Associations of Psychologic Factors with Multiple Chronic Overlapping Pain Conditions

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Submitted August 8, 2019;
accepted February 11, 2020.

Aims: To characterize psychologic functioning across five chronic overlapping pain conditions (COPCs)—temporomandibular disorders, fibromyalgia, low back pain, headache, and irritable bowel syndrome—and their overlaps. **Methods:** Participants were 655 adults in the OPPERA study. Psychologic variables were standardized in separate logistic regression models to compare their relative strength of association with each COPC. Random forest regression was used to explore the association of all psychologic measures with COPCs simultaneously. Linear regression analyses examined whether the count of COPCs was associated with psychologic measures. **Results:** In univariate and multivariable analyses, measures of somatic symptom burden showed the strongest associations with individual COPCs and with the number of COPCs. Additional psychologic variables that showed significant associations with individual COPCs and their overlap included negative mood, perceived stress, and pain catastrophizing. **Conclusion:** These findings highlight the importance of psychologic functioning in the assessment and management of these overlapping pain conditions. *J Oral Facial Pain Headache 2020;34(suppl):s85–s100. doi: 10.11607/ofph.2584*

Keywords: *chronic overlapping pain conditions, headache, low back pain, pain assessment, psychological factors, temporomandibular disorder*

Chronic overlapping pain conditions (COPCs) refer to a group of pain disorders that occur frequently in the population and whose underlying pathophysiology remains poorly understood. COPCs include conditions such as temporomandibular disorders (TMD), fibromyalgia or widespread pain, low back pain (LBP), headache, and irritable bowel syndrome (IBS), among others.[1,2] These five pain conditions have been described using labels such as "idiopathic pain disorders,"[3] "chronic overlapping pain conditions,"[2] "central sensitivity syndromes,"[4] and, with the exception of headache, "functional pain syndromes."[5] Hereafter, the collective term "chronic overlapping pain conditions" is used, consistent with the current terminology favored by the National Institutes of Health.[6] While COPCs represent distinct conditions and are often managed by specialists who focus on one type of COPC, COPCs share high levels of comorbidity—that is, the presence of one COPC significantly increases the likelihood of experiencing another COPC.[2] Moreover, factors associated with one COPC are often also associated with other COPCs, such as female sex, heightened pain sensitivity, and even genetic variants. This pattern of overlap implies the potential for common pathophysiologic mechanisms and risk factors for multiple COPCs.[1,2,7]

In particular, certain psychologic features have been associated with multiple COPCs.[8] Separate studies of individual COPCs, including TMD,[2,9] fibromyalgia,[10] LBP,[11] IBS,[12] and headache conditions,[13] have demonstrated that each is associated with high levels of somatic symptoms and affective distress. Similarly, psychologic stress is reported at higher levels among patients with COPCs compared to pain-free controls, and stress is associated with increased clinical symptoms among individuals with different COPCs.[14–16] Importantly, these psychologic profiles cannot be explained as consequences of living with COPCs, given evidence from longitudinal studies showing that premorbid levels

of these psychologic factors predict risk for future development of COPCs.[14,17,18] Additional support for the clinical relevance of these psychologic factors across different COPCs comes from studies demonstrating that similar psychologic interventions show efficacy for each of these COPCs.[19–24]

The findings described above have identified common psychologic factors that are associated with different COPCs. However, most previous research exploring pain-related psychologic functioning has done so in a specific COPC and has not addressed whether psychologic functioning may be differentially affected by different combinations of COPCs experienced by individuals. In addition, there is limited prior research that has examined the influence of multiple COPCs on psychologic characteristics and whether greater psychologic dysfunction occurs in the presence of multiple COPCs. Therefore, the purpose of this study was to characterize psychologic functioning across five selected COPCs: TMD, headache, IBS, LBP, and fibromyalgia. The associations between the count of COPCs and psychologic factors were further explored. The psychosocial measures assessed in this project included a subset of psychosocial measures administered in the original OPPERA study. The original battery of instruments was selected to assess psychosocial functioning across multiple domains in order to identify associations with chronic TMD and risk factors for new-onset TMD.[9,18] In the current study, a subset of these instruments was administered to reduce participant burden. The instruments for this project were selected to represent the constructs found to be significantly associated with both chronic TMD and risk of first-onset TMD in the previous work, including somatic symptom burden, negative mood/affect, psychosocial stress, and pain coping.[9,18]

Using information from the most recent wave of data collection in the OPPERA study, the following hypotheses were tested: *(1)* multiple measures of psychologic function would indicate significant commonality in psychologic features across all five COPCs; *(2)* some COPCs may be associated with greater psychologic distress than other COPCs; and *(3)* increasing numbers of COPCs would be monotonically associated with higher levels of psychologic distress.

Materials and Methods

Reporting of this observational study conforms with the STROBE guidelines.[25] The primary data collection was from National Institute of Dental and Craniofacial Research (NIDCR) Study Protocol 12-050-E, conducted in the second phase of the OPPERA project (OPPERA-2). The Office of Human Research Ethics at each participating institution reviewed and approved the study.

Study Design, Setting, and Participants

The cross-sectional design used data from adults originally recruited into the first phase of OPPERA between May 2006 and May 2013. At that time, subjects aged 18 to 44 years were selected for a community-based, case-control study of chronic TMD. Cases were 1,008 adults with examiner-verified painful temporomandibular disorders (TMD). Controls were 3,258 adults with examiner-verified absence of TMD. All subjects were recruited at US academic health centers located at: University of Maryland, Baltimore, Maryland; University at Buffalo, Buffalo, New York; University of North Carolina, Chapel Hill, North Carolina; and University of Florida, Gainesville, Florida. Previous papers have described details of recruitment and baseline data collection, as well as methods used for a subsequent prospective cohort study of the TMD-free individuals who were followed up for up to 5 years to investigate incidence of first-onset TMD.[26,27]

This analysis reports findings from the most recent wave of data collection in OPPERA. Between December 2014 and May 2016, attempts were made to contact all original enrollees. Data were then collected using clinical examinations, quantitative sensory testing, cardiovascular measures of autonomic function, blood samples, and self-report questionnaires. Further details of recruitment and data collection methods are provided elsewhere in this volume (see Slade et al, current issue).

