded Chronic Pain Scale (GCPS) version-2.0 [www.rdc-tmdinternational.org] in according to the DC/TMD protocol.^{23,35,56–58} This scale combines pain intensity and pain-related disability into five ordinal categories of chronic facial pain severity.⁵⁸ It demonstrated satisfactory internal consistency when used for patients with TMDs (Cronbach’s alpha 0.84).⁵⁷

TMJ mechanosensitivity

According to the Taxonomy Classification of TMD, different types of TMD are described: TMJ disorders, masticatory muscle disorders, headache attributed to TMD, associated structures disorders, and mixed forms disorders.⁵⁹ The TMD classification for each patient was obtained from their medical records. Moreover, maximal mouth opening (MMO) without pain was measured in millimetres using a ruler as described in the DC/TMD protocol.²³ The measurements were taken in a neutral craniocervical position (e.g., sitting or supine).^{19,23} Mechanical pain reported during mouth opening and clenching were also recorded. Similarly, the presence of pain during palpation of temporomandibular joints (TMJs) and masticatory muscles was assessed according to DC/TMD protocol.^{19,23} Finally,

Finally, a clinical test (named JAw-test)¹⁹ was adopted to assess the

response to a tissue-based intervention by evaluating the immediate effects of four brief intraoral manual therapy techniques on TMD pain and on TMJ range of motion.¹⁹ The Jaw test was performed as the final test in the baseline assessment to avoid the possibility of influencing other outcome measures.

Statistical analysis

All analyses were conducted using R software (version 4.2.1). Descriptive statistics were used to present demographic characteristics and the biopsychosocial variables of interest. Mean and standard deviation were used for continuous variables and frequencies for ordinal variables. Questionnaire scores were assessed and reported based on the corresponding guidelines. Outcome measures were grouped into four domains to further evaluate their relationships within the network analysis. These domains were general health, psychosocial, pain characteristics and TMJ mechanosensitivity (Table 1). This comprehensive organization facilitates the exploration of different mechanism-based categories of pain.

Network analysis

To initially explore the relationships between all the variables of interest, bivariate correlations were conducted using Spearman correlation. For the NA, the variables of interest were grouped into different domains in accordance with those presented in Table 1. Overall, four variables were present in the general health domain (i.e., quality of life [QoL], health status [HS], sleep quality [Sleep], oral behaviour [OBC]), four in the psychosocial domain (i.e., pain catastrophising [CSQ-C], anxiety, depression, central sensitization [CSI]), five in the pain characteristics domain (i.e., pain duration [Pain Dur], pain intensity [Pain Int], number of pain locations [Pain Locs], characteristics of pain and disability [GCPS]), and six in the TMJ mechanosensitivity domain (i.e., pain mouth opening [Pain MO], pain clenching [Pain Clen], maximal mouth opening [MMO], pain TMJ palpation [Pain TMJ], pain muscle palpation [Pain M], immediate response to manual therapy [MT response]). Given the exploratory approach of the present work and the absence of previous studies using a similar cohort of patients, an a priori sample size calculation was not possible. However, a post-hoc sample size analysis was conducted by performing simulations where six metrics (i.e., betweenness, closeness, correlation, sensitivity, specificity, strength) obtained from the estimated network were assessed against those obtained from re-estimated networks using different sample sizes (i.e., 50, 75, 100, 150, 200, 500).⁵⁴ Such an approach aims to facilitate the replicability of results in future studies and provide an estimate of the required sample size.⁶⁰

The NA was conducted using the R-package bootnet.⁶⁰ In a network, the variables are visually reported as nodes, while the relationships between them, defined by partial correlation coefficients, are represented by edges.^{60,61} Such partial correlations are also defined as conditional (in)dependence associations since they are calculated after considering all other nodes in the network.⁶⁰ Consequently, the presence of an edge between two nodes indicates a conditional dependency, or independency when not present.⁶¹ The graphical display of edges in the network uses different colors to represent positive and negative correlations, with the thickness of the edge reflecting the strength of the correlation (referred to as edge weight). To address the presence of both continuous and ordinal variables, Spearman correlation was used.⁶² Moreover, to mitigate spurious associations (i.e., false positive) and address the dense structure that often arises from partial correlations, a common regularization technique known as “graphical least absolute shrinkage and selection operator” (lasso) was utilized.⁶⁰ The lasso algorithm sets weak coefficients to zero, effectively controlling for spurious correlations. The algorithm also optimizes the structure of the network by minimizing the Extended Bayesian Information Criterion (EBIC).

Once the network structure was estimated, centrality indices such as

strength, closeness, and betweenness were assessed to examine the extent to which each feature was associated with the others, as well as identify the most relevant variables in the network.⁶⁰ For example, when a variable has a high strength value, any changes in that variable would have a large impact on the other variables. From a clinical perspective, this implies that the treatment of a variable with high strength value should receive special attention because the improvement of that particular variable is likely to have a notable influence on the inter-connected ones. Non-parametric bootstrapping (resample with replacement, $n = 1000$) was used to obtain an estimate of the variability of the centrality indices.⁶⁰ Moreover, to determine the importance of a node to connect different domains, we calculated its bridge strength. The bridge strength corresponds to the sum of absolute values for all connections between node A and all nodes outside its domain, i.e., nodes that do not belong to the same domain as node A.⁶³ To assess the accuracy of edge weights, we used bootstrapping, similar to the approach used for the centrality indices.⁶⁰ Edge weights are reported using the original value obtained in the estimated network along with the 95 % confidence intervals (CIs) resulting from the bootstrapping analysis.

Cluster analysis

To address the second aim of this study and identify potential mechanism-based subgroups of patients with TMD, Agglomerative Hierarchical Clustering (AHC) was performed. AHC is an established technique in unsupervised machine learning, and its objective is to identify clusters or groups of observations within a dataset without requiring predetermined characteristics for each cluster, or a different importance of the variables to identify such clusters.⁶⁴ Overall, similar characteristics are expected within the same cluster and dissimilar characteristics are expected between different clusters. Furthermore, AHC allows us to visualise the similarities (and dissimilarities) across patients using the dendrogram, an upside-down tree structure.⁶⁴ The algorithm follows an iterative process where the two most similar observations (i.e., patients or groups of patients) are merged to create a higher-level cluster. This process continues until all observations are part of a single cluster. Two main parameters are necessary to define the final clustering structure, the distance metric and the linkage method. To address continuous and ordinal variables, the distance matrix was obtained using the Gower distance metric, and the final structure was retrieved by applying the Ward linkage method.⁶⁵ Continuous variables were standardized to have a mean of zero and a variance of one (z-score standardization) so that the scale on which the features were measured does not impact the similarity between clusters.

After identifying the structure of the dendrogram, different numbers of clusters ranging between 2 and 10 were tested. The Silhouette score and the Calinski-Harabasz index (or Variance Ratio Criterion) were computed to evaluate the goodness of splitting the sample into k different clusters and verifying our hypothesis to separate the sample into two clusters.^{50,66} Once the optimal number of clusters was identified, the relative importance of each variable to the separability between clusters was evaluated based on the cluster centroid (average value for each cluster symptom). Finally, differences between subgroups were tested for each variable using the Wilcoxon rank-sum test in order to handle both continuous and ordinal variables. Categorical variables were compared between subgroups using chi-square tests.

Results

From 131 patients with TMD screened for eligibility, 102 (80 females, age: 36.45 ± 14.05) were recruited and included in the analyses. Descriptive statistics on demographic characteristics and the variables of interest of the total sample are presented in Table 2. No missing data were present in the dataset.

