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Identification of clusters of individuals relevant to temporomandibular disorders and other chronic pain conditions: the OPPERA study

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Abstract

The classification of most chronic pain disorders gives emphasis to anatomical location of the pain to distinguish one disorder from the other (eg, back pain vs temporomandibular disorder [TMD]) or to define subtypes (eg, TMD myalgia vs arthralgia). However, anatomical criteria overlook etiology, potentially hampering treatment decisions. This study identified clusters of individuals using a comprehensive array of biopsychosocial measures. Data were collected from a case–control study of 1031 chronic TMD cases and 3247 TMD-free controls. Three subgroups were identified using supervised cluster analysis (referred to as the adaptive, pain-sensitive, and global

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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symptoms clusters). Compared with the adaptive cluster, participants in the pain-sensitive cluster showed heightened sensitivity to experimental pain, and participants in the global symptoms cluster showed both greater pain sensitivity and greater psychological distress. Cluster membership was strongly associated with chronic TMD: 91.5% of TMD cases belonged to the pain-sensitive and global symptoms clusters, whereas 41.2% of controls belonged to the adaptive cluster. Temporomandibular disorder cases in the pain-sensitive and global symptoms clusters also showed greater pain intensity, jaw functional limitation, and more comorbid pain conditions. Similar results were obtained when the same methodology was applied to a smaller case–control study consisting of 199 chronic TMD cases and 201 TMD-free controls. During a median 3-year follow-up period of TMD-free individuals, participants in the global symptoms cluster had greater risk of developing first-onset TMD (hazard ratio = 2.8) compared with participants in the other 2 clusters. Cross-cohort predictive modeling was used to demonstrate the reliability of the clusters.

Keywords

Temporomandibular disorders; Clustering; Classification of chronic pain

1. Introduction

Chronic pain conditions affect 100 million Americans and incur annual health care costs of $635 billion.[32] They are difficult to manage in part because they are commonly defined as anatomically based disorders (eg, temporomandibular disorder [TMD], back pain, etc) without adequate recognition of mediating nonanatomical etiological processes.[13,18] For example, low-back pain is distinguished from TMD because symptoms are felt in different parts of the body, yet both types of pain share many common characteristics.[13,74] The predominantly anatomical focus of pain classification is in contrast to other types of diseases that additionally consider etiology in their classification. For example, myocardial infarction and stroke are anatomically distinct diseases, yet both have subtypes etiologically classified as atherosclerosis. If anatomically classified pain disorders were additionally classified using etiological criteria, pain management could be tailored to address underlying etiological mechanisms.

Temporomandibular disorders are a case in point. Temporomandibular disorder diagnosis is based on painful symptoms in the orofacial region.[59] Rigorous classification methods use these criteria, allowing users to provide valid anatomic-based diagnoses. However, risk factors are not currently part of the diagnosis. Researchers, in contrast, have identified TMD-related risk factors that point to different etiological mechanisms such as psychological distress and neurosensory regulatory processes, although these mechanisms have not yet been used to subclassify TMD.

The objective of this study was to identify clinically relevant groups of individuals (hereafter, “clusters”) who have similar profiles of risk factors for chronic pain that can be reliably distinguished statistically. Specifically, we focus on risk factors signifying biopsychosocial processes that influence chronic pain, such as pain sensitivity and psychological distress. Because there are multiple such risk factors, it is useful to envisage

sets of individual risk factors that, in combination, represent sufficient component causes.[56] This study focused primarily on chronic TMD, although TMD shares risk factors with other chronic pain conditions,[13,74] so clusters associated with the frequency and severity of TMD are likely to also be associated with other painful conditions. Among people with TMD, we expect some clusters to be associated with more severe TMD symptoms. We further hypothesize that some individuals who are currently TMD pain free will nevertheless have characteristics similar to those with chronic TMD. That is, if this hypothesis is correct, we would expect to observe currently TMD pain–free individuals who cluster together with chronic TMD cases and exhibit higher risk of developing first-onset TMD. This is a step toward the ultimate goal of a classification system for chronic pain that includes etiology[62] and builds on existing anatomically based classification systems such as Axis I of the Diagnostic Criteria for Temporomandibular Disorders[59] and multidimensional systems such as the ACTTION-American Pain Society Pain Taxonomy.[18]

One challenge is that traditional clustering methods have poor reproducibility. To address this problem, we used the gap statistic[70] to determine the optimal number of clusters and used split-half methodology to verify cluster assignment reliability. Finally, we sought evidence of etiological validity by examining the extent to which cluster classification predicted incidence of first-onset TMD.

2. Methods

Data were analyzed from 2 observational studies. After summarizing each study and the data collected, the sections that follow describe 4 steps used in data analysis, namely: (1) variable selection for supervised cluster analysis; (2) cluster discovery; (3) evaluation of cluster reliability; and (4) cluster validation.

2.1. Description of the OPPERA study

The Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) study is a prospective cohort study described previously. [61] The study recruited participants with and without chronic TMD (cases and controls, respectively) through advertisements, emails, flyers, and word of mouth. Participants were community-based volunteers, recruited from areas surrounding academic health centers at 4 U.S. study sites: Baltimore, MD; Buffalo, NY; Chapel Hill, NC; and Gainesville, FL. Participants were recruited from May 2006 to May 2013. Chronic TMD was classified based on the Research Diagnostic Criteria for Temporomandibular Disorder (RDC/TMD).[15] In summary, the 2 criteria for TMD cases were (1) history of ≥5 days of facial pain in the preceding 30 days and (2) during examination, evoked pain in response to jaw movement or examiner palpation of masticatory muscles and/or temporomandibular joints.

Participants enrolled as controls were followed for up to 5 years to identify incident cases of first-onset TMD. After enrollment, they completed a questionnaire every 3 months to screen for TMD symptoms. Those reporting symptoms were examined by clinicians to determine whether the participant had developed first-onset TMD using the same 2 criteria. See Ref. 1 for a more detailed description of the OPPERA follow-up protocol to evaluate first-onset TMD.

2.2. Description of the UNC study

The second study (hereafter referred to as "the UNC cohort") used a case–control design, recruiting non-Hispanic white female participants between 2005 and 2009 from individuals reporting for treatment at the Orofacial Pain Clinic at the University of North Carolina in Chapel Hill (UNC) and from communities around Chapel Hill, NC using advertisements, flyers, and mass email. Temporomandibular disorder was classified using the same RDC/TMD criteria described for the OPPERA study.[15] See Refs. 7 and 8 for a more detailed description of the UNC cohort, including the full inclusion and exclusion criteria.

The study protocol for both studies was approved by the institutional review boards at all participating institutions. All participants in both studies provided written informed consent for all study procedures.

2.3. Study instruments and measures

At enrollment, participants in each study completed a similar battery of questionnaires, measurements, and clinical assessments as summarized below and in detail elsewhere.[1,20,26,41,48,61,64] Unless otherwise noted, the same measures were collected using the same methods in each study.

2.3.1. Sociodemographic characteristics—The study participants' age, sex, race, and ethnicity were recorded.

2.3.2. Clinical characteristics—Participants completed the *Comprehensive Pain and Symptom Questionnaire*,[48] which evaluated the frequency and intensity of headaches, the presence of 6 nonspecific orofacial symptoms (eg, stiffness, cramping, etc), and the presence of 20 conditions known to be comorbid with TMD (eg, fibromyalgia, depression, etc). The *Graded Chronic Pain Scale*[75] evaluated pain intensity and pain interference separately for orofacial pain and chronic pain outside the orofacial region.

For participants with TMD pain, the *Screening Pain Self Report* questionnaire evaluated the participant's current level of orofacial pain and percentage of the waking day with pain. Pain unpleasantness and intensity were also evaluated using the Gracely Box Scale.[24]

Participants completed the 12-item Short Form Health Survey (SF-12) questionnaire yielding a Physical Functioning Scale and a Mental Health Scale. Participants in OPPERA study also completed the *Jaw Functional Limitation Scale*,[43,47] a 20-item instrument that measures limitation in the use of the jaw, and the *Oral Behaviors Checklist*,[49,50] which is a 21-item instrument that evaluates the frequency of a series of parafunctional oral behaviors.