Classification of COPCs

The presence or absence of five chronic overlapping pain conditions (COPCs) was classified as described in detail elsewhere in this issue (see Ohrbach et al, et al, current issue) and is summarized below.

TMD was classified by examiners who used the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD).[28] In summary, to be classified a TMD case, subjects had to have all four of the following findings: *(1)* history of orofacial pain in examiner-verified locations of the masseter, temporalis, submandibular, or temporomandibular joint (TMJ) areas and/or history of headache in the verified location of the temporal region that had occurred on 5 or more of the 30 days preceding the examination; *(2)* evoked pain in the same muscles and/or TMJs following palpation of those structures or jaw maneuver(s); *(3)* reported "familiarity" of evoked pain, as judged by a positive response to the question "Was the pain you felt [during palpation or jaw maneuver] familiar to the pain [or temporal headache] that you reported during the last 30 days?"; and *(4)* pain that

was modified by jaw function, as judged by a positive response to the question "During the last 30 days, was any of the pain modified by chewing hard food, opening the mouth, jaw habits such as clenching, or other jaw activities?"

Headache was classified using responses to a questionnaire designed for OPPERA that asked about symptoms of tension-type headache (TTH) and migraine during the preceding 12 months. Subjects who experienced more than one type of headache recorded responses separately for up to three different types of headache. Questions about TTH were from the International Classification of Headache Disorders, third edition (ICHD-3).[29] Symptoms of migraine were based on questions used in the ID-Migraine questionnaire.[30] Migraine was classified when subjects reported headache(s) on 1 or more day per month and at least two of three symptoms accompanying the headache: nausea, sensitivity to light, or being kept from everyday activities. For this analysis, headache was classified for any subject who reported symptoms consistent with probable TTH, TTH, or migraine, and who had experienced such headache(s) in the preceding 3 months.

IBS was classified using responses to four questions about abdominal pain from the Rome III diagnostic criteria.[31] Subjects were classified with IBS if they met both of the following criteria: *(1)* abdominal pain on at least 1 day in the preceding 3 months that was not related to menstrual periods; and *(2)* pain that was associated with at least two symptoms of bowel function (ie; pain altered by bowel movements, greater frequency of bowel movements; less frequency of bowel movements; looser stools; harder stools).

LBP was classified using responses to screening questions recommended for studies of back pain prevalence.[32] Subjects were classified with LBP if they reported pain that occurred in the lower back (as illustrated to the participant with a shaded manikin drawing) during the preceding 3 months that was not related to fever or menstruation and that restricted usual activities for at least 1 day.

Fibromyalgia was classified based on findings from examinations and questionnaires, consistent with the 1990 American College of Rheumatology (ACR) criteria.[33] Subjects were classified with fibromyalgia when ≥ 11 of 18 body sites were tender to algometer-delivered pressure of up to 4.0 kg/cm^2 and when the tenderness occurred in both the axial skeleton and in at least one set of opposing diagonal quadrants of the body. Also, fibromyalgia cases had to report a history of pain lasting for at least 1 day per month in the preceding 3 months.

This paper focuses on the relationship between COPCs and explanatory variables measuring psychologic characteristics, which were assessed as follows.

Assessment of Explanatory Psychologic Variables

Pennebaker Inventory of Limbic Languidness. The Pennebaker Inventory of Limbic Languidness (PILL) assesses the frequency with which individuals are bothered by each of 54 common physical symptoms and sensations on a 5-category scale (never or almost never; less than 3 or 4 times a year; every month or so; every week or so; more than once every week). The single-summary PILL score, derived by summing the individual item responses, is related to the construct of somatic awareness or the general tendency to report physical symptoms. The PILL has shown high internal consistency (Cronbach's α = 0.88) and adequate test-retest reliability (0.70 over 2 months).[34]

Symptom Checklist 90-Revised Somatization and Depression Subscales. The Symptom Checklist 90-Revised (SCL-90-R) somatization subscale assesses somatic symptom burden across multiple bodily systems, and the depression subscale assesses depressed mood and related symptoms. On both subscales, participants report the extent to which they have been bothered by each symptom on a 5-category scale (not at all; a little bit; moderately; quite a bit; extremely).[35] These subscales show good internal consistency (Cronbach's α for ranging from 0.86 to 0.90) and test-retest reliability (0.68 to 0.86).[36]

State-Trait Anxiety Inventory. The State-Trait Anxiety Inventory (STAI) is a 20-item questionnaire assessing general anxiety.[37] For each item, participants are asked to indicate how they "generally feel" using a four-category scale (not at all; somewhat; moderately so; extremely so). Test-retest reliability for the STAI has been adequate, with a Cronbach's α ranging from 0.73 to 0.86 over intervals of 20 to 104 days.[37]

Profile of Mood States-Bipolar. The Profile of Mood States-Bipolar (POMS-Bi) consists of 72 mood-related items, and participants indicate the extent to which each item describes their mood state over the past week, including today, using a four-category scale (much unlike this; slightly unlike this; slightly like this; much like this).[38] This questionnaire assesses both positive and negative affective dimensions and yields global indices of positive affect and negative affect. The POMS has been well validated with other mood measures and is sensitive to subtle differences in affective state.