Table 2

Demographic characteristics and variables of interest in the total sample and in the two subgroups identified with the cluster analysis. Data are reported as mean (standard deviation) or number of patients (frequency).

| Variable | Total sample (n = 102) | Nociceptive cluster (n = 57) | Nociplastic cluster (n = 45) | Effect Size | p_value |
|--|------------------------|------------------------------|------------------------------|-------------|---------|
| Demographic characteristics | | | | | |
| Gender (n): | | | | 0.16 | 0.112 |
| – Female | 82 (80.4 %) | 49 (86.0 %) | 33 (73.3 %) | | |
| – Male | 20 (19.6 %) | 8 (14.0 %) | 12 (26.7 %) | | |
| Age | 36.45 (14.05) | 35.21 (14.20) | 38.02 (13.85) | 0.12 | 0.243 |
| TMD classification (n): | | | | 0.37 | < 0.001 |
| – Muscular | 21 (20.6 %) | 5 (8.8 %) | 16 (35.6 %) | | |
| – Articular | 17 (16.7 %) | 14 (24.6 %) | 3 (6.7 %) | | |
| Mixed | 64 (62.7 %) | 38 (66.7 %) | 26 (57.8 %) | | |
| Biopsychosocial variables of interest | | | | | |
| Sleep quality (0–10) | 5.52 (2.43) | 6.56 (2.26) | 4.20 (1.96) | 0.48 | < 0.001 |
| Anxiety (0–21) | 7.62 (3.87) | 5.53 (2.63) | 10.27 (3.56) | 0.64 | < 0.001 |
| Depression (0–21) | 4.65 (3.96) | 2.47 (2.20) | 7.40 (4.00) | 0.67 | < 0.001 |
| Quality of life (0–1) | 0.82 (0.16) | 0.89 (0.08) | 0.73 (0.19) | 0.57 | < 0.001 |
| Health status (0–100) | 78.36 (16.15) | 83.86 (13.53) | 71.40 (16.65) | 0.41 | < 0.001 |
| Pain catastrophizing (0–36) | 8.75 (8.26) | 5.14 (6.68) | 13.33 (7.84) | 0.55 | < 0.001 |
| Central sensitization (0–100) | 34.62 (13.21) | 27.00 (8.02) | 44.27 (12.17) | 0.64 | < 0.001 |
| Oral behaviours (0–84) | 30.70 (10.18) | 28.23 (9.11) | 33.82 (10.71) | 0.26 | 0.009 |
| Characteristics of pain & disability (n): | | | | 0.26 | 0.008 |
| – I | 31 (30.4 %) | 23 (40.4 %) | 8 (17.8 %) | | |
| – II | 44 (43.1 %) | 23 (40.4 %) | 21 (46.7 %) | | |
| – III | 12 (11.8 %) | 6 (10.5 %) | 6 (13.3 %) | | |
| – IV | 15 (14.7 %) | 5 (8.8 %) | 10 (22.2 %) | | |
| Pain duration (months) | 10.08 (17.40) | 6.24 (12.36) | 15.12 (21.48) | 0.40 | < 0.001 |
| Pain intensity (VAS, 0–100) | 52.90 (19.21) | 48.90 (19.86) | 57.96 (17.27) | 0.24 | 0.016 |
| Number of pain locations | 2.40 (1.43) | 1.74 (0.84) | 3.24 (1.58) | 0.52 | < 0.001 |
| Pain-free max mouth opening (mm) | 31.45 (9.04) | 27.40 (6.72) | 36.58 (9.05) | 0.50 | < 0.001 |
| Pain tmj palpation (n): | | | | 0.33 | < 0.001 |
| – Yes | 81 (79.4 %) | 52 (91.2 %) | 29 (64.4 %) | | |

Table 2 (continued)

| Variable | Total sample (n = 102) | Nociceptive cluster (n = 57) | Nociplastic cluster (n = 45) | Effect Size | p_value |
|--------------------------------|------------------------|------------------------------|------------------------------|-------------|---------|
| – No | 21 (20.6 %) | 5 (8.8 %) | 16 (35.6 %) | | |
| Pain muscle palpation (n): | | | | 0.24 | 0.017 |
| – Yes | 85 (83.3 %) | 43 (75.4 %) | 42 (93.3 %) | | |
| – No | 17 (16.7 %) | 14 (24.6 %) | 3 (6.7 %) | | |
| Pain mouth opening (VRS, 0–10) | 4.80 (3.17) | 5.61 (2.49) | 3.77 (3.64) | 0.22 | 0.030 |
| Pain clenching (VRS, 0–10) | 2.79 (3.06) | 3.14 (2.89) | 2.36 (3.23) | 0.15 | 0.123 |
| Immediate response to MT (n): | | | | 0.46 | < 0.001 |
| – No change | 11 (10.8 %) | 2 (3.5 %) | 9 (20.0 %) | | |
| – Partial improvement | 31 (30.4 %) | 10 (17.5 %) | 21 (46.7 %) | | |
| – Improvement | 60 (58.8 %) | 45 (78.9 %) | 15 (33.3 %) | | |

Network analysis

An overview presenting the bivariate correlations between the biopsychosocial variables included as nodes in the NA is reported in Fig. 1. The partial correlation network estimated from the 18 nodes reported in Table 1 is illustrated in Fig. 2. Of 153 possible edges, 64 were retained after regularization. The within-domain edges with larger weights were mainly observed in the TMJ mechanosensitivity domain (0.35 [0.19 to 0.50] for *Pain Clen* – *Pain MO*, 0.27 [0.12 to 0.44] for *MT response* – *Pain MO*, –0.21 [–0.36 to –0.08] for *Pain TMJ* – *MMO*) and in the psychosocial domain (0.34 [0.19 to 0.46] for *CSQ-C* – *depression* and 0.23 [0.07 to 0.34] for *CSI* – *anxiety*). The strongest relationships across domains were between *n Pain Locs* – *CSI* (0.37 [0.20 to 0.50]) and between *GCPS* – *HS* (–0.22 [–0.37 to –0.07]).

An overview with the estimate of edge weights and 95 % quantile confidence interval obtained through bootstrapping is presented in Fig. 3. *MMO* was the node with the highest number of connections for the TMJ mechanosensitivity domain, whereas *CSI* and *depression* were the nodes with more connections for the psychosocial domain (11 and 12, respectively). Moreover, *CSI* was the node with the highest strength in the network (followed by *Pain MO* and *anxiety*), and also the one with the highest bridge strength (i.e., across domain connections). A summary of the strength of all nodes in the estimated network, as well as bridge strength, are presented respectively in Fig. 4A and B. According to the correlation stability indices obtained from non-parametric bootstrapping (Suppl File 1), Strength was the only centrality index showing adequate stability (Cscor=0.7 = 0.52). Instead, the stability of Closeness was critical (Cscor=0.7 = 0.21), whereas the variability of Betweenness was too large because of its wide confidence interval (Cscor=0.7=0.13).

The post-hoc sample size analysis (Suppl File 2) revealed that 100 participants are sufficient to retain a correlation of at least 0.7 for all the six performance indices considered, except for betweenness which requires a sample size of at least n = 200. Furthermore, the largest improvement in the correlations is observed by increasing the sample size from 50 to 75.