2.3.3. Autonomic function—Blood pressure readings were taken from a cuff placed on the upper left arm. In the OPPERA cohort, heart rate variability (HRV) was measured with electrical leads placed at the left second rib (ground), right second rib, and lower left torso. Electrocardiogram signals were examined for impedance (defined as below 300 kΩ), digitized (1024 samples per second), filtered for artifacts, displayed in real time, and stored for offline analysis. Autonomic profiles consisting of resting blood pressure, heart rate, and

base 10 logarithmic HRV measures of total power, high-frequency values, and low-frequency values were computed based on a 20-minute rest period as described previously.[41]

2.3.4. Psychophysical measures of responsiveness to experimentally evoked pain—For the OPPERA cohort, pressure pain thresholds (PPTs) were measured using a hand-held algometer with 1 cm^2 flat tip and a digital display (Somedic, Hörby, Sweden). Measurements were obtained from 5 sites on the face, shoulder, and arm. For the UNC cohort, PPTs were measured using a 1 cm^2 flat-tipped algometer (Pain Diagnostics and Treatment, GreatNeck, NY) that was applied to the same locations that were used in the OPPERA study.

Heat pain thresholds and tolerance were determined using a computer-controlled thermode (2.56 cm^2 ATS Pathway thermode, Medoc Inc). The threshold was measured using an ascending method of limits. The baseline temperature of the probe was 32°C, which was increased at a rate of 0.5°C/s. After threshold and tolerance measures, brief, repetitive suprathreshold thermal stimuli were applied to measure suprathreshold pain intensity and the temporal summation of heat pain (5.73 cm^2 CHEPS Pathway thermode, Medoc Inc). This was performed in 3 iterations in the OPPERA study, with target temperatures of 46°C, 48°C, and 50°C, where the temperature was delivered at a rate of 20°C/s for approximately 1 second to produce a hold time of 750 milliseconds at the desired target temperature. The interpulse interval was between 2.4 and 2.5 seconds to yield a peak-to-peak interpulse interval of 3. The procedure was performed at only 2 temperatures (namely, 47°C and 50°C) in the UNC cohort (2.56 cm^2 ATS thermode, Medoc Inc), where the target temperature was delivered at 9°C/s for 1 second with a 2-second interpulse interval, which also resulted in a peak-to-peak interpulse interval of 3 seconds. The perceived intensity of each thermal pulse was reported by the participants on a 0-to-100 numeric scale, as previously described.[40] Several measures derived from the heat pain temporal summation protocol were considered, including the first pulse rating for series of thermal pulses, a measure of the area under the temporal summation curve derived by summing the numerical ratings for each pulse in a train of thermal stimuli delivered at the specified target temperature (ie, 46°C, 48°C, and 50°C), and “delta” (defined as the difference between the maximum pain rating and the first pulse rating). After sensation pain ratings were collected at 15 and 30 seconds after the delivery of the final pulse for each thermal train.

In the OPPERA cohort, pricking pain sensitivity was assessed using a set of weighted probes and protocols similar to those used by the German Neuropathic Pain Network.[54] Stimuli were applied to the dorsum of digits 2 to 4. Measures included pain threshold, ratings of pain intensity in response to the 256-mN and 512-mN probes, and temporal summation of pain using the same 2 probes. After sensations were also collected at 15 and 30 seconds after the last stimulus in each train of stimuli.

2.3.5. Psychosocial questionnaires—*The Coping Strategies Questionnaire–Revised* evaluates how individuals cope with pain on cognitive and behavioral scales.[55] Coping Strategies Questionnaire–Revised responses have previously been related to experimental pain responses.[22] The *Eysenck Personality Questionnaire* assesses the major personality dimensions of extroversion, neuroticism, and psychoticism. [17] Extroversion and neuroticism

have been associated with affective distress and illness behavior in patients with chronic pain.[27] The *Kohn Reactivity Scale* measures an individual's level of reactivity or nervous system arousability, which has been shown to have a negative correlation with pain tolerance and perception.[14] The *Life Experiences Survey* provides a measure of stressful life changes and their associated impact.[58] The *Lifetime Stressor List/Post-Traumatic Stress Disorder (PTSD) Checklist-Civilian Version* (LSL) asks participants to indicate whether they have experienced a traumatic event and to evaluate the degree to which they experienced PTSD symptoms related to the event.[77] The *Pain Catastrophizing Scale* assesses pain catastrophizing in an individual[67] and is associated with higher levels of pain and physical disability.[51] The *Pennebaker Inventory for Limbic Languidness* measures the frequency with which a person experiences common physical symptoms and sensations.[52] Patients with chronic pain have higher scores on the Pennebaker Inventory for Limbic Languidness than pain-free controls.[44] *The Profile of Mood States* provides an assessment of both positive and negative mood dimensions. Subjects respond to various mood-related items by indicating the extent to which they describe their current mood.[38] The *Pittsburgh Sleep Quality Index* evaluates the quality of the respondent's sleep in the previous month.[6] The *Perceived Stress Scale* measures the degree to which respondents appraise situations that occurred during the last month as stressful.[9] The *Symptom Checklist-90-Revised* (SCL-90R) assesses an individual's psychological distress in 9 symptom areas, including anxiety, depression, and somatization.[12] The *State-Trait Anxiety Inventory* assesses anxiety through 2 questionnaires. One assesses state anxiety, or current, event-related anxiety, whereas the other assesses trait anxiety, or general, personality-based anxiety.[65]

Participants in OPPERA completed all of the above questionnaires. Participants in the UNC study did not complete the Eysenck Personality Questionnaire, Life Experiences Survey, LSL, or Pittsburgh Sleep Quality Index but completed the others.

2.3.6. Environmental risk factors—Three putative environmental risk factors were considered for both studies: self-reported lifetime history of jaw injury, self-reported lifetime history of smoking, and history of at least one traumatic life event on the LSL. Each of these environmental risk factors has been previously shown to be strongly associated with chronic TMD.[20,48] Two additional putative risk factors were considered for the OPPERA study, namely, self-reported lifetime history of oral contraceptive use and current oral contraceptive use. (Males were excluded for the analysis on oral contraceptive use.) Some previous studies have found an association between hormonal contraceptive use and TMD.[36]

2.4. Clustering methodology

2.4.1. Variable selection for supervised cluster analysis—Clusters were identified using a supervised clustering method that was originally proposed by Bair and Tibshirani.[2] Supervised clustering is useful in situations when one wishes to identify clusters associated with an outcome of interest based on a large number of variables, some of which are weakly (or not at all) associated with the outcome. The first step in this procedure selects variables that are most strongly associated with TMD from among the measures of pain sensitivity and psychological distress. This step of variable selection is one of the novel aspects of supervised cluster analysis, a method designed to overcome shortcomings of

conventional k-means clustering. The conventional approach can be problematic, particularly for high-dimensional data sets, when clusters may differ from one another with respect to only a subset of the variables. If one attempts to identify clusters using all the variables in such a data set, the quality of the resulting clusters is likely to be poor because the irrelevant variables will add "noise" to the clusters.[2,65]

Another shortcoming of conventional clustering methods is that they are unsupervised, meaning that they do not consider outcome variables. In many situations, one wishes to identify clusters that are associated with an outcome of interest. For example, in this study, we wish to identify clusters that are associated with the presence and severity of TMD. In many data sets, there are multiple possible clusters, and not all clusters will be associated with the outcome of interest. Conventional clustering methods may identify clusters that are unrelated to the outcome of interest. In contrast, supervised clustering has been shown to identify clusters associated with an outcome of interest when conventional clustering fails to identify such clusters.[2]

In the first step, we therefore selected the variables most strongly associated with the outcome of interest. The number of variables selected may affect the results, so it is necessary to choose the number of variables to use to form the clusters. We denote the number of variables used to form the clusters by M, so we select the M variables most strongly associated with chronic TMD. We considered 4 different values of M: 15, 20, 25, and 30. The strength of the association between each variable and chronic TMD in the OPPERA cohort was evaluated by performing logistic regression to predict TMD case status based on the variable of interest plus dummy variables for the 4 OPPERA study sites. Because there was only one study site for the UNC cohort (and hence no need to use logistic regression to control for this possible confounder), the strength of the association between each variable and chronic TMD was evaluated by performing t-tests to test the null hypothesis that the mean value of each variable did not differ between cases and controls.