Perceived Stress Scale. The Perceived Stress Scale (PSS) is a 14-item scale that assesses the degree to which individuals appraise situations as stressful and their perceived ability to cope with stressful situations.[39] For each item, participants indicate how often they felt or thought that way in the past month using a five-category scale (never; almost never; sometimes; fairly often; very often). The PSS

yields a single overall perceived stress score by summing the numeric weights of each item after reverse scoring seven of the items. Internal consistency is good with Cronbach's α of 0.84 or greater, and construct validity has been demonstrated, as the PSS correlates significantly with other measures of stress appraisal.[39]

Life Experiences Survey. The Life Experiences Survey (LES) is a 57-item instrument that assesses the frequency of life events that have occurred over the past year, as well as the impact of these events.[40] Impact ratings range from –3 (extremely negative) to +3 (extremely positive), with 0 indicating no impact. For this analysis, the impact of negative events was computed by summing the negative impact scores for all reported negative events.

Modified Posttraumatic Stress Disorder Symptom Scale. The Modified Posttraumatic Stress Disorder Symptom Scale (MPSS) is a 17-item self-report scale designed to assess the frequency and severity of PTSD symptoms. Items are rated on 4-point frequency (ranging from 0 = not at all, to 3 = 5 or more times per week) and intensity (ranging from A = not at all upsetting, to D = extremely upsetting) scales. The MPSS has shown good psychometric properties in people reporting previous exposure to traumatic events, with high internal consistency (α = 0.96 to 0.97) and good concurrent validity against PTSD diagnostic instruments.[41]

Coping Strategies Questionnaire-Revised. The Coping Strategies Questionnaire-Revised (CSQ-R) is a revised version of the original CSQ,[42] consisting of 27 items relating to how individuals cope with pain. Participants indicate the frequency with which they engage in specific coping activities when experiencing pain using a 7-category numeric scale, ranging from 0 (never do that) to 6 (always do that). It yields 6 subscales reflecting the pain coping strategies that individuals use: diverting attention; catastrophizing; praying and hoping; ignoring pain sensations; reinterpreting pain sensations; and coping self-statements. The subscales have shown adequate internal consistency, with Cronbach's α ranging from 0.82 to 0.92 in a sample of healthy young adults.[18] The CSQ-R has been shown to have stable factor structure in patients with chronic pain[43] and in healthy populations.[44]

Statistical Methods

Raw values of each psychologic measure were used to generate descriptive statistics for cases and controls of each COPC and according to the number of COPCs. All other analyses of continuous variables used *z*-transformed values of psychologic measures, and the data were weighted during analysis. For each psychologic variable, if up to one-half of the items for the scale were missing, the value of the variable was imputed using the expectation maximization method. However, if more than one-half of the items were missing, or if it was a single-item variable with a missing value, the observation for subject was excluded from the model. The goal of data transformation was to produce measures of association (eg, odds ratios [ORs], regression estimates) that could be readily compared between health measures that use different scales of measurement.

The goal of weighting was to adjust for the sampling design in OPPERA-2. This took into consideration sampling for the OPPERA-1 case-control study (where TMD cases were oversampled relative to their prevalence in the population) to adjust for differential loss to follow-up of subjects between enrollment in OPPERA-1 and recruitment into OPPERA-2. Such weighting is important for this analysis to permit valid estimates of association between any two variables (eg, health measures and headache) in a sample that was originally stratified according to a third variable (presence or absence of chronic TMD in OPPERA-1).[45] The analytic weights for OPPERA-2 were computed as the inverse of sampling probability for OPPERA-1, multiplied by the inverse of loss to follow-up probability between OPPERA-1 and OPPERA-2. With the exception of univariate statistics describing the distribution of explanatory variables, all means, percentages, and measures of association were calculated using generalized estimating equations (GEE) with the GENMOD procedure in SAS version 9.4 (IBM), with analytic weights and robust error variance calculation.[46]

The analysis first assessed associations between psychologic variables and the presence or absence of each COPC using statistical methods for case-control analysis of cross-sectional data. For descriptive purposes, mean values of continuous variables and percentages of categorical variables were generated for cases and controls for each of the five COPCs. To quantify univariate associations, adjusted odds ratios (ORs) were estimated in separate binary logistic regression models, one for each COPC, where the main explanatory variable was the standardized (using *z*-score transformation) value of a single psychologic variable. The models adjusted for study site (four categories) and subjects' demographic characteristics: age (measured in years); gender (two categories); and race/ethnicity (five categories: white, Black/African American, Asian, Hispanic, or other). In order to determine independent associations between individual COPCs and psychologic variables, all five COPCs were modeled as separate binary variables in a multivariable model to predict the dependent variable, with tests of the null hypotheses that individual COPCs did not contribute independently to the dependent variable.