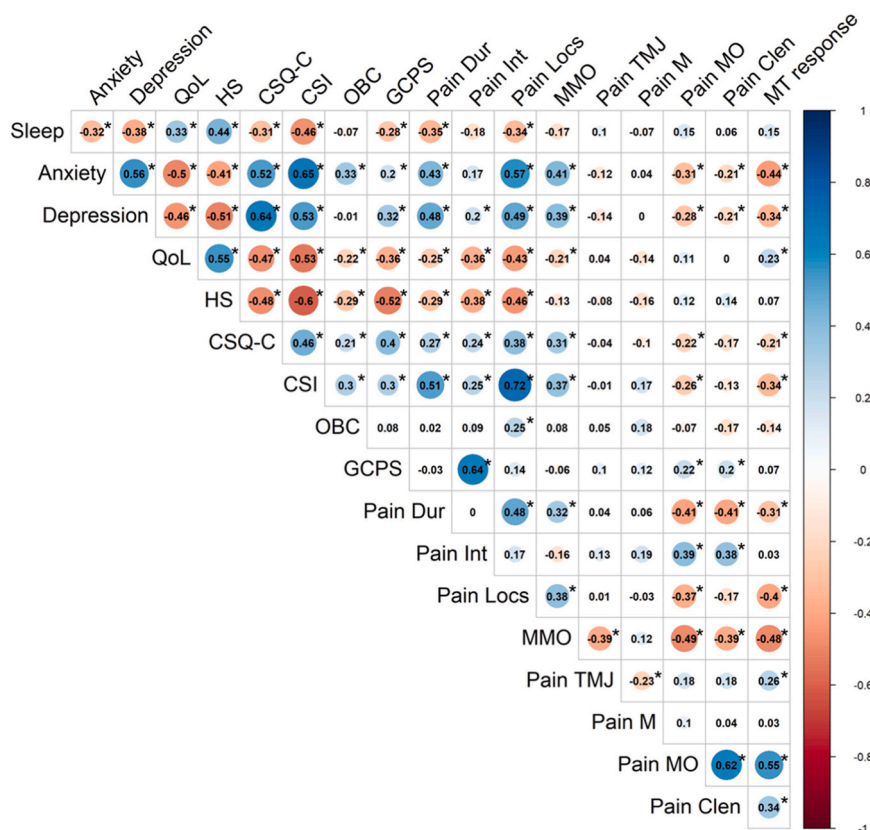


Fig. 1. Bivariate correlations between the variables of interest using the Spearman correlation method. *p-value < 0.05. Abbreviations: QoL, quality of life; HS, Health Status; CSQ-C, pain catastrophizing; CSI, central sensitization inventory; OBC, oral behaviours; GCPS, graded chronic pain scale; MMO, maximal mouth opening; Pain M, pain muscle palpation; Pain MO, pain mouth opening; MT response, immediate response to manual therapy.

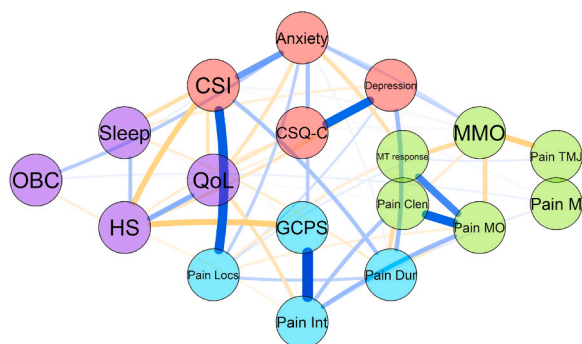


Fig. 2. Estimated network. The variables of interest are presented as nodes in the network and grouped into four domains. Positive partial correlations are identified by blue edges and negative partial correlations in yellow. Abbreviations: QoL, quality of life; HS, Health Status; CSQ-C, pain catastrophizing; CSI, central sensitization inventory; OBC, oral behaviours; GCPS, graded chronic pain scale; MMO, maximal mouth opening; Pain M, pain muscle palpation; Pain MO, pain mouth opening; MT response, immediate response to manual therapy.

Cluster analysis

The dendrogram showing the results of the AHC is presented in Fig. 5. In accordance with the hypothesis and the metrics evaluating the quality of clustering solutions, an optimal number of two clusters was selected which also resulted in a balanced number of patients in both subgroups (n = 57 and 45). Specifically, the highest values of the silhouette score and Calinski-Harabasz index were observed when the number of clusters was two (Suppl File 3). As illustrated in Fig. 6, psychological factors (CSI, anxiety, and depression), number of pain

locations, and MMO were the variables contributing the most to the overall separability between clusters (43.2 %).

By inspecting the distribution and median values of the variables of interest illustrated in Fig. 7, the two clusters were labelled following our hypothesis as potential nociceptive and potential nociplastic pain mechanism subgroups. Differences between subgroups were supported by the large effect size for psychological variables showing higher anxiety, depression, pain catastrophisation, central sensitization, pain duration, number of pain locations and worst sleep quality, quality of life, and health status in the potential nociplastic group (p < 0.001 for all variables). In contrast, variables related to nociceptive pain revealed that MMO was restricted and higher pain was elicited by TMJ palpation, as well as, mouth opening in the nociceptive cluster. Compared to the potential nociplastic group, more TMD patients in the nociceptive group reported an immediate improvement in response to manual therapy (33.3 vs 78.9 %, respectively, p < 0.001). Differences between subgroups for all of the variables of interest are presented in Table 2. Age and gender did not differ between the two clusters (p > 0.05).

Discussion

This study represents the first application of a NA in a cohort of patients with TMDs which aimed to reveal the intricate relationships between biopsychosocial variables within and across different domains. The results supported our primary hypothesis and the presence of feature domains since notable correlations were primarily observed among variables belonging to the same domains. Due to their high strength and number of associations with other features, pain during mouth opening and MMO for the TMJ mechanosensitivity domain, and CSI, depression, and anxiety for the psychological domain were the most influential features in the network. Also, important between-domain

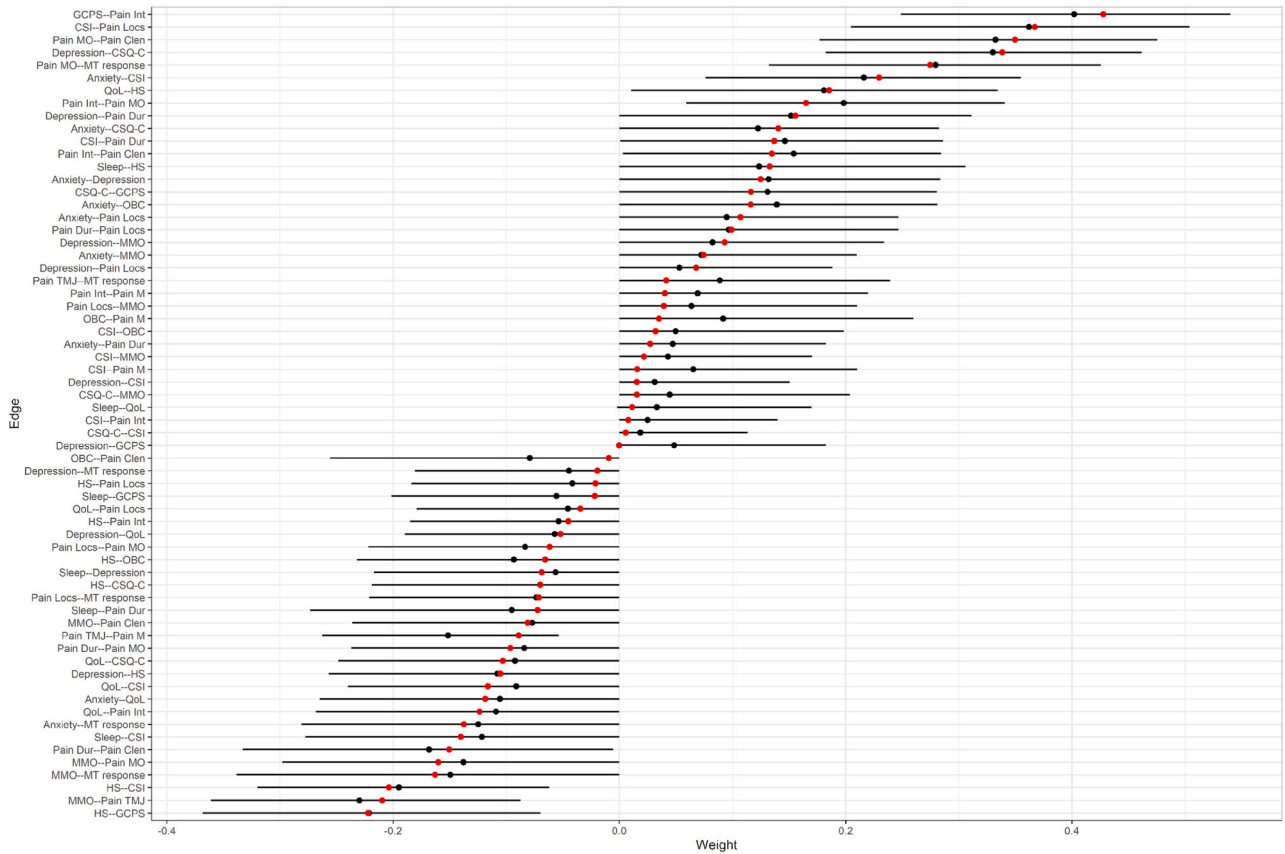


Fig. 3. Estimated edge weights and 95 % quantile confidence interval obtained through bootstrapping. The dots in red represent the magnitude of the edge weight obtained from the original network and the ones in black represent the average magnitude of edge weights computed from bootstrapped samples.