Pain sensitivity and psychological distress were the domains of interest based on our previously described model; wherein, these types of measures represent the primary etiological risk factors for TMD and other chronic pain conditions.[11,33] Other variables collected in the 2 studies (such as clinical variables) were excluded because of concern that they may represent consequences of TMD rather than possible underlying mechanisms. A minimum of 15 variables was used to ensure that both domains of pain sensitivity and psychological distress were included in the model.

2.4.2. Cluster discovery—In addition to choosing the M variables used to identify the clusters, it is also necessary to choose the number of clusters. We denote the number of clusters by k. In the second step, sets of M variables were used to identify k clusters within each cohort, with k varying from 1 to 8. The gap statistic was used to choose k by evaluating the quality of each cluster solution. This second step overcomes another shortcoming of conventional cluster analysis, which is that it will produce clusters for any value of k even when statistical evaluation fails to reject the null hypothesis that no clusters exist. The gap statistic[70] can be used as a criterion to address this issue. The gap statistic estimates the difference between the within-cluster sum of squares of a putative set of clusters and the

expected within-cluster sum of squares under a suitable null distribution with no clusters. Because the within-cluster sum of squares should be small for truly "significant" clusters, the "best" set of clusters should produce a within-cluster sum of squares that is much smaller than expected under the null hypothesis. Thus, one can choose the optimal number of clusters by choosing the set of clusters that maximize the gap statistic. If the gap statistic is maximized for k = 1 cluster, the implication is that no clusters exist in the data.

Both TMD cases and TMD-free controls were used to identify the clusters. All variables were normalized to have mean 0 and SD 1 before applying the clustering method. The association between the clusters and chronic TMD and several demographic variables of interest was evaluated using chi-square tests. The mean values (and associated SEs) of each variable of interest were calculated for each cluster, and the null hypothesis of no difference between the cluster means was tested using *t*-tests and analysis of variance.

To provide further insight into characteristics that distinguished clusters, the association between the clusters and several chronic pain conditions known to be comorbid with TMD was also evaluated for the OPPERA cohort using chi-square tests. The 4 comorbid conditions were irritable bowl syndrome, pelvic pain, chronic headache, and chronic low-back pain. Irritable bowel syndrome was evaluated based on the Rome III criteria,[37] and pelvic pain was evaluated using a series of screening questions that have been shown to have high sensitivity and specificity for pelvic pain diagnosis.[28,46] Chronic headache was defined as reporting headaches 15 days or more per month,[31] and chronic low-back pain was defined as reporting "constant" low-back pain. All 4 conditions were diagnosed based on questions from the Comprehensive Pain and Symptom Questionnaire.

2.4.3. Cluster reliability—The third step was undertaken to verify that the putative clusters were reproducible. In both the OPPERA cohort and the UNC cohort, data sets were randomly partitioned into a training set and a test set such that the number of TMD cases and controls was the same in both partitions. The clustering methodology was applied to the training set and the test set of both cohorts. After identifying these putative clusters on both halves of the data, a nearest centroid classifier[30] was used to predict the test set clusters based on the training set clusters. Nearest centroid models calculate the distance between a given observation and the centroids of each cluster. The centroid of a cluster is defined to be the means of all the observations in that cluster with respect to each variable. Nearest centroid classifiers tend to be more accurate than classifications' methods such as logistic regression or linear discriminant analysis when predicting clusters produced by k-means clustering. The predictive accuracy of the models was evaluated. The nearest centroid model was fit using 4 variables (the trapezius PPT and the somatization, anxiety, and depression subscales of the SCL-90R). The rationale for choosing these 4 variables is discussed below.

Two additional nearest centroid classifiers were used to further evaluate the reproducibility of the clusters. One classifier predicted the clusters identified in the OPPERA cohort based on the clusters identified in the UNC cohort, and the other classifier predicted the UNC cohort clusters based on the OPPERA clusters. However, some modifications of the earlier procedure were required because of methodological differences in the 2 studies. Because different protocols were used when collecting the pain sensitivity and autonomic data in the

2 cohorts, one cannot easily fit a model to predict the clusters on one cohort and apply it to the other cohort, because the measured variables would be different. Aside from dealing with exigencies in these particular data sets, we adopted this strategy in the spirit of a "real-world" test, in which slightly different protocols are used in different patient care settings, yet each protocol is evaluating similar constructs relevant to individuals' pain. This strategy therefore provides insight into the likely utility of using just a handful of measures to classify clusters, even when the measures are not identical to the measures used in the discovery phase. This procedure also improves generalizability.

Thus, we chose one set of psychological measures (namely, the somatization, anxiety, and depression subscales of the SCL-90R) based on their strong association with the clusters in both cohorts, because psychosocial summary scores should be comparable across the 2 cohorts. A single PPT (namely, the trapezius PPT) was also included in the model because the distribution of the trapezius PPT measures was comparable in the 2 cohorts, despite the fact that different types of algometers were used. The 2 nearest centroid models were fit using these 4 variables. Furthermore, when the model that was fit to the OPPERA data was applied to the UNC cohort, the data in the UNC cohort were normalized using the mean values and SDs calculated in the OPPERA cohort (rather than simply standardized to mean 0 and SD 1 based on the mean values/SDs in the UNC cohort). This was performed to demonstrate that such a model could be used to assign future patients to a cluster, because such a classifier would need to be based on the data collected previously. Similarly, the model to classify OPPERA cohort participants based on the UNC cohort standardized the variables using mean values and SDs calculated based on the UNC cohort.

2.4.4. Cluster validation—The fourth step evaluated predictive validity[66] and was based on our premise that, in people without TMD, cluster assignment should be a significant predictor of their subsequent risk of developing TMD. The association between the putative clusters and first-onset TMD in the OPPERA cohort was evaluated using Cox proportional hazards models. Study site was included as a covariate in the model. Only initially TMD-free individuals (controls) were included in the analysis. The association between the clusters and first-onset TMD was also visualized using a Kaplan–Meier plot. Note that this model is intended to predict the likelihood of developing TMD for the groups of study participants (ie, participants in a given cluster), not individual participants. The nearest centroid model described previously would be used to assign an individual to a cluster.

3. Results

3.1. Demographic characteristics of study participants

Demographic characteristics of study participants are described in Table 1. The present analysis included a total of 1031 chronic TMD cases and 3247 controls from the OPPERA cohort and 199 chronic TMD cases and 201 TMD-free controls from the UNC cohort. Note that all participants in the UNC cohort are non-Hispanic white females, so no information on the sex or race of participants in the UNC cohort is reported in Table 1.

3.2. Variable selection and cluster discovery

In the first step of variable screening, the variables most strongly associated with chronic TMD were dominated by PPTs and subscales of the SCL-90R, both in the OPPERA and UNC cohorts (Supplementary Tables 1 and 2, respectively; available online at http://links.lww.com/PAIN/A248). When all variables were used in the second step of cluster discovery, the gap statistics were maximized for k = 1 cluster, indicating that no clusters are present in the data set (Supplementary Figures 1a and 1b, available online at http://links.lww.com/PAIN/A248). However, when only the top 25 variables were used (or the top 15 variables for the UNC cohort), the gap statistic was maximized for k = 3 clusters. (Note that the values of the gap statistic for different values of M are not comparable. Thus, the fact that some values of k produced larger gap statistics when all variables were used does not imply that these putative clusters are preferable to the clusters produced for smaller values of M. The gap statistic is used only to compare different values of k for a fixed value of M). For the results that follow, we therefore applied supervised 3-means clustering to both the OPPERA cohort and the UNC cohort based on the M variables that were mostly strongly associated with chronic TMD, where M = 25 for the OPPERA cohort and M = 15 for the UNC cohort.