Table 1 Sample Counts and Weighted Estimates for Demographic Characteristics

Classification	Group	Weighted no.	Mean (SE) age, y	% (SE) female	% (SE) white
TMD	Case	108	33.0 (0.6)	61.2 (3.6)	50.7 (3.7)
	Control	547	35.4 (0.4)	57.0 (2.3)	52.2 (2.3)
Headache	Case	201	34.6 (0.5)	71.1 (2.8)	55.5 (3.0)
	Control	454	35.3 (0.4)	51.7 (2.6)	50.4 (2.6)
IBS	Case	134	34.6 (0.7)	53.7 (4.0)	60.1 (3.9)
	Control	521	35.2 (0.3)	58.7 (2.2)	49.8 (2.2)
LBP	Case	99	37.6 (0.7)	56.7 (4.2)	62.9 (4.1)
	Control	556	34.6 (0.3)	57.9 (2.2)	50.0 (2.2)
Fibromyalgia	Case	24	34.3 (1.1)	77.2 (5.9)	52.7 (7.0)
	Control	631	35.1 (0.3)	56.9 (2.0)	51.9 (2.0)
No. of COPCs	0	307	35.6 (0.5)	54.0 (3.1)	46.5 (3.1)
	1	209	34.4 (0.5)	60.0 (3.7)	55.5 (3.7)
	2	83	33.6 (0.8)	57.5 (4.8)	58.7 (4.7)
	3	33	36.5 (1.1)	63.6 (5.8)	68.4 (5.6)
	4	15	38.7 (1.4)	92.2 (4.7)	39.7 (8.6)
	5	6	30.9 (1.7)	48.8 (15.1)	52.8 (15.1)

SE = standard error.

Random forest modeling explored multivariable contributions of all psychologic variables to each binary COPC case classification. Missing values of explanatory variables were imputed using on-the-fly imputation, which is the decision tree analog of multiple imputation.[47] Random forests are nonparametric statistical models that can handle interactions and nonlinear associations without the need to pre-specify the interactions or the form of the nonlinearities. Due to this flexibility, random forests demonstrate excellent classification performance across a broad range of tasks. Through a combination of the bootstrap aggregating and random subspace methods used in the construction of random forests, they achieve this classification performance without overfitting to the training dataset, thus maintaining good out-of-sample performance.[48]

Contributions of individual variables in the random forest models were quantified using variable importance scores, which estimate the relative contribution of each predictor to the model's classification of true positives and true negatives. Overall classification performance of the models was quantified with area under the receiver operating characteristic curve (AUROC) and area under the precision recall curve (AUPR). In datasets with unequal numbers of cases and controls, AUPR is a better measure of classification performance than AUROC, though no single metric can adequately capture classification performance.[49] However, both measures accord equal weight to false positives and false negatives, whereas the relative importance of those errors may vary according to COPC. Therefore, the Brier score was also computed,[50] which provides an analog to mean squared error, as well as proportion of variance explained for the binary prediction models. Mutual information provides sensible rankings of classifiers in scenarios, such as class imbalance, that break more commonly used measures like precision, recall, and AUROC.[51] A second set of analyses examined associations with the subjects' count of COPCs. For these analyses, the standardized psychologic variable was used as the dependent variable in a linear regression model where the main predictor variable was the number of COPCs, and covariates were adjusted for study site and demographics (coded as described above). The count of COPCs was modeled using three approaches to evaluate patterns of association: *(1)* the number of COPCs was modeled as a categorical variable to evaluate potential nonlinear relationships with the explanatory variable, and pairwise comparisons were used to test for differences between subjects with no COPCs (the reference group) vs the other five possibilities (1, 2, 3, 4 or 5 COPCs); *(2)* the count of COPCs was modeled as a continuous variable to reveal a potential linear relationship with the dependent variable, with a test of the null hypothesis of no linear relationship ($\beta = 0$); and *(3)* all five COPCs were modeled as separate binary predictor variables, with parameter estimates tested for independent contributions of each COPC to the psychologic measure.

Results

Demographic characteristics of the cases and controls are provided in Table 1. Age was generally similar for cases and controls across all COPCs, although TMD cases were slightly younger than controls, while LBP cases were slightly older than controls. No consistent pattern of age with number of COPCs emerged. A greater proportion of cases vs controls were women for TMD, headache, and fibromyalgia, and non-Hispanic white race/ethnicity was overrepresented in cases vs controls for all COPCs.

Table 2 Descriptive Statistics for Psychologic Variables for the Five COPCs and Controls