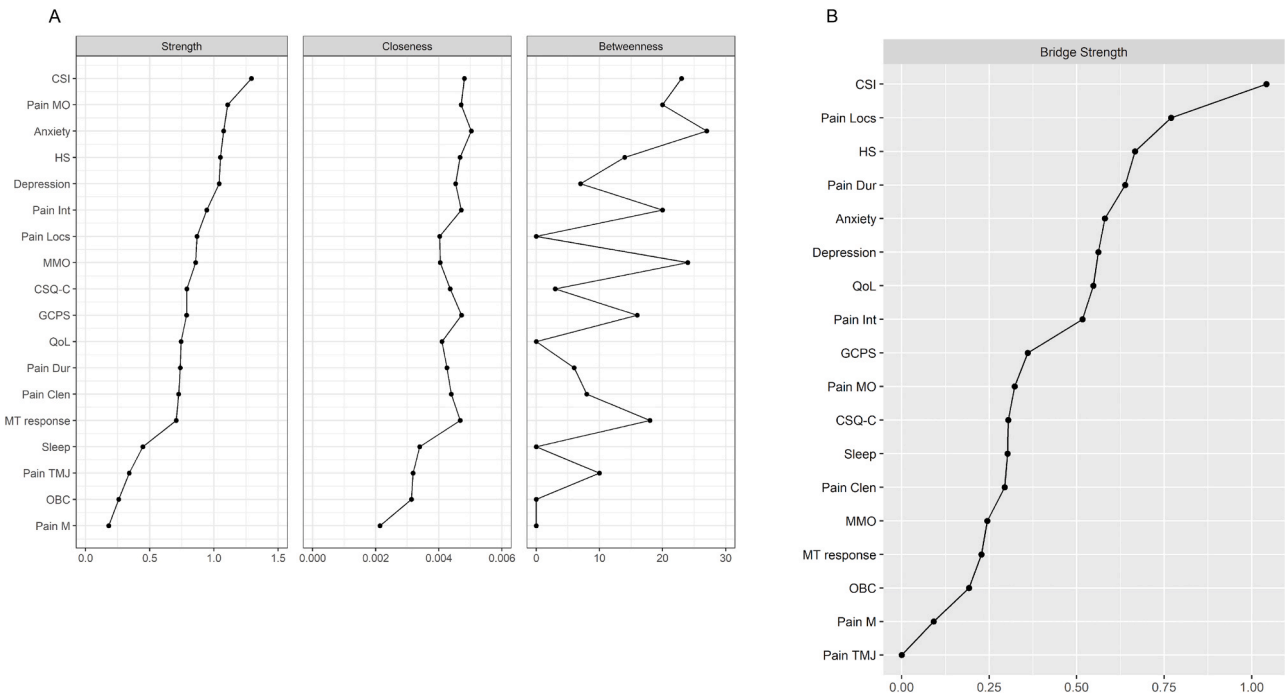


Fig. 4. A: Raw values of centrality indices, B: Raw values of bridge strength.

associations were identified, including the one between the response to manual therapy and anxiety, as well as between the number of pain locations and central sensitization. This is the first study performing a

data-driven approach for the classification of patients with TMDs into pain-mechanism clusters, specifically distinguishing between nociceptive and potential nociplastic mechanisms, which supports our

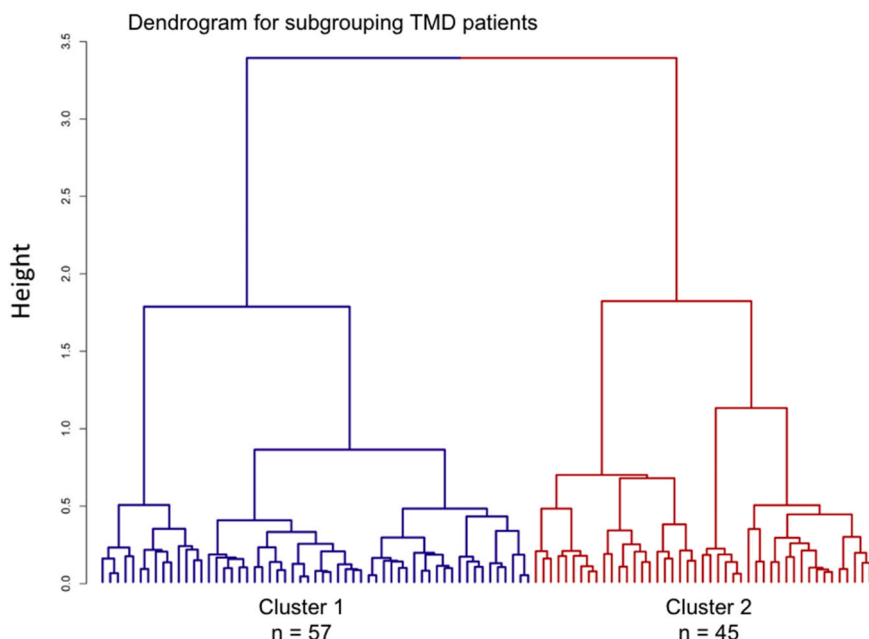


Fig. 5. Dendrogram resulting from agglomerative hierarchical clustering. The colors of the branches (red and blue) identify two clusters. Each TMD patient represents one terminal branch of the dendrogram (bottom side of the graph).

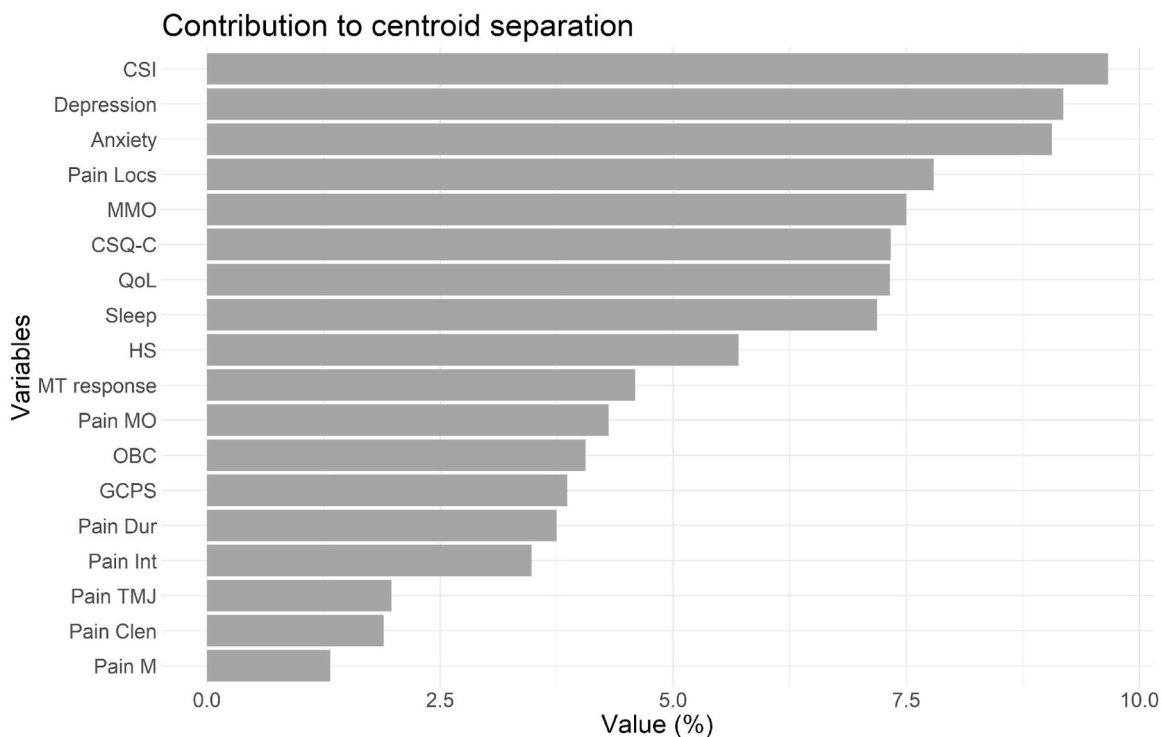


Fig. 6. Contribution of each variable of interest in the separation of the centroids.

secondary hypothesis.