The association between the 3 clusters and demographics and chronic TMD in the OPPERA cohort is shown in Table 1. We called these 3 clusters the “adaptive cluster,” the “pain-sensitive cluster,” and the “global symptoms clusters” for reasons that will be described in more detail below. The adaptive cluster had the lowest proportion of TMD cases, and the global symptoms clusters had the highest proportion of cases. Females and participants aged 25 and older were more likely to belong to the pain-sensitive and adaptive clusters, although no association was observed between the clusters and race. The clusters were also strongly associated with TMD case status. Only 8.5% of cases were in the adaptive cluster compared with 41.2% of controls, whereas 39.1% of cases were in the global symptoms cluster compared with 11.9% of controls.

Figure 1A shows the mean values and associated 95% confidence intervals for a selected subset of the pain sensitivity and psychosocial variables in the OPPERA cohort. Each variable displayed in the figure was normalized to have mean 0 and SD 1. The mean values and associated SEs for all the psychosocial, pain sensitivity, and autonomic variables in each cluster in the OPPERA cohort are shown in Supplementary Table 3 (available online at http://links.lww.com/PAIN/A248). An interesting pattern emerges when comparing these mean values across the 3 clusters. Compared with the adaptive cluster, participants in the pain-sensitive cluster are more sensitive to pain-evoking pressure stimuli (ie, PPTs for muscle pain sensitivity). Participants in the pain-sensitive cluster also had higher levels of various measures of psychological distress compared with the adaptive cluster, although the differences were more modest. A different pattern emerged when comparing the pain-sensitive and global symptoms clusters. Only modest differences were observed between these 2 clusters with respect to experimental pain sensitivity, with participants in the pain-sensitive cluster showing slightly greater sensitivity than those in the global symptoms cluster. In contrast, large differences between the pain-sensitive and global symptoms clusters were observed with respect to nearly every psychosocial instrument included in the

analysis. Thus, individuals in the adaptive cluster have lower pain sensitivity and lower psychological distress, individuals in the pain-sensitive cluster have higher pain sensitivity but lower psychological distress, and individuals in the global symptoms cluster have higher pain sensitivity and higher psychological distress.

Cluster variation in autonomic function in OPPERA is also shown in Supplementary Table 3. In general, participants in the global symptoms cluster had lower HRV across all frequency domain measures than participants in the other 2 clusters. The differences in HRV between the adaptive and pain-sensitive clusters were much smaller (and generally not statistically significant). Participants in the pain-sensitive cluster generally had lower blood pressure than participants in the adaptive cluster. Participants in the global symptoms cluster tended to have slightly higher blood pressure than participants in the pain-sensitive cluster, although the differences were generally modest. In contrast to measures of blood pressure, mean resting heart rates were lowest for participants in the adaptive cluster and highest for participants in the global symptoms cluster.

The mean values (and associated SEs) of the clinical variables in each of the 3 clusters for TMD cases in the OPPERA cohort are shown in Table 2. Supplementary Table 4 shows these results for the full cohort (available online at http://links.lww.com/PAIN/A248). In general, participants in the pain-sensitive and global symptoms clusters reported greater levels of clinical pain, greater frequency of headaches and other comorbid pain conditions, and more bodily pain, including widespread bodily pain, than participants in the adaptive cluster, with the global symptoms cluster showing the most severe symptoms. Among TMD cases, participants in the global symptoms cluster generally showed more severe and anatomically widespread clinical symptoms than participants in the other 2 clusters. Participants in the pain-sensitive cluster also reported greater levels of pain, functional limitation, and comorbid conditions than those in the adaptive cluster, although the differences were smaller than the differences between the global symptoms cluster and the other 2 clusters.

Measures of physical functioning and mental health also varied with respect to cluster membership. Participants in the adaptive and pain-sensitive clusters reported similar physical function, whereas participants in the global symptoms cluster reported much lower physical function than those in the other 2 clusters. Mental health function also varied as a function of cluster assignment with a clear gradation of highest functioning reported for participants in the adaptive cluster and lowest for participants in the global symptoms cluster.

The associations between the 3 clusters and chronic TMD and age in the UNC cohort are shown in Table 1. Figure 1B shows the mean values and associated 95% confidence intervals for a selected subset of the pain sensitivity and psychosocial variables in the UNC cohort. (Again, each variable was normalized to have mean 0 and SD 1 in the figure). The mean values and associated SEs for all the psychosocial, pain sensitivity, and autonomic variables in each cluster in the UNC cohort are shown in Supplementary Table 5 (available online at http://links.lww.com/PAIN/A248). The results are consistent with what was observed in the OPPERA cohort. The pain-sensitive cluster had a higher proportion of cases than the

adaptive cluster, and the global symptoms cluster had a higher proportion of cases than the other 2 clusters. In general, participants in the pain-sensitive cluster had higher levels of pain sensitivity compared with the adaptive cluster, and participants in the global symptoms cluster also had higher levels of pain sensitivity and psychological distress than participants in the other 2 clusters. However, the differences in psychological distress between the adaptive and pain-sensitive clusters were modest compared with the differences between the pain-sensitive and global symptoms clusters. Likewise, the differences in pain sensitivity between the adaptive and pain-sensitive clusters were much larger than the differences in pain sensitivity between the pain-sensitive and global symptoms clusters, which is consistent with what was observed in the OPPERA cohort.

The mean values and associated SEs of the clinical variables in each of the 3 clusters for TMD cases in the UNC cohort are shown in Table 3, and Supplementary Table 6 shows these results for the full cohort (available online at http://links.lww.com/PAIN/A248). Again, the results are consistent with what was observed in the OPPERA cohort. Participants in the pain-sensitive and global symptoms clusters reported greater levels of clinical pain, a greater number of comorbid pain conditions, and more bodily pain than the participants in the adaptive cluster, with the global symptoms cluster showing the most severe symptoms. Among TMD cases, participants in the global symptoms cluster reported greater levels of pain than participants in the other 2 clusters with respect to every measure of interest. The differences between the adaptive and pain-sensitive clusters were not statistically significant (with the exception of the number of tender muscle groups/palpation sites during the TMD examination). Participants in the global symptoms cluster also reported diminished physical function and mental health compared with those in the other 2 clusters.

The association between the clusters and 4 chronic pain conditions known to be comorbid with TMD (namely, irritable bowel syndrome, pelvic pain, chronic headache, and chronic low-back pain) in the OPPERA cohort is shown in Table 4. Participants in the pain-sensitive cluster had higher odds of all 4 conditions than participants in the adaptive cluster, and participants in the global symptoms cluster had much higher odds of all 4 conditions than participants in the other 2 clusters. The increased odds of these conditions in the pain-sensitive and global symptoms clusters compared with the adaptive cluster were all strongly statistically significant ($P < 0.0001$).

The association between the clusters and the putative environmental risk factors for TMD is shown in Table 5. In both cohorts, participants in the global symptoms cluster were more likely to report a lifetime history of smoking or a traumatic life event than participants in the other 2 clusters. In the OPPERA cohort, participants in the pain-sensitive and global symptoms clusters were more likely to report a lifetime history of jaw injury (with participants in the global symptoms cluster most likely to report a history of jaw injury). A similar trend was apparent in the UNC cohort, although the differences were not statistically significant. Similarly, female participants in the pain-sensitive and global symptoms clusters in the OPPERA cohort were more likely to report a lifetime history of hormonal contraception use, with participants in the global symptoms cluster most likely to report history of hormonal contraception use. However, participants in the global symptoms cluster were least likely to report that they are currently using hormonal contraceptives.