Psychologic measure	TMD		Headache		IBS		LBP		Fibromyalgia	
	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
Somatic symptoms										
PILL score (54–270)	117.38 (2.28), 180	88.92 (1.06), 469	111.06 (1.72), 269	86.73 (1.22), 380	114.62 (2.58), 156	91.18 (1.10), 493	117.76 (2.85), 137	91.21 (1.06), 512	132.05 (4.69), 52	93.75 (1.05), 597
SCL-90-R : Somatization (0–4)	0.69 (0.04), 181	0.26 (0.01), 472	0.56 (0.03), 270	0.25 (0.02), 383	0.60 (0.04), 158	0.31 (0.02), 495	0.80 (0.05), 139	0.27 (0.01), 514	0.98 (0.09), 52	0.33 (0.02), 601
Mood/affect										
SCL-90-R: Depression (0–4)	0.73 (0.05), 181	0.34 (0.02), 472	0.58 (0.04), 270	0.35 (0.02), 383	0.67 (0.06), 158	0.37 (0.02), 495	0.74 (0.06), 139	0.37 (0.02), 514	0.84 (0.10), 52	0.41 (0.02), 601
POMS: Negative affect (30–120)	62.89 (1.43), 180	51.58 (0.75), 470	59.69 (1.17), 269	51.20 (0.82), 381	61.11 (1.50), 156	52.70 (0.77), 494	63.72 (1.66), 137	52.31 (0.74), 513	64.42 (2.83), 52	53.87 (0.71), 598
POMS: Positive affect (30–120)	78.46 (1.08), 180	84.97 (0.63), 470	80.68 (0.87), 269	84.93 (0.71), 381	80.64 (1.12), 156	83.97 (0.64), 494	79.85 (1.26), 137	84.05 (0.62), 513	80.98 (2.08), 52	83.36 (0.58), 598
STAI: Trait anxiety (20–80)	41.81 (0.87), 180	35.33 (0.47), 468	39.70 (0.71), 269	35.31 (0.51), 379	40.85 (0.88), 156	35.96 (0.48), 492	42.25 (0.96), 137	35.76 (0.46), 511	43.67 (1.88), 52	36.56 (0.43), 596
Psychosocial stress										
PSS (0–56)	24.32 (0.73), 180	18.78 (0.40), 467	22.69 (0.59), 269	18.64 (0.45), 378	23.58 (0.70), 156	19.28 (0.42), 491	24.50 (0.82), 136	19.21 (0.39), 511	25.67 (1.38), 52	19.85 (0.37), 595
MPSS (0–51)	19.57 (1.96), 150	8.96 (0.78), 426	16.02 (1.42), 237	8.71 (0.88), 339	16.63 (1.84), 137	10.19 (0.86), 439	20.41 (2.13), 120	9.44 (0.80), 456	20.68 (4.12), 42	11.02 (0.79), 534
LES: Sum of negative life events	7.10 (0.63), 181	3.81 (0.23), 472	6.01 (0.46), 269	3.82 (0.26), 384	7.11 (0.66), 157	3.96 (0.24), 496	7.51 (0.74), 138	3.97 (0.24), 515	8.04 (1.09), 52	4.43 (0.25), 601
Pain coping										
CSQ-R: Distraction (0–6)	2.45 (0.11), 178	2.27 (0.07), 468	2.29 (0.09), 267	2.34 (0.08), 379	2.40 (0.12), 153	2.29 (0.07), 493	2.62 (0.13), 136	2.24 (0.07), 510	2.78 (0.20), 51	2.28 (0.06), 595
CSQ-R: Catastrophizing (0–6)	1.30 (0.09), 178	0.76 (0.05), 468	1.11 (0.07), 267	0.77 (0.05), 379	1.12 (0.09), 153	0.85 (0.05), 493	1.49 (0.12), 136	0.75 (0.04), 510	1.70 (0.20), 51	0.84 (0.04), 595
CSQ-R: Ignoring pain (0–6)	2.67 (0.11), 178	2.59 (0.07), 468	2.62 (0.09), 267	2.60 (0.08), 379	2.61 (0.13), 153	2.61 (0.07), 493	2.43 (0.11), 136	2.66 (0.07), 510	2.64 (0.21), 51	2.61 (0.06), 595
CSQ-R: Distancing (0–6)	1.29 (0.11), 178	1.03 (0.06), 468	1.25 (0.09), 267	0.99 (0.07), 379	1.16 (0.12), 153	1.08 (0.06), 493	1.37 (0.13), 136	1.03 (0.06), 510	1.46 (0.19), 51	1.07 (0.06), 595
CSQ-R: Coping statements (0–6)	3.80 (0.10), 178	3.55 (0.07), 468	3.73 (0.08), 267	3.54 (0.08), 379	3.62 (0.12), 153	3.62 (0.07), 493	3.66 (0.11), 136	3.61 (0.07), 510	4.02 (0.19), 51	3.58 (0.06), 595
CSQ-R: Praying and hoping (0–6)	2.27 (0.16), 178	2.19 (0.10), 468	2.29 (0.13), 267	2.15 (0.11), 379	2.02 (0.17), 153	2.27 (0.10), 493	2.64 (0.19), 136	2.10 (0.09), 510	2.64 (0.30), 51	2.17 (0.09), 595

Data are reported as mean (standard error), number of unweighted participants.
MPSS = Modified Posttraumatic Stress Disorder Symptom Scale; STAI = State-Trait Anxiety Inventory; CSQ-R = Coping Strategies Questionnaire-Revised.

Table 3 Univariate Associations of *z* Scores for Psychologic Measures and Individual COPCs, Adjusted for Study Site and Demographics