According to the NA, CSI emerged as a crucial variable for patients with TMDs due to its connections with numerous variables, even across different domains. In particular, CSI exhibits conditional dependence on anxiety within the same domain, aligning with existing literature that suggests that CSI reflects psychological hypervigilance rather than a CS syndrome.⁵⁰ Although bivariate correlations also show significant associations between CSI, depression, and catastrophizing (Fig. 1), the partial correlations in the NA reveal stronger conditional dependence

between anxiety and CSI and between catastrophism and depression (Fig. 2). This is because in the NA partial correlations are estimated after controlling for other variables.¹⁵ However, CSI remains a central feature as it shares conditional dependence on other domains. Notably, CSI demonstrates substantial connections with the pain characteristics domain, showing a partial correlation with longer pain duration and a high number of painful body sites. This finding is consistent with recent evidence linking CSI scores to widespread pain.⁵⁰ Partial correlations between CSI and the general health domain are also observed, indicating

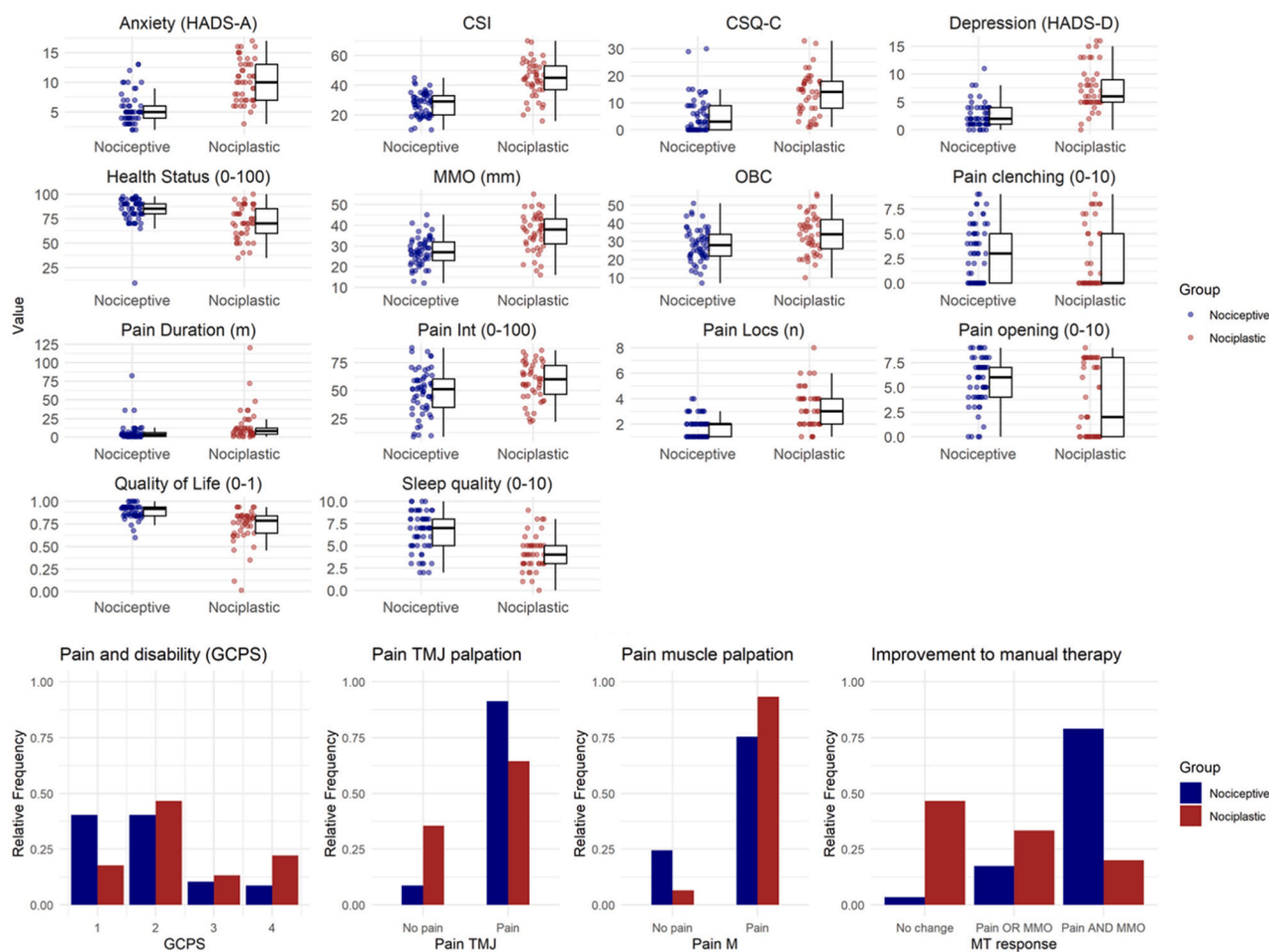


Fig. 7. Characteristics of the identified subgroups (potentially nociceptive and nociplastic) considering all the biopsychosocial variables of interest.

a negative association with quality of life, health status, and sleep quality. These findings agree with previous studies investigating the relationship between CSI and quality of life variables in various patient populations.^{50,67}

It is of relevance to observe that the CSI is not the only variable with partial inter-domain correlations. The OBC also shows these connections. The OBC exhibits moderate correlations with both anxiety and palpatory muscle pain in the masticatory muscles, suggesting a potential mediating role between the two variables. This hypothesis is supported by the literature, given the association between stress and anxiety with negative oral behaviours,^{32,68} and between the latter and muscle pain in the masticatory muscles.^{32,69} Noteworthy inter-domain correlations are observed between the psychosocial and TMJ mechanosensitivity domains. Specifically, anxiety demonstrates a partial correlation with the immediate response to manual therapy, suggesting that patients with psychological distress may respond less favorably to tissue-based interventions like manual therapy. This hypothesis is supported by the literature.^{12,14,18} Indeed, high levels of anxiety could be associated with a centralized form of pain (e.g. nociplastic) which is known to be not responsive to peripheral intervention and characterized by a non-mechanical pattern of pain.^{12,14} In contrast, manual therapy is a movement-based therapy providing effects on peripheral tissue.^{70,71} Lastly, it is interesting to note that there is a possible bridge between the mechanical characteristics of pain, depression/anxiety, and duration/extent of pain; partial correlations were detected between pain during mouth opening, pain duration, and depression/anxiety. Similarly, correlations were found between MMO, anxiety, and pain extension. This could potentially imply that patients with painful TMD, who lack

mechanical features but experience psychological distress, may be more prone to experiencing pain with extended duration and larger extent. These findings align with previous studies indicating associations between non-mechanical pain conditions, anxiety/depression, and widespread pain.^{11,72,73}

This study represents the first attempt to investigate the presence of different pain mechanism subgroups within a cohort of TMD patients, based on the recent consensus generated by experts.¹² The findings demonstrate the existence of two distinct groups in our TMD cohort: a nociceptive pain group and a potential nociplastic pain group. The nociceptive group experiences pain with mechanical characteristics (e.g., their pain changes with movement and/or is associated with reduced mouth opening), with localized pain, which is not associated with significant psychosocial distress or reduced quality of life. In contrast, the potential nociplastic group exhibits high levels of psychosocial impairment, reduced quality of life, and widespread pain which is often unaffected by movement. These results align with previous studies investigating pain mechanisms in various populations with musculoskeletal disorders.^{12,69,72-74} To the best of our knowledge, no other experimental studies have specifically examined these two mechanism-based subgroups within a TMD patient cohort. The study conducted by Bair et al. in 2016 partially overlaps with our findings.¹¹ While their "pain-sensitive" cluster shares similarities with our nociceptive pain group in terms of mechanical pain symptoms (e.g., pain on movement and/or pressure stimuli), the "global symptom" cluster corresponds to our potential nociplastic pain group, characterized by greater psychological distress, higher pain intensity, more functional limitations, and comorbid pain conditions.¹¹ Although direct

comparisons are limited due to differences in scales and outcome measures used, these similarities strengthen the hypothesis that there are two different categories of patients in TMD population. Regarding the type of TMD, it is interesting to note that although the majority of participants have mixed TMD, myogenous TMD is the second most frequent in the potentially nociplastic group. Indeed, this form of TMD is often associated with high comorbidity.⁷⁵ In contrast, the nociceptive group primarily presents with arthrogenous TMD, which may be linked to a peripheral inflammatory phenomenon. Furthermore, the potentially nociplastic group had an average pain duration of approximately one year, compared to about six months for the nociceptive group. This finding aligns with previous studies that have identified longer pain duration associated with nociplastic pain.⁷⁶