3.3. Cluster reliability

The cluster reliability results are shown in Table 6. When each cohort was partitioned into a training set and a test set, the clusters identified in the training set could be used to predict the clusters in the test set with very high accuracy. That is, 96.4% of the observations in the OPPERA cohort were classified to the correct cluster, and 83.4% of the observations in the UNC cohort were classified correctly. When the clusters in one cohort were used to predict the cluster in the other cohort, the predictive accuracy was lower, but still very good. Specifically, 80.9% of the observations in the OPPERA cohort were classified to the correct cluster based on the UNC cohort data, and 78.3% of the observations in the UNC cohort were correctly classified based on the OPPERA cohort data.

3.4. Cluster validation

The validity of clusters in predicting first-onset TMD was verified with Kaplan–Meier plots illustrating a significantly greater hazard of first-onset TMD for subjects in the global symptoms cluster compared with either of the other clusters (Figure 2). Participants in the global symptoms cluster had significantly higher incidence of first-onset TMD than participants in the other 2 clusters (hazard ratio = 2.8, $P < 0.0001$).

4. Discussion

Through a novel application of statistical methods, this study identified clusters of individuals using a comprehensive array of biopsychosocial risk factors for chronic pain measured in each individual.[39,62] The numerically smallest global symptoms cluster had a profile that, on face value, signified vastly increased risk and severity of pain and also physical and mental dysfunction compared with the other 2 clusters. Temporomandibular disorder–free participants in the global symptoms cluster had higher risk of first-onset TMD compared with the other 2 clusters, consistent with our hypothesis. Meanwhile, among participants who had TMD, those in the global symptoms cluster had, by far, the most severe symptoms of TMD and the greatest burden of comorbid pain. The supervised clustering method proved to be highly reproducible in split-sample reliability assessments, and the method was replicated in 2 cohorts. Furthermore, clusters were reliably reproduced using a model based on only 4 variables that would be feasible to apply in clinical care. These findings provide strong support for the suggestion that TMD is a heterogeneous condition consisting of a mosaic of complex biopsychosocial phenotypes. Findings from follow-up of initially TMD-free participants also show that it is possible to identify a subgroup of the general population that has a higher risk of developing TMD (and possibly other chronic pain conditions).

Compared with the adaptive cluster, participants in the pain-sensitive cluster had substantially greater sensitivity to experimental pain. They also had slightly greater psychological distress, but the differences were modest compared with the differences between the global symptoms cluster and the other 2 clusters. Among TMD cases, they had greater intensity of TMD pain and more comorbid pain. Although the psychological characteristics distinguishing the adaptive and pain-sensitive clusters were strong predictors of TMD incidence in the OPPERA study,[19] most measures of pain sensitivity were not,[25]

which probably explains why these 2 clusters did not differ in their likelihood of developing TMD. However, some pain sensitivity measures increased significantly after TMD developed,[63] which might explain differences between cases in severity of clinical TMD. Taken together, these findings suggest that the adaptive and pain-sensitive clusters differ primarily with respect to characteristics that develop as a consequence of TMD or other painful conditions, implying that the 2 clusters are more useful in distinguishing between individuals with pain than in predicting who will develop pain. Specifically, individuals in the adaptive cluster may have more localized pathology, whereas individuals in the pain-sensitive and global symptoms clusters may have greater general pain sensitivity secondary to central sensitization phenomenon. Thus, individuals in the pain-sensitive and global symptoms may be more responsive to treatments that target such central mechanisms.

Other studies have used cluster analysis to identify pain-related subtypes among individuals with chronic pain or healthy controls.[4,10,11,21,23,29,33–35,45,53,60,68,69,72] Among these, the Multidimensional Pain Inventory[33] (MPI) is probably the best known. The MPI emerged from biopsychosocial theory, and studies assessing outcomes based on MPI classification indicate that anatomically distinct disorders (headache, TMD, back pain) respond to treatments similarly within each cluster.[71] The provision of item-response scaling has resulted in the recommendation to use dimensional scaling rather than the original clusters,[57] and problems with temporal stability of the MPI have been identified.[5] Finally, MPI administration is restricted to individuals who already have pain.

In contrast to these previous cluster efforts, the present approach has several distinguishing features. Most previous studies were based on much smaller samples consisting of either only individuals with chronic pain or only pain-free controls, whereas our clusters were identified using a large cohort (and a smaller secondary cohort for confirmation) that consisted of both chronic TMD cases and TMD-free controls. This methodology allowed us to identify pain-free individuals who had higher risk of developing chronic pain. This study also used a much larger set of biopsychosocial risk factors for pain than previous studies. Furthermore, we demonstrated the across-sample reliability and validity of our clusters. This is an important step in cluster analysis, because clustering methods will output clusters even in homogeneous data sets where no subtypes exist. Most previous clustering studies in the area of chronic pain did not demonstrate the reliability of the putative clusters. Finally, we showed how one could assign future individuals to clusters using a small set of variables, demonstrating that the methodology could be used in a clinical setting.

Other systems have been proposed for classifying individuals with pain that are not based on cluster analysis.[16,42,73,76] In particular, Mallen et al.[42] used a set of 3 questions to accurately identify individuals who would develop chronic musculoskeletal pain. Although these classification systems are potentially powerful tools, they are somewhat limited by the fact that they are only applicable after an individual has developed pain. Our putative clusters allow for the identification of a high-risk subpopulation of individuals who are currently pain free. Also, our proposed clusters are based on putatively etiological variables rather than clinical measures of pain, so they are more likely to represent biologically meaningful subtypes rather than simply variations in the severity of pain or consequences of the pain.[39,62]

A strength of our study is that clusters were reproducible using only 4 variables that are feasible to measure in clinical settings. This indicates that it is possible to assign future individuals to clusters using a short questionnaire and a few simple algometer measurements: cluster membership could be identified quickly and accurately in a clinical setting. Our current results provide a “proof of concept” that such a classification method is feasible, but it is likely that the classification process can be streamlined by reducing the number of items on the questionnaires or selecting different items. Optimizing the model for predicting cluster membership to maximize accuracy and minimize patient burden is an area for future research.

There are several important implications that stem from this work. First, this method represents a new tool by which one can identify subpopulations of individuals with chronic pain conditions. Because the method is agnostic to the anatomical location of a persistent pain condition, it is likely that the method used in this study will prove useful for stratifying individuals with other chronic pain conditions into subtypes or clusters that are based on etiological mechanisms rather than anatomically specific signs and symptoms. As such, after verifying the reproducibility of these clusters among individuals with other chronic pain conditions, we should consider diagnosing individuals with these conditions into these clusters. This has the potential to better inform treatment selection and patient management. It is possible that the relative efficacy and side-effect profiles of pain treatments will be dependent on cluster membership.[3]

A second implication of this work is its relevance for individuals who have similar biopsychosocial characteristics regardless of their anatomically classified chronic pain conditions. It is likely that many of these individuals already have higher levels of pain, including orofacial pain, compared with the general population. Thus, it is not surprising that these individuals are more likely to meet the (anatomically defined) diagnostic criteria for TMD in the future. This is likely to be true for other painful conditions and also evidenced by the greater number of common persistent pain conditions seen in the global symptoms cluster. The identification of individuals at risk for developing more severe chronic pain conditions permits the development of proactive pharmacological and behavioral approaches that can be used to mitigate this risk.

Several unanswered questions still remain. This study was limited to individuals with TMD and TMD-free controls, and we do not know if these clusters apply to other persistent pain conditions. Multidimensional Pain Inventory research suggests that generalizability is likely, but this needs to be evaluated. We do not know whether one’s cluster assignment is temporally stable or whether treatments and future environment events (positive or negative) permit an individual to move from one cluster assignment to another. Indeed, only a few environmental risk factors were examined in this study, so the association between environmental variables and the clusters is still unclear. In addition, we do not know whether our approach can be used to predict the severity of acute pain and pain management requirements after surgical procedures. Given the impairments seen in pain processing in the global symptoms cluster, one would predict that individuals in this cluster should be less responsive to treatments, experience more severe acute pain, and be more likely to transition into a chronic pain state after injury or a surgical procedure. Future research is needed to

verify this hypothesis and to find effective targeted treatments to prevent this transition to a chronic pain state.