	TMD		Headache		IBS		LBP		Fibromyalgia	
Psychologic measure	OR (95% CL)	*P*	OR (95% CL)	*P*	OR (95% CL)	*P*	OR (95% CL)	*P*	OR (95% CL)	*P*
Somatic symptoms										
PILL score	2.30 (1.60, 3.32)	< .001	2.08 (1.57, 2.75)	< .001	1.82 (1.37, 2.43)	< .001	2.22 (1.61, 3.07)	< .001	4.41 (2.70, 7.22)	< .001
SCL-90-R: Somatization	3.15 (2.14, 4.63)	< .001	2.12 (1.38, 3.24)	.001	2.33 (1.70, 3.18)	< .001	4.13 (2.75, 6.22)	< .001	3.04 (1.98, 4.68)	< .001
Mood/affect										
SCL-90-R: Depression	1.80 (1.37, 2.38)	< .001	1.46 (1.13, 1.87)	.003	1.73 (1.34, 2.23)	< .001	1.76 (1.37, 2.27)	< .001	1.70 (1.31, 2.20)	< .001
POMS: Negative affect	1.53 (1.14, 2.04)	.004	1.45 (1.13, 1.85)	.003	1.43 (1.05, 1.94)	.023	1.69 (1.30, 2.20)	< .001	1.60 (0.98, 2.62)	.063
POMS: Positive affect (reverse scoring)	1.37 (0.91, 2.05)	.130	1.31 (1.06, 1.64)	.014	1.22 (0.96, 1.55)	.107	1.44 (1.12, 1.83)	.004	0.85 (0.51, 1.42)	.536
STAI: T rait anxiety	1.62 (1.24, 2.11)	< .001	1.51 (1.19, 1.91)	.001	1.70 (1.32, 2.18)	< .001	1.79 (1.39, 2.31)	< .001	1.86 (0.98, 3.52)	.057
Psychosocial stress										
PSS	1.61 (1.19, 2.17)	.002	1.58 (1.23, 2.04)	< .001	1.68 (1.25, 2.26)	.001	1.91 (1.44, 2.54)	< .001	1.72 (0.92, 3.21)	.091
MPSS	1.70 (1.21, 2.38)	.002	1.49 (1.16, 1.91)	.002	1.32 (1.05, 1.66)	.019	1.61 (1.23, 2.11)	.001	1.57 (1.20, 2.06)	.001
LES: Negative affect	1.53 (1.17, 2.01)	.002	1.26 (0.99, 1.60)	.063	1.52 (1.13, 2.05)	.006	1.57 (1.18, 2.10)	.002	1.81 (1.49, 2.21)	< .001
Pain coping										
CSQ-R: Distraction	1.50 (1.10, 2.05)	.010	0.99 (0.79, 1.25)	.959	1.11 (0.88, 1.41)	.379	1.38 (1.08, 1.76)	.010	2.07 (1.36, 3.16)	.001
CSQ-R: Catastrophizing	1.56 (1.11, 2.18)	.010	1.41 (1.10, 1.81)	.007	1.20 (0.93, 1.54)	.158	1.49 (1.18, 1.88)	.001	1.82 (1.22, 2.72)	.003
CSQ-R: Ignoring Pain	1.01 (0.77, 1.33)	.951	1.01 (0.79, 1.28)	.964	1.00 (0.78, 1.28)	.987	1.01 (0.77, 1.34)	.918	1.06 (0.72, 1.55)	.766
CSQ-R: Distancing	1.44 (1.08, 1.92)	.014	1.30 (1.03, 1.64)	.029	1.05 (0.81, 1.36)	.686	1.29 (0.97, 1.71)	.085	1.46 (1.01, 2.10)	.043
CSQ-R: Coping statements	1.04 (0.80, 1.35)	.767	1.00 (0.80, 1.24)	.971	1.02 (0.79, 1.30)	.904	1.13 (0.89, 1.44)	.318	1.53 (0.99, 2.35)	.056
CSQ-R: Praying and hoping	1.40 (1.03, 1.90)	.029	1.20 (0.94, 1.53)	.149	1.03 (0.81, 1.32)	.782	1.25 (0.94, 1.65)	.120	1.58 (1.08, 2.29)	.017

The odds ratio (OR) (adjusted for study site and demographics) reflects the extent to which the psychologic measure is associated with an increased likelihood of having a specific COPC vs not having that COPC. For example, every 1 standard deviation increase in PILL score was associated with a 2.3 times greater likelihood of being a TMD case vs a noncase.
PILL = Pennebaker Inventory of Limbic Languidness; SCL-90-R = Symptom Checklist 90-Revised; POMS = Profile of Mood States-Bipolar; STAI = State-Trait Anxiety Inventory; PSS = Perceived Stress Scale; MPSS = Modified Posttraumatic Stress Disorder Symptom Scale; LES = Life Experiences Survey; CSQ-R = Coping Strategies Questionnaire-Revised.

Univariate Association of Psychologic Variables with Individual COPCs. Descriptive statistics for all psychologic variables for cases and controls for each of the five COPCs are presented in Table 2. Univariate ORs depicting the association of each psychologic variable with case status for each of the COPCs (after controlling for age, race/ethnicity, sex, and study site) are presented in Table 3. Measures of somatic symptom burden (ie, PILL, SCL-90-R somatization subscale) were the strongest predictors of case status across all COPCs (ORs ranging from 1.82 to 4.41, all $P < .001$). Also, measures of negative mood and affect (eg, SCL-90-R depression, POMS negative affect, trait anxiety) were significantly associated with case status across all COPCs (ORs ranging from 1.43 to 1.86, all $P < .001$), as