This study provides a valuable understanding of the complex nature of TMDs, but it is important to interpret the results cautiously considering the following study limitations. Firstly, the sample size for the NA may be considered limited. However, post-hoc sample size calculations confirm the robustness of the network metrics. This is consistent with previous studies having a similar sample size and using a NA to unravel the interaction between psychological and physical features in other musculoskeletal conditions.^{16,17} Secondly, the study was conducted at a single centre, which limits the generalizability of the results. Also, the assessment of sleep quality was performed with an NRS from 0 to 10, evaluating the quality of sleep over the preceding 6 months.¹⁹ Whilst practical, it may have been subject to potential recall bias. Moreover, the interpretation and understanding of the role of features in the network were partially compromised by the large confidence intervals associated with some centrality indices, like betweenness and closeness. This problem has been observed in other research exploring psychological domains, causing some researchers to doubt the effectiveness of these measures.⁷⁷ In addition, cluster analysis is an unsupervised method that relies on the selection of cluster parameters, and further validation in independent samples is necessary. Finally, it is important to note that certain variables not included in this study, such as quantitative sensory testing, could have more accurately identified nociplastic and nociceptive subgroups.⁷⁶ Specifically, the absence of data on evoked pain hypersensitivity limited our ability to meet all the criteria recommended by the literature for precisely identifying nociplastic pain.⁷⁶ Additionally, incorporating other variables like quantitative sensory testing could have facilitated the identification of additional patient subgroups, such as those with mixed pain mechanisms (however not neuropathic pain since its presence was an exclusion criterion).^{76,78} Future research should aim to replicate and enhance these findings by including a more comprehensive array of variables.

The study boasts several notable strengths. Firstly, it pioneers the use of NA to conduct a comprehensive examination of multi-domain variables in individuals with TMD. This innovative approach uncovers a rich tapestry of interactions, providing clinicians with a deeper understanding of TMDs and provides them with the knowledge to devise more effective treatment plans for their patients. Secondly, the study adopts a data-driven approach to classify TMD subgroups based on pain mechanisms, offering valuable insights for tailored interventions. The sample population accurately represents individuals with painful TMDs, as evidenced by the moderate pain levels reported (average pain intensity, VAS: 52.9). These findings hold significant clinical implications. A NA identifies key variables within each domain that play prominent roles, such as the CSI in the psychosocial domain, MMO in TMJ mechanosensitivity, the number of painful body sites in the pain characteristics domain, and quality of life in the general health domain. By assessing these four variables, clinicians managing patients with TMDs can obtain a comprehensive overview of their patients, streamlining and expediting their clinical decision-making process. Furthermore, the study facilitates clinicians in identifying subgroups of patients based on distinct pain mechanisms, aligning with the understanding that comprehending the neurobiological underpinnings of pain is crucial for optimizing clinical outcomes.⁷⁻¹²

In conclusion, this study utilized a NA to uncover the intricate relationships between biopsychosocial variables in a cohort of patients with TMDs, shedding light on the complex nature of the condition. The findings revealed correlations within and across different domains, identified two distinct subgroups of TMD patients distinguishable from pain-mechanism clusters (potentially nociceptive and nociplastic), and highlighted key variables such as CSI, MMO, number of painful body sites, and quality of life to aid in classification. These findings hold significant clinical implications, emphasizing the critical importance of understanding the neurobiological underpinnings of pain for optimizing clinical outcomes. By comprehending the underlying mechanisms, clinicians can better tailor interventions and make informed decisions, ultimately enhancing treatment efficacy and patient care.

Funding

No funding was obtained for this study.

Declaration of Competing Interest

The authors declare no conflict of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.jpain.2024.104721](https://doi.org/10.1016/j.jpain.2024.104721).

References

- Conti PC, Pinto-Fiamengui LM, Cunha CO, Conti AC. Orofacial pain and temporomandibular disorders: the impact on oral health and quality of life. *Braz Oral Res.* 2012;26(1):120–123. <https://doi.org/10.1590/s1806-83242012000700018>.
- Okeson JP. *Orofacial pain: guidelines for assessment, diagnosis and management*. Quintessence Publishing; 1996.
- De Leeuw R, Klasser GD. *Orofacial pain guidelines for assessment, diagnosis, and management*. 5th ed. Quintessence Publishing; 2013.
- Filligim RB, Bruehl S, Dworkin RH, et al. The ACTTION-American Pain Society Pain Taxonomy (AAPT): an evidence-based and multidimensional approach to classifying chronic pain conditions. *J Pain.* 2014;15(3):241–249. <https://doi.org/10.1016/j.jpain.2014.01.004>.
- Filligim RB, Ohrbach R, Greenspan JD, et al. Psychological factors associated with development of TMD: the OPPERA prospective cohort study. *J Pain.* 2013;14(12):T75–T90. <https://doi.org/10.1016/j.jpain.2013.06.009>.
- Smith SB, Maixner DW, Greenspan JD, et al. Potential genetic risk factors for chronic TMD: genetic associations from the OPPERA case control study. *J Pain.* 2011;12(11):T92–T101. <https://doi.org/10.1016/j.jpain.2011.08.005>.
- Costigan M, Scholz J, Woolf CJ. Neuropathic pain: a maladaptive response of the nervous system to damage. *Annu Rev Neurosci.* 2009;32:1–32. <https://doi.org/10.1146/annurev.neuro.051508.135531>.
- Gifford LS, Butler DS. The integration of pain sciences into clinical practice. *J Hand Ther.* 1997;10(2):86–95. [https://doi.org/10.1016/s0894-1130\(97\)80063-4](https://doi.org/10.1016/s0894-1130(97)80063-4).
- Smart KM, O'Connell NE, Doody C. Towards a mechanisms-based classification of pain in musculoskeletal physiotherapy? *Phys Ther Rev.* 2008;13(1):1–10. <https://doi.org/10.1179/174328808X251984>.
- Vardeh D, Mannion RJ, Woolf CJ. Toward a mechanism-based approach to pain diagnosis. *J Pain.* 2016;17(9):T50–T69. <https://doi.org/10.1016/j.jpain.2016.03.001>.
- Bair E, Gaynor S, Slade GD, et al. Identification of clusters of individuals relevant to temporomandibular disorders and other chronic pain conditions: the OPPERA study. *Pain.* 2016;157(6):1266–1278. <https://doi.org/10.1097/j.pain.0000000000000518>.
- Shraim MA, Sluka KA, Sterling M, et al. Features and methods to discriminate between mechanism-based categories of pain experienced in the musculoskeletal system: a Delphi expert consensus study. *Pain.* 2022;163(9):1812–1828. <https://doi.org/10.1097/j.pain.0000000000002577>.
- Chen H, Comnick C, Norman GJ, Caplan DJ, Xie XJ, Filligim RB. Triad multisystem phenotype with high risk for developing temporomandibular disorders—characteristics and potential pathophysiology results from the orofacial pain: prospective evaluation and risk assessment dataset. *Pain.* 2023;164(5):1027–1038. <https://doi.org/10.1097/j.pain.0000000000002797>.
- Fernández-de-Las-Peñas C, Von Piekartz H. Clinical reasoning for the examination and physical therapy treatment of Temporomandibular Disorders (TMD): a narrative literature review. *J Clin Med.* 2020;9(11):3686. <https://doi.org/10.3390/jcm9113686>.