In summary, we have used cluster analysis to validly and reliably identify groups of individuals based on biopsychosocial risk factors for TMD. Our method shows considerable promise as a new approach for classifying individuals with pain into subtypes in a manner that is etiologically based and is agnostic to the anatomical location of pain. The findings hold promise for individualized diagnosis and treatment of patients with TMD complaints and possibly other patients experiencing acute or chronic pain in other regions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix A. Supplemental Digital Content

Supplemental Digital Content associated with this article can be found online at http://links.lww.com/PAIN/A248.

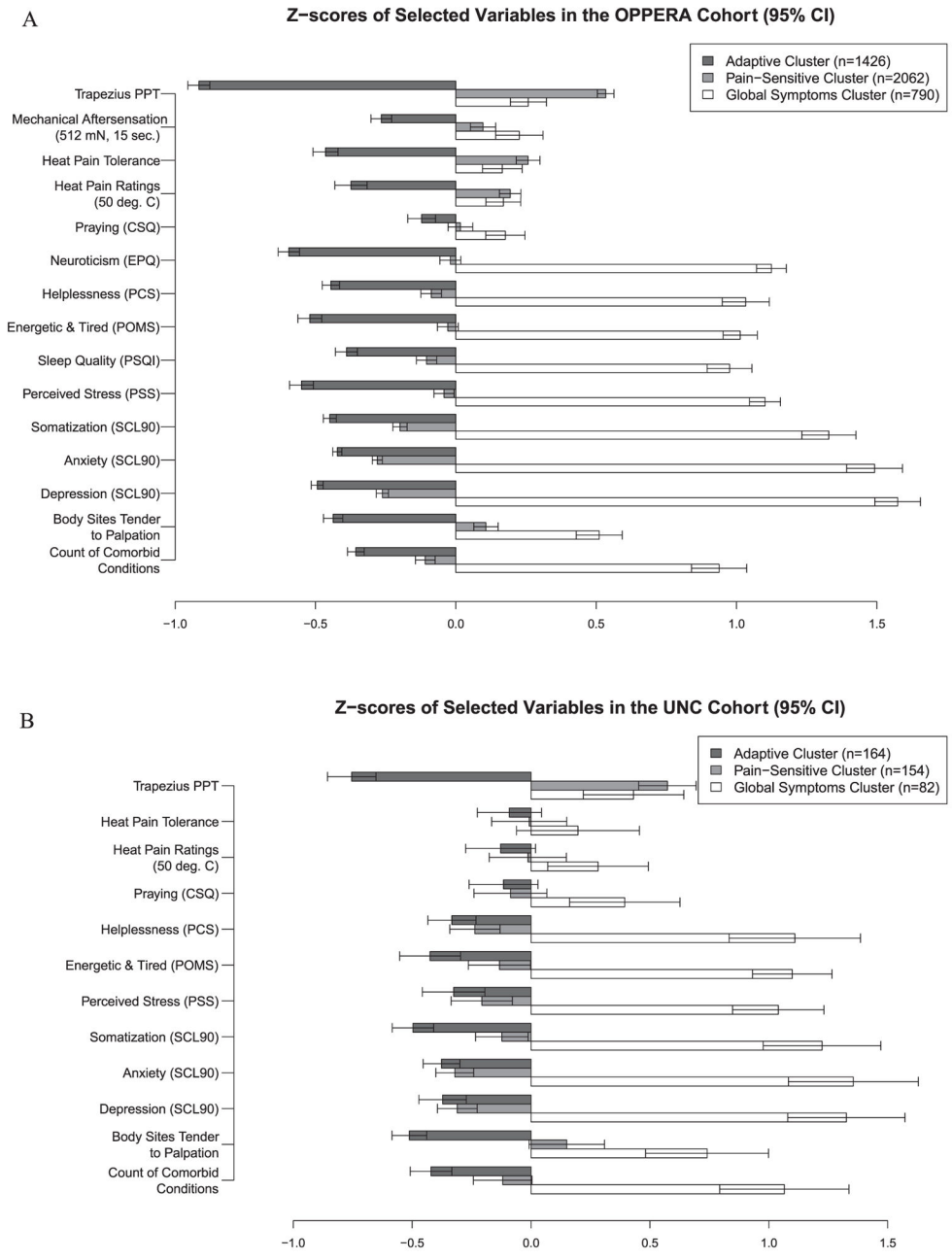

Figure 1.

Z-scores of selected variables. These plots show the mean values (and associated 95% confidence intervals) for a selected subset of the pain sensitivity and psychosocial variables in the (A) OPPERA cohort and (B) UNC cohort. Each variable displayed in the figure was normalized to have mean 0 and SD 1. PPT, pressure pain threshold.

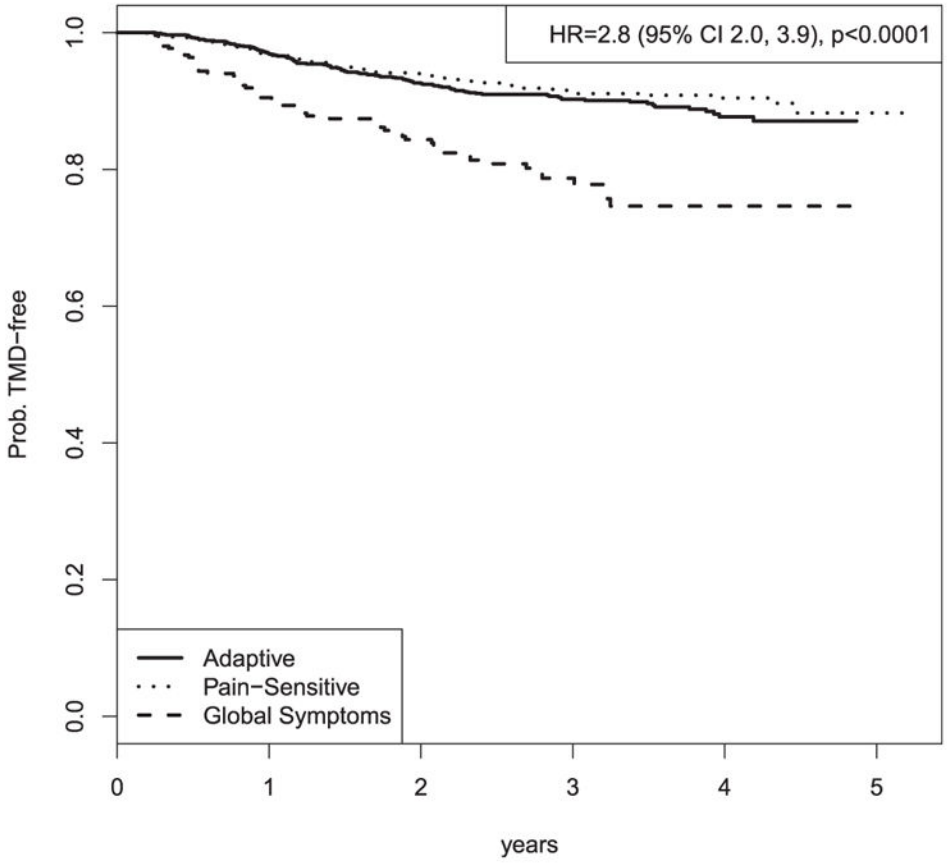

Figure 2.

Kaplan–Meier plots for first-onset temporomandibular disorder (TMD). This plot shows the probability that a participant in a given cluster remains TMD free after a specified number of years. HR, hazard ratio.

Table 1

Demographics, temporomandibular disorder case status, and cluster membership.