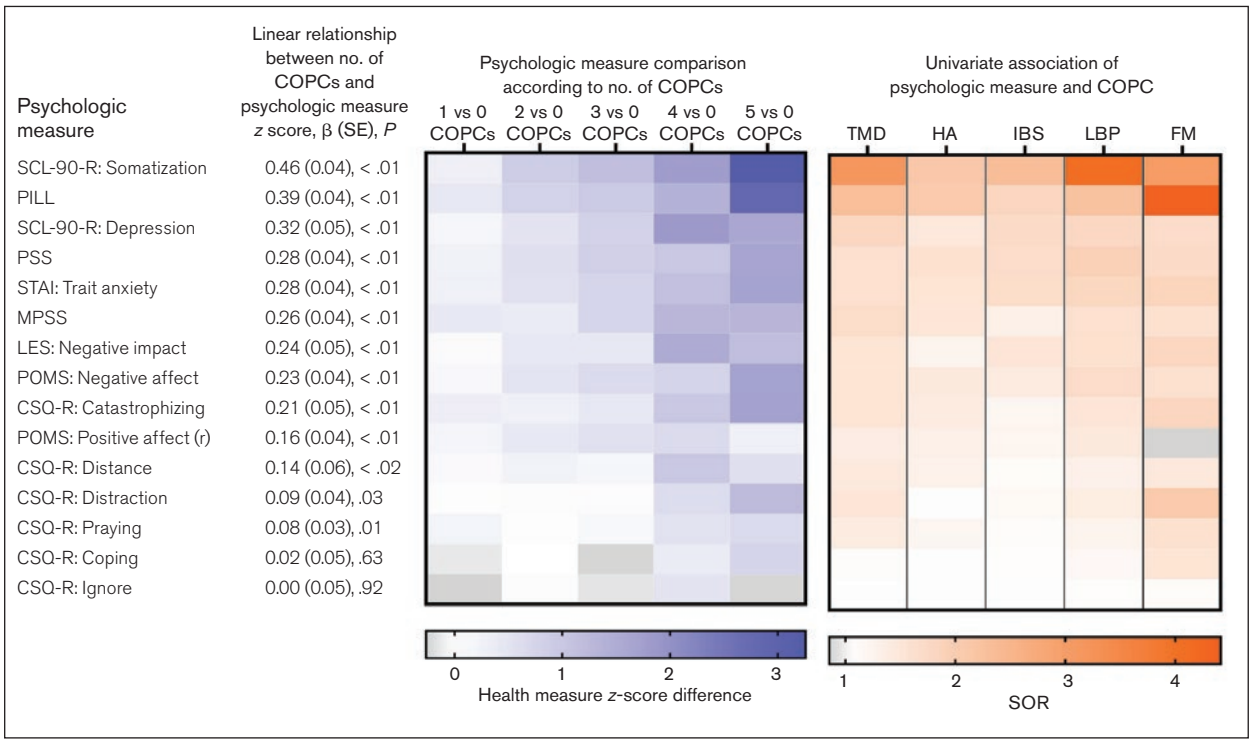

Fig 1 The blue heat map depicts psychologic measure *z*-score differences according to the number of COPCs, based on data presented in Appendix 1. For example, the first cell in the top row depicts the mean SCL-90-R somatization subscale *z*-score difference between groups with 1 COPC vs 0 COPCs. Rows are ordered in descending strength of association, as determined by beta coefficients (standard error), reported in Appendix 2. The orange heat map depicts standardized odds ratios (SORs), reported in Table 4, that quantify the strength of association between psychologic measures and each individual COPC. SCL-90-R = Symptom Checklist 90-Revised; PILL = Pennebaker Inventory of Limbic Languidness; PSS = Perceived Stress Scale; STAI = Stait-Trait Anxiety Inventory; MPSS = Modified Posttraumatic Stress Disorder Symptom Scale; LES = Life Experiences Survey; POMS = Profile of Mood States-Bipolar; (r) = reverse scoring (negative z scores used for standardized odds ratios represent increase in odds of being a case associated with reduction of 1 SD in the value of the variable); CSQ-R = Coping Strategies Questionnaire-Revised.

were measures of stress (PSS, PTSD symptoms, impact of negative events; ORs ranging from 1.26 to 1.91, all $P < .085$). Pain catastrophizing was significantly associated with all COPCs (ORs ranging from 1.41 to 1.82, all $P < .01$), except for IBS. Other scales from the CSQ-R were inconsistently and weakly associated with case status. Distraction, distancing, and praying were each associated with both TMD and fibromyalgia (ORs 1.40 to 2.07, $P < .043$). Distancing was also associated with LBP, and distraction with headache. Positive affect was protective against case status for headache and LBP. The overall pattern of these associations is depicted visually in Fig 1.

Multivariable Association of Psychologic Variables with Individual COPCs

The independent association of psychologic variables with individual COPCs was first tested using regression models that included all individual COPCs as predictors of each psychologic variable (Appendix 1; see all appendices in the online version of this article at www.quintpub.com/journals). These revealed that somatic symptoms were independently associated with all COPCs, and depression and perceived stress were independently associated with most COPCs. Other psychologic measures were not consistently independently associated with individual COPCs.

Next, random forest algorithms explored associations of all psychologic variables with each COPC. As shown in Fig 2, the strongest independent predictors of case status were measures of somatic symptoms (ie, PILL, SCL-90-R somatization subscale), with the strongest associations being observed for fibromyalgia, followed by TMD and LBP. Other psychologic variables showed weaker independent associations with some COPCs, including: SCL-90-R depression (for fibromyalgia, TMD, and LBP), perceived stress (headache), negative affect (all COPCs except fibromyalgia), trait anxiety (IBS), and pain catastrophizing (fibromyalgia and LBP). Indices of model fit are provided in Appendix 2.