15. Thurner S, Hanel R, Klimek P. *Introduction to the theory of complex systems*. Oxford University Online Press; 2018. <https://doi.org/10.1093/oso/9780198821939.001.0001>. Accessed 28 December 2022.
16. Devecchi V, Alalawi A, Liew B, Falla D. A network analysis reveals the interaction between fear and physical features in people with neck pain. *Sci Rep*. 2022;12(1), 11304. <https://doi.org/10.1038/s41598-022-14696-8>.
17. Anarte-Lazo E, Liew BXW, Devecchi V, Bernal-Utrera C, Rodriguez-Blanco C, Falla D. Network analyses reveal the interaction between physical features, fear of movement and neck pain and disability in people with acute and chronic whiplash-associated disorders. *Eur J Pain*. 2024;28(2):322–334. <https://doi.org/10.1002/ejp.2184>.
18. Asquini G, Devecchi V, Borromeo G, et al. Predictors of pain reduction following a program of manual therapies for patients with temporomandibular disorders: a prospective observational study. *Musculoskeletal Sci Pract*. 2022;62, 102634. <https://doi.org/10.1016/j.msksp.2022.102634>.
19. Asquini G, Bianchi AE, Heneghan NR, et al. Predictors of pain reduction following manual therapy in patients with temporomandibular disorders: a protocol for a prospective observational study. *BMJ Open*. 2019;9(11), e032113. <https://doi.org/10.1136/bmjopen-2019-032113>.
20. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol*. 2008;61(4):344–349. <https://doi.org/10.1016/j.jclinepi.2007.11.008>.
21. Burger J, Isvoranu AM, Lunansky G, et al. Reporting standards for psychological network analyses in cross-sectional data. *Psychol Methods*. 2023;28(4):806–824. <https://doi.org/10.1037/met0000471>.
22. International classification of orofacial pain, 1st ed. (ICOP). Cephalalgia. 2020;40(2):129–221. DOI: [10.1177/0333102419893823](https://doi.org/10.1177/0333102419893823).
23. Schiffman E, Ohrbach R, Truelove E, et al. Diagnostic criteria for temporomandibular disorders (DC/TMD) for clinical and research applications: recommendations of the international RDC/TMD consortium network* and orofacial pain special interest group. *J Oral Facial Pain Headache*. 2014;28(1):6–27. <https://doi.org/10.11607/jop.1151>.
24. Ohrbach R, Michelotti A, Segù M, Wrenn C, Rongo R. *Criteri diagnostici per i disordini temporomandibolari: Strumenti valutativi (DC/TMD)*. INFORM; 2017. Accessed December 28, 2022 (<https://www.rdc-tmdinternational.org>).
25. Clark J, Nijs J, Yeowell G, Goodwin PC. What are the predictors of altered central pain modulation in chronic musculoskeletal pain populations? A systematic review. *Pain Physician*. 2017;20(6):487–500.
26. Kapos FP, Look JO, Zhang L, Hodges JS, Schiffman EL. Predictors of long-term temporomandibular disorder pain intensity: an 8-year cohort study. *J Oral Facial Pain Headache*. 2018;32(2):113–122. <https://doi.org/10.11607/ofph.1819>.
27. Janssen MF, Birnie E, Haagsma JA, Bonsel GJ. Comparing the standard EQ-5D three-level system with a five-level version. *Value Health*. 2008;11(2):275–284. <https://doi.org/10.1111/j.1524-4733.2007.00230.x>.
28. Slade GD, Ohrbach R, Greenspan JD, et al. Painful temporomandibular disorder: decade of discovery from OPFERA studies. *J Dent Res*. 2016;95(10):1084–1092. <https://doi.org/10.1177/0022034516653743>.
29. Cappelleri JC, Bushmakina AG, McDermott AM, Sadosky AB, Petrie CD, Martin S. Psychometric properties of a single-item scale to assess sleep quality among individuals with fibromyalgia. *Health Qual Life Outcomes*. 2009;7:54. <https://doi.org/10.1186/1477-7525-7-54>.
30. Brooks R. EuroQol: the current state of play. *Health Policy*. 1996;37(1):53–72.
31. Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Qual Life Res*. 2013;22(7):1717–1727. <https://doi.org/10.1007/s11136-012-0322-4>.
32. Ohrbach R, Michelotti A. The role of stress in the etiology of oral parafunction and myofascial pain. *Oral Maxillofac Surg Clin N Am*. 2018;30(3):369–379. <https://doi.org/10.1016/j.coms.2018.04.011>.
33. Glaros AG, Marszalek JM, Williams KB. Longitudinal multilevel modeling of facial pain, muscle tension, and stress. *J Dent Res*. 2016;95(4):416–422. <https://doi.org/10.1177/0022034515625216>.
34. Ohrbach R, Markiewicz MR, McCall Jr WD. Waking-state oral parafunctional behaviors: specificity and validity as assessed by electromyography. *Eur J Oral Sci*. 2008;116(5):438–444. <https://doi.org/10.1111/j.1600-0722.2008.00560.x>.
35. Ohrbach R, Knibbe W. *Diagnostic criteria for temporomandibular disorders: scoring manual for self-report instruments*. INFORM; 2016. Accessed December 28, 2022 (<https://www.rdc-tmdinternational.org>).
36. Markiewicz MR, Ohrbach R, McCall Jr WD. Oral behaviors checklist: reliability of performance in targeted waking-state behaviors. *J Orofac Pain*. 2006;20(4):306–316.
37. Kight M, Gatchel RJ, Wesley L. Temporomandibular disorders: evidence for significant overlap with psychopathology. *Health Psychol*. 1999;18(2):177–182. <https://doi.org/10.1037/0278-6133.18.2.177>.
38. Fernández-de-las-Peñas C, Galán-del-Río F, Fernández-Carnero J, Pesquera J, Arendt-Nielsen L, Svensson P. Bilateral widespread mechanical pain sensitivity in women with myofascial temporomandibular disorder: evidence of impairment in central nociceptive processing. *J Pain*. 2009;10(11):1170–1178. <https://doi.org/10.1016/j.jpain.2009.04.017>.
39. Dworkin SF, Von Korff M, LeResche L. Multiple pains and psychiatric disturbance. An epidemiologic investigation. *Arch Gen Psychiatry*. 1990;47(3):239–244. <https://doi.org/10.1001/archpsyc.1990.01810150039007>.
40. Keefe FJ, Rumble ME, Scipio CD, Giordano LA, Perri LM. Psychological aspects of persistent pain: current state of the science. *J Pain*. 2004;5(4):195–211. <https://doi.org/10.1016/j.jpain.2004.02.576>.
41. Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: scientific advances and future directions. *Psychol Bull*. 2007;133(4):581–624. <https://doi.org/10.1037/0033-2909.133.4.581>.
42. Asquini G, Bianchi AE, Borromeo G, Locatelli M, Falla D. The impact of Covid-19-related distress on general health, oral behaviour, psychosocial features, disability and pain intensity in a cohort of Italian patients with temporomandibular disorders. *PLoS One*. 2021;16(2), e0245999. <https://doi.org/10.1371/journal.pone.0245999>.
43. Iani L, Lauriola M, Costantini M. A confirmatory bifactor analysis of the Hospital Anxiety and Depression Scale in an Italian community sample. *Health Qual Life Outcomes*. 2014;12:84. <https://doi.org/10.1186/1477-7525-12-84>.
44. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67(6):361–370. <https://doi.org/10.1111/j.1600-0447.1983.tb09716.x>.
45. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res*. 2002;52(2):69–77. [https://doi.org/10.1016/s0022-3999\(01\)00296-3](https://doi.org/10.1016/s0022-3999(01)00296-3).
46. Monticone M, Ferrante S, Giorgi I, Galandra C, Rocca B, Foti C. The 27-item coping strategies questionnaire-revised: confirmatory factor analysis, reliability and validity in Italian-speaking subjects with chronic pain. *Pain Res Manag*. 2014;19(3):153–158. <https://doi.org/10.1155/2014/956828>.
47. Robinson ME, Riley JL, 3rd, Myers CD, et al. The Coping Strategies Questionnaire: a large sample, item level factor analysis. *Clin J Pain*. 1997;13(1):43–49. <https://doi.org/10.1097/00002508-199703000-00007>.
48. Häggman-Henrikson B, Bechara C, Pishdari B, Visscher CM, Ekberg E. Impact of catastrophizing in patients with temporomandibular disorders—a systematic review. *J Oral Facial Pain Headache*. 2020;34(4):379–397. <https://doi.org/10.11607/ofph.2637>.
49. van Wilgen CP, Vuijk PJ, Kregel J, et al. Psychological distress and widespread pain contribute to the variance of the central sensitization inventory: a cross-sectional study in patients with chronic pain. *Pain Pract*. 2018;18(2):239–246. <https://doi.org/10.1111/papr.12600>.
50. Adams GR, Gandhi W, Harrison R, et al. Do "central sensitization" questionnaires reflect measures of nociceptive sensitization or psychological constructs? A systematic review and meta-analysis. *Pain*. 2023;164(6):1222–1239. <https://doi.org/10.1097/j.pain.0000000000002830>.
51. Chiarotto A, Viti C, Sulli A, Cutolo M, Testa M, Piscitelli D. Cross-cultural adaptation and validity of the Italian version of the central sensitization inventory. *Musculoskeletal Sci Pract*. 2018;37:20–28. <https://doi.org/10.1016/j.msksp.2018.06.005>.
52. Mayer TG, Neblett R, Cohen H, et al. The development and psychometric validation of the central sensitization inventory. *Pain Pract*. 2012;12(4):276–285. <https://doi.org/10.1111/j.1533-2500.2011.00493.x>.
53. Haefeli M, Elfering A. Pain assessment. *Eur Spine J*. 2006;15(1):S17–S24. <https://doi.org/10.1007/s00586-005-1044-x>.
54. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2005;113(1-2):9–19. <https://doi.org/10.1016/j.jpain.2004.09.012>.
55. Davis CE, Stockstill JW, Stanley WD, Wu Q. Pain-related worry in patients with chronic orofacial pain. *J Am Dent Assoc*. 2014;145(7):722–730. <https://doi.org/10.14219/jada.2014.37>.
56. Ohrbach R, Bair E, Fillingim RB, et al. Clinical orofacial characteristics associated with risk of first-onset TMD: the OPFERA prospective cohort study. *J Pain*. 2013;14(12):T33–T50. <https://doi.org/10.1016/j.jpain.2013.07.018>.
57. Von Korff M, Ormel J, Keefe FJ, Dworkin SF. Grading the severity of chronic pain. *Pain*. 1992;50(2):133–149. [https://doi.org/10.1016/0304-3959\(92\)90154-4](https://doi.org/10.1016/0304-3959(92)90154-4).
58. Dworkin SF, LeResche L. Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique. *J Craniomandib Disord*. 1992;6(4):301–355.
59. Peck CC, Goulet JP, Lobbezoo F, et al. Expanding the taxonomy of the diagnostic criteria for temporomandibular disorders. *J Oral Rehabil*. 2014;41(1):2–23. <https://doi.org/10.1111/joor.12132>.
60. Epskamp S, Borsboom D, Fried EI. Estimating psychological networks and their accuracy: a tutorial paper. *Behav Res Methods*. 2018;50(1):195–212. <https://doi.org/10.3758/s13428-017-0862-1>.
61. Costantini G, et al. State of the art personality research: a tutorial on network analysis of personality data in R. *J Res Personal*. 2015;54:13–29. <https://doi.org/10.1016/j.jrp.2014.07.003> (2015).
62. Isvoranu AM, Epskamp S. Which estimation method to choose in network psychometrics? Deriving guidelines for applied researchers. *Psychol Methods*. 2023;28(4):925–946. <https://doi.org/10.1037/met0000439>.
63. Jones PJ, Ma R, McNally RJ. Bridge centrality: a network approach to understanding comorbidity. *Multivar Behav Res*. 2021;56(2):353–367. <https://doi.org/10.1080/00273171.2019.1614898>.
64. James G, Witten D, Hastie T, Tibshirani R. *An introduction to statistical learning*. 2nd ed. Springer; 2021.
65. Podani J. *Extending Gower's general coefficient of similarity to ordinal characters*. TAXON Publications; 1999. <https://doi.org/10.2307/1224438>.
66. Rousseeuw PJ. Silhouettes: a graphical aid to the interpretation and validation of cluster analysis. *J Comput Appl Math*. 1987;20:53–65.
67. Kregel J, Schumacher C, Dolphens M, et al. Convergent validity of the dutch central sensitization inventory: associations with psychophysical pain measures, quality of life, disability, and pain cognitions in patients with chronic spinal pain. *Pain Pract*. 2018;18(6):777–787. <https://doi.org/10.1111/papr.12672>.
68. Chow JC, Cioffi I. Effects of trait anxiety, somatosensory amplification, and facial pain on self-reported oral behaviors. *Clin Oral Invest*. 2019;23(4):1653–1661. <https://doi.org/10.1007/s00784-018-2600-1>.