OPPERA cohort, n (%)	Adaptive cluster (n = 1426)	Pain-sensitive cluster (n = 2062)	Global symptoms cluster (n = 790)	*P**
Male	839 (58.8)	558 (27.1)	240 (30.4)	<0.0001
Female	587 (41.2)	1504 (72.9)	550 (69.6)	
Non-Hispanic white	780 (54.7)	1126 (54.6)	455 (57.6)	0.0806
African American	381 (26.7)	596 (28.9)	194 (24.6)	
Asian	111 (7.8)	160 (7.8)	69 (8.7)	
Hispanic	102 (7.2)	129 (6.3)	42 (5.3)	
Other	52 (3.6)	51 (2.5)	30 (3.8)	
Age 18–24	730 (51.2)	1027 (49.8)	310 (39.2)	<0.0001
Age 25–34	379 (26.6)	593 (28.8)	256 (32.4)	
Age 35–44	317 (22.2)	442 (21.4)	224 (28.4)	
Cases	88 (6.2)	540 (26.2)	403 (51.0)	<0.0001
Controls	1338 (93.8)	1522 (73.8)	387 (49.0)	
UNC cohort, n (%)	**Adaptive cluster (n = 164)**	**Pain-sensitive cluster (n = 154)**	**Global symptoms cluster (n = 82)**	***P****
Age 18–24	73 (44.5)	42 (27.3)	19 (23.2)	0.0029
Age 25–34	42 (25.6)	46 (29.9)	26 (31.7)	
Age 35–60	49 (29.9)	66 (42.9)	37 (45.1)	
Cases	32 (19.5)	99 (64.3)	68 (82.9)	<0.0001
Controls	132 (80.5)	55 (35.7)	14 (17.1)	

*P value for the null hypothesis that the percentage in each cluster does not differ with respect to the levels of the variable.

Table 2

Potential clinical risk factors for temporomandibular disorder (TMD) and cluster membership (OPPERA cohort; TMD cases only).

	A	SE	n	PS	SE	n	GS	SE	n	*P**	A vs PS†	PS vs GS†	A vs GS†
Duration of orofacial pain (y)	6.08	0.07	85	7.15	0.01	529	6.84	0.02	400	0.3318	0.1292	0.4697	0.2887
Facial pain intensity (0–100)	45.67	0.23	84	52.41	0.04	529	61.53	0.05	398	<0.0001	0.0037	<0.0001	<0.0001
Facial pain interference (0–100)	12.50	0.25	84	19.80	0.04	524	30.92	0.07	394	<0.0001	0.0039	<0.0001	<0.0001
Count of 6 nonspecific orofacial symptoms	4.28	0.02	85	4.63	0.00	533	5.12	0.00	400	<0.0001	0.0368	<0.0001	<0.0001
Count of 20 comorbid conditions	1.14	0.02	85	1.91	0.00	525	4.25	0.01	393	<0.0001	<0.0001	<0.0001	<0.0001
Headaches in the past year (%)	94.25	0.27	87	96.25	0.04	533	98.75	0.03	400	0.0219	0.4518	0.0120	0.0835
No. different types of headaches	2.30	0.01	87	2.49	0.00	527	2.84	0.00	400	<0.0001	0.1562	<0.0001	0.0001
Headache intensity (0–2)	1.14	0.01	86	1.23	0.00	525	1.42	0.00	398	<0.0001	0.1297	<0.0001	<0.0001
Chronic pain in areas other than the face (%)	32.18	0.54	87	42.17	0.10	517	64.19	0.12	391	<0.0001	0.0713	<0.0001	<0.0001
Nonorofacial pain intensity (0–100)	16.21	0.31	87	22.99	0.06	523	40.86	0.09	395	<0.0001	0.0322	<0.0001	<0.0001
Nonorofacial pain interference (0–100)	11.43	0.26	86	14.70	0.05	515	31.57	0.08	390	<0.0001	0.2228	<0.0001	<0.0001
Pain-free jaw opening (mm)	37.92	0.12	87	34.30	0.02	537	33.44	0.03	398	0.0043	0.0051	0.2550	0.0008
Maximum unassisted jaw opening (mm)	48.36	0.10	87	46.67	0.02	537	46.36	0.02	397	0.1893	0.1078	0.6095	0.0637
Maximum assisted jaw opening (mm)	52.00	0.12	72	51.82	0.02	397	51.70	0.03	292	0.9583	0.8714	0.8496	0.7908
No. muscle groups with pain on unassisted opening (0–8)	1.79	0.02	86	2.08	0.00	515	2.19	0.00	385	0.0637	0.0870	0.2730	0.0246
No. orofacial sites tender to palpation (0–38)	15.61	0.12	87	21.61	0.03	532	25.32	0.03	388	<0.0001	<0.0001	<0.0001	<0.0001
No. neck sites tender to palpation (0–14)	3.20	0.04	87	4.83	0.01	537	6.43	0.01	400	<0.0001	0.0002	<0.0001	<0.0001
No. body sites tender to palpation (0–14)	4.16	0.04	87	5.53	0.01	538	7.08	0.01	400	<0.0001	0.0015	<0.0001	<0.0001
Current rating of pain (0–100)	15.63	0.21	88	18.42	0.04	531	29.46	0.06	399	<0.0001	0.2023	<0.0001	<0.0001
% of waking day with pain	35.41	0.40	87	32.63	0.06	531	48.31	0.09	399	<0.0001	0.4832	<0.0001	0.0021
Rating of pain unpleasantness (0–20)	5.14	0.05	85	5.54	0.01	527	8.07	0.01	395	<0.0001	0.4436	<0.0001	<0.0001
Rating of pain intensity (0–20)	5.74	0.06	85	6.12	0.01	524	8.98	0.01	396	<0.0001	0.5223	<0.0001	<0.0001
SF12v2 Physical Functioning Scale (0–100)	91.07	0.22	84	89.30	0.04	528	73.24	0.08	398	<0.0001	0.4342	<0.0001	<0.0001
SF12v2 Mental Health Scale (0–100)	76.47	0.16	85	68.31	0.03	529	43.44	0.05	400	<0.0001	<0.0001	<0.0001	<0.0001
JFLS global score (0–10)	1.29	0.02	63	1.98	0.00	381	2.41	0.01	273	<0.0001	0.0002	0.0006	<0.0001
OBC sum score (0–62)	29.17	0.12	82	31.23	0.02	510	36.57	0.03	380	<0.0001	0.0917	<0.0001	<0.0001

* *P* value for the null hypothesis that the mean value of the risk factor does not differ between the 3 clusters.

† *P* value for the null hypothesis that the mean value of the risk factor does not differ between clusters, the A and PS (or the PS/GS or A/GS, respectively).

A, adaptive cluster; GS, global symptoms cluster; JFLS, Jaw Functional Limitation Scale; OBC, Oral Behaviors Checklist; PS, pain-sensitive cluster.

Table 3

Potential clinical risk factors for temporomandibular disorder (TMD) and cluster membership (UNC cohort; TMD cases only).