69. Câmara-Souza MB, Bracci A, Colonna A, Ferrari M, Rodrigues Garcia RCM, Manfredini D. Ecological momentary assessment of awake bruxism frequency in patients with different temporomandibular disorders. *J Clin Med*. 2023;12(2):501. <https://doi.org/10.3390/jcm12020501>.
70. Bialosky JE, Bishop MD, Price DD, Robinson ME, George SZ. The mechanisms of manual therapy in the treatment of musculoskeletal pain: a comprehensive model. *Man Ther*. 2009;14(5):531–538. <https://doi.org/10.1016/j.math.2008.09.001>.
71. Bialosky JE, Beneciuk JM, Bishop MD, et al. Unraveling the mechanisms of manual therapy: modeling an approach. *J Orthop Sports Phys Ther*. 2018;48(1):8–18. <https://doi.org/10.2519/jospt.2018.7476>.
72. Shraim MA, Massé-Alarie H, Hall LM, Hodges PW. Systematic review and synthesis of mechanism-based classification systems for pain experienced in the musculoskeletal system. *Clin J Pain*. 2020;36(10):793–812. <https://doi.org/10.1097/AJP.0000000000000860>.
73. Shraim MA, Massé-Alarie H, Hodges PW. Methods to discriminate between mechanism-based categories of pain experienced in the musculoskeletal system: a systematic review. *Pain*. 2021;162(4):1007–1037. <https://doi.org/10.1097/j.pain.0000000000002113>.
74. Smart KM, Blake C, Staines A, Doody C. The discriminative validity of "nociceptive," "peripheral neuropathic," and "central sensitization" as mechanism-based classifications of musculoskeletal pain. *Clin J Pain*. 2011;27(8):655–663. <https://doi.org/10.1097/AJP.0b013e318215f16a>.
75. Barjandi G, Kosek E, Hedenberg-Magnusson B, Velly AM, Ernberg M. Comorbid conditions in temporomandibular disorders myalgia and myofascial pain compared to fibromyalgia. *J Clin Med*. 2021;10(14):3138. <https://doi.org/10.3390/jcm10143138>.
76. Kosek E, Clauw D, Nijs J, et al. Chronic nociplastic pain affecting the musculoskeletal system: clinical criteria and grading system. *Pain*. 2021;162(11):2629–2634. <https://doi.org/10.1097/j.pain.0000000000002324>.
77. Bringmann LF, Elmer T, Epskamp S, Krause RW, Schoch D, Wichers M, Wigman JTW, Snippe E. What do centrality measures measure in psychological networks? *J Abnorm Psychol*. 2019;128(8):892–903.
78. Baad-Hansen L, Pigg M, Ivanovic SE, et al. Chairside intraoral qualitative somatosensory testing: reliability and comparison between patients with atypical odontalgia and healthy controls. *J Orofac Pain*. 2013;27(2):165–170. <https://doi.org/10.11607/jop.1062>.