	A	SE	n	PS	SE	n	GS	SE	n	*P**	A vs PS†	PS vs GS†	A vs GS†
Duration of orofacial pain (mo)	143.15	22.45	27	128.95	8.85	75	103.61	11.60	46	0.2072	0.5950	0.1486	0.1683
Facial pain intensity (0–100)	39.64	3.74	28	49.69	2.01	85	53.47	2.46	48	0.0167	0.0325	0.3007	0.0072
Facial pain interference (0–100)	10.90	2.88	26	18.96	1.94	83	24.86	3.07	46	0.0253	0.0406	0.1729	0.0059
Count of 6 nonspecific orofacial symptoms	3.50	0.29	28	4.48	0.14	85	4.38	0.18	48	0.0075	0.0073	0.6757	0.0249
Count of 20 comorbid conditions	2.61	0.31	28	2.19	0.20	85	5.11	0.41	46	<0.0001	0.2970	<0.0001	0.0001
Headaches in the past year (%)	96.43	3.34	28	100.00	0.00	85	100.00	0.00	46	0.0959	0.3262	NA	NA
No. different types of headaches	2.29	0.20	28	2.52	0.10	85	2.71	0.14	45	0.2404	0.3426	0.3302	0.1263
Headache intensity (0–2)	1.22	0.09	27	1.26	0.04	85	1.36	0.06	45	0.4124	0.7377	0.2670	0.2765
Chronic pain in areas other than the face (%)	50.00	9.00	28	46.43	5.04	84	76.09	5.23	46	0.0036	0.7485	0.0006	0.0281
Nonorofacial pain intensity (0–100)	21.67	4.33	28	24.75	2.87	85	46.23	3.63	46	0.0001	0.5829	0.0001	0.0003
Nonorofacial pain interference (0–100)	13.10	3.28	28	14.98	2.22	85	33.62	3.87	46	0.0001	0.6591	0.0007	0.0008
Pain-free jaw opening (mm)	35.28	1.56	32	33.89	0.86	99	33.66	1.10	68	0.6732	0.4395	0.8710	0.3996
Maximum unassisted jaw opening (mm)	43.94	1.32	32	45.35	0.80	99	44.26	0.96	68	0.5544	0.3618	0.3850	0.8414
Maximum assisted jaw opening (mm)	47.56	1.36	32	48.49	0.80	99	47.43	0.94	68	0.6514	0.5561	0.3873	0.9346
No. muscle groups with pain (0–8)	4.06	0.29	32	5.54	0.18	99	5.71	0.24	68	0.0001	0.0001	0.5684	<0.0001
No. orofacial sites tender to palpation (0–38)	12.22	1.17	32	18.58	0.84	99	19.66	1.14	68	0.0002	<0.0001	0.4447	<0.0001
No. neck sites tender to palpation (0–8)	0.81	0.33	32	2.21	0.25	99	2.74	0.33	68	0.0018	0.0011	0.2072	0.0001
No. body sites tender to palpation (0–18)	3.25	0.82	32	5.96	0.55	99	8.28	0.71	68	0.0001	0.0078	0.0109	<0.0001
Current rating of pain (0–100)	23.74	4.58	31	23.55	2.21	98	40.19	2.99	67	<0.0001	0.9706	<0.0001	0.0044
% of waking day with pain	38.10	5.99	31	48.72	3.19	97	67.76	3.78	67	<0.0001	0.1294	0.0002	0.0001
Rating of pain unpleasantness (0–20)	7.39	0.66	28	7.44	0.36	89	10.09	0.49	54	0.0001	0.9549	0.0001	0.0037
Rating of pain intensity (0–20)	8.14	0.81	28	8.59	0.43	91	11.64	0.45	53	<0.0001	0.6465	<0.0001	0.0011
SF12v2 Physical Functioning Scale (0–100)	83.06	5.02	31	85.28	2.35	90	65.57	4.47	61	0.0003	0.6980	0.0004	0.0140
SF12v2 Mental Health Scale (0–100)	69.35	2.48	31	71.20	1.57	92	51.41	2.25	62	<0.0001	0.5413	<0.0001	<0.0001

* *P* value for the null hypothesis that the mean value of the risk factor does not differ between the 3 clusters.

† *P* value for the null hypothesis that the mean value of the risk factor does not differ between clusters, the A and PS (or the PS/GS or A/GS, respectively).

A, adaptive cluster; GS, global symptoms cluster; NA, not applicable; PS, pain-sensitive cluster.

Table 4

Other chronic pain conditions and cluster membership (OPPERA cohort).

	Adaptive cluster	Pain-sensitive cluster	Global symptoms cluster	*P**
No IBS, n (%)	1387 (34.70)	1944 (48.64)	666 (16.66)	<0.0001
IBS, n (%)	21 (9.95)	87 (41.23)	103 (48.82)	
No pelvic pain, n (%)	1368 (35.08)	1906 (48.87)	626 (16.05)	<0.0001
Pelvic pain, n (%)	23 (11.22)	89 (43.41)	93 (45.37)	
No chronic headache, n (%)	1351 (35.00)	1891 (48.99)	618 (16.01)	<0.0001
Chronic headache, n (%)	15 (6.25)	86 (35.83)	139 (57.92)	
No constant low-back pain, n (%)	1350 (34.26)	1945 (49.37)	645 (16.37)	<0.0001
Constant low-back pain, n (%)	44 (17.96)	81 (33.06)	120 (48.98)	

* *P* value for the null hypothesis that the proportion with the condition does not differ between the 3 clusters.

IBS, irritable bowel syndrome.

Table 5

Potential environmental risk factors for temporomandibular disorder and cluster membership.

	A, %	SE, %	n	PS, %	SE, %	n	GS, %	SE, %	n	*P**	A vs PS†	PS vs GS†	A vs GS†
OPPERA cohort													
Lifetime history of jaw injury	8.2	0.8	1339	11.5	0.7	1824	18.9	1.6	608	<0.0001	0.0034	<0.0001	<0.0001
Lifetime history of smoking	22.0	1.1	1426	24.7	1.0	2056	41.8	1.8	789	<0.0001	0.0777	<0.0001	<0.0001
Lifetime history of hormonal contraceptive use (females)	64.9	2.0	579	70.1	1.2	1480	72.9	1.9	536	0.0121	0.0277	0.2295	0.0048
Current hormonal contraceptive use (females)	18.2	1.6	583	17.1	1.0	1494	11.7	1.4	540	0.0032	0.6166	0.0034	0.0030
Traumatic life event (LSL)	36.2	1.3	1421	40.1	1.1	2054	61.1	1.7	786	<0.0001	0.0207	<0.0001	<0.0001
UNC cohort													
Lifetime history of jaw injury	28.9	3.7	152	32.6	4.0	138	44.1	6.5	59	0.1172	0.5839	0.1699	0.0535
Lifetime history of smoking	17.1	3.1	152	26.6	3.7	139	43.1	6.1	65	0.0004	0.0679	0.0286	0.0001
Traumatic life event (LSL)	25.6	3.4	164	27.3	3.6	154	41.5	5.4	82	0.0318	0.8345	0.0380	0.0168

* *P* value for the null hypothesis that the mean value of the risk factor does not differ between the 3 clusters.

† *P* value for the null hypothesis that the mean value of the risk factor does not differ between clusters, the A and PS (or the PS/GS or A/GS, respectively).

A, adaptive cluster; GS, global symptoms cluster; LSL, Lifetime Stressor List; PS, pain-sensitive cluster.

Table 6

Cluster reliability.

Within-cohort validation*							
OPPERA cohort				**UNC cohort**			
Observed cluster	**Predicted cluster**			**Observed cluster**	**Predicted cluster**		
	A	**PS**	**GS**		**A**	**PS**	**GS**
A	685	10	4	A	67	4	4
PS	51	993	0	PS	13	65	5
GS	0	13	384	GS	2	5	36

Across-cohort validation†							
OPPERA cohort predictions				**UNC cohort predictions**			
Observed cluster	**Predicted cluster**			**Observed cluster**	**Predicted cluster**		
	A	**PS**	**GS**		**A**	**PS**	**GS**
A	999	405	22	A	151	9	4
PS	166	1781	115	PS	40	110	4
GS	28	82	680	GS	12	18	52

"Observed cluster" denotes the clusters identified when clustering was applied to a given cohort (or half of a cohort). "Predicted cluster" denotes the predicted cluster assignment based on the model fit to the other half of the data (or the other cohort). For example, when the OPPERA cohort was split into 2 halves, there were 685 participants who were predicted to be in the adaptive cluster based on the model and who were actually assigned to the adaptive cluster when the clustering method was applied to this half of the data. The misclassification error rate can be calculated by dividing the number of misclassified observations (ie, observations that do not fall in the main diagonal) by the total number of observations.

*For within-cohort validation, each data set was partitioned in half, and clusters on one-half of the data were used to predict the clusters on the other half.

†For across-cohort validation, the clusters from the UNC cohort were used to predict the clusters in the OPPERA cohort (and vice versa).

A, adaptive cluster; GS, global symptoms cluster; PS, pain-sensitive cluster.