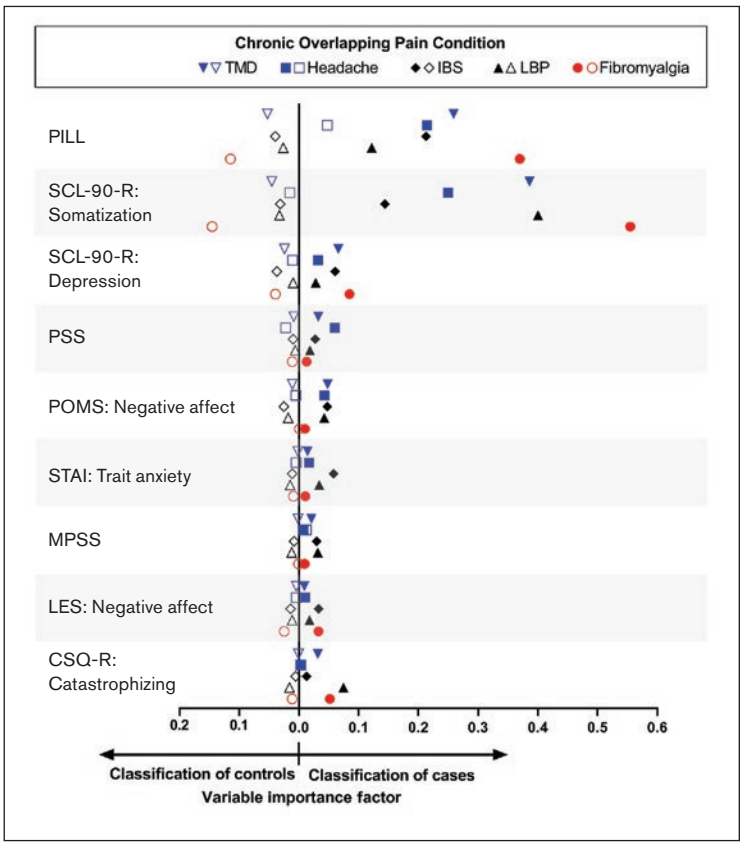

Fig 2 Multivariable contributions of psychologic measures to COPCs in the OPPERA-2 study (n = 655 participants). Random forest modeling explored multivariable contributions of all psychologic measures to each binary COPC case classification, with study site, age, gender, and race/ethnicity also included as covariates. Contributions of individual variables in the random forest models were quantified using variable importance scores, which estimate the relative contribution of each predictor to the model's classification of true positives and true negatives. Other health measures were included in the models, but are not plotted because their variable importance factors did not exceed 0.0004. Filled symbols = COPC cases; open symbols = controls; PILL = Pennebaker Inventory of Limbic Languidness; SCL-90-R = Symptom Checklist 90-Revised; PSS = Perceived Stress Scale; STAI = State-Trait Anxiety Inventory; MPSS = Modified Posttraumatic Stress Disorder Symptom Scale; LES = Life Experiences Survey; CSQ-R = Coping Strategies Questionnaire-Revised.

Univariate Association of Psychologic Variables with the Number of COPCs

Descriptive statistics for psychologic variables according to number of COPCs are presented in Table 4. Univariate analyses revealed an increasing strength of association with an increased number of COPCs for most psychologic measures relative to the reference group of individuals with 0 COPCs (ie, 0 vs 1; 0 vs 2, etc), with the exception of several CSQ subscales, where inconsistent differences emerged (Table 5). For example, the estimated mean difference in the SCL-90-R somatization subscale increased from 0.31 when comparing 1 vs 0 COPCs to 3.26 when comparing 5 vs 0 COPCs. Thus, compared to those with 0 COPCs, the mean difference in the somatization score was 10-fold greater for people with 5 COPCs than for people with 1 COPC. A generally similar, though less dramatic, pattern emerged for several other measures, including depression (SCL-90-R), perceived stress, negative affect, trait anxiety, and catastrophizing. These results are depicted visually as a heat map in Fig 2. Likewise, regression analyses testing for a linear effect of number of COPCs showed that most psychologic measures increased linearly with the number of COPCs, again with the exception of several CSQ subscales (Table 5). Examples of these linear associations for several psychologic measures are depicted in Fig 3. As observed for specific COPCs, the strongest associations emerged for measures of somatic symptoms, such that increasing numbers of COPCs were linearly associated with greater somatic symptoms. Positive affect decreased linearly with the number of COPCs. An overall summary of the findings is provided in Fig 3.

Discussion

In this study of psychologic characteristics in people with up to five COPCs, univariate findings generally indicate that psychologic functioning is similarly adversely affected across all COPCs. Specifically, all five COPCs were associated with higher somatic symptom burden, increased negative and decreased positive affect, greater psychologic stress, and higher pain catastrophizing. The magnitude of association of certain psychologic measures appeared somewhat more pronounced for some COPCs than for others. For example, somatic symptom burden was more strongly associated with fibromyalgia, TMD, and LBP than with headache and IBS. Also, the association of perceived stress with LBP was slightly greater than for the other COPCs. In multivariable

Table 4 Descriptive Statistics for Psychologic Variables by Number of COPCs

	No. of COPCs					
Psychologic measure	0	1	2	3	4	5
Somatic symptoms						
PILL score (54–270)	80.43 (1.24), 248	93.15 (1.58), 178	109.19 (2.20), 109	115.67 (2.83), 70	135.36 (5.05), 32	164.72 (10.25), 12
SCL-90-R: Somatization (0–4)	0.15 (0.01), 251	0.31 (0.02), 177	0.54 (0.04), 109	0.64 (0.05), 71	1.02 (0.10), 33	1.52 (0.21), 12
Mood/affect						
SCL-90-R: Depression (0–4)	0.26 (0.02), 251	0.39 (0.04), 177	0.55 (0.06), 109	0.70 (0.08), 71	1.02 (0.15), 33	1.17 (0.23), 12
POMS: Negative affect (30–120)	49.10 (0.99), 249	52.37 (1.19), 178	59.67 (1.70), 109	61.85 (2.14), 70	69.88 (3.64), 32	78.75 (5.62), 12
POMS: Positive affect (30–120)	86.10 (0.86), 249	84.40 (1.01), 178	79.68 (1.44), 109	78.06 (1.77), 70	77.23 (2.37), 32	81.42 (4.04), 12
STAI: Trait anxiety (20–80)	33.45 (0.59), 247	36.74 (0.78), 178	39.60 (1.07), 109	41.54 (1.37), 70	44.86 (2.11), 32	50.00 (2.96), 12
Psychosocial stress						
PSS (0–56)	17.23 (0.53), 247	19.79 (0.64), 177	22.44 (0.97), 109	24.43 (1.04), 70	27.18 (1.59), 32	30.42 (2.60), 12
MPSS (0–51)	6.65 (0.93), 225	11.29 (1.47), 161	14.01 (2.05), 93	16.98 (2.71), 60	27.88 (5.27), 26	35.42 (8.87), 11
LES: Sum of negative life events	2.96 (0.26), 252	4.11 (0.41), 177	6.00 (0.58), 109	6.94 (1.00), 70	11.03 (2.01), 33	8.75 (2.39), 12
Pain coping						
CSQ-R: Distraction (0–6)	2.30 (0.10), 248	2.28 (0.11), 177	2.14 (0.14), 109	2.27 (0.18), 69	3.03 (0.26), 32	3.33 (0.34), 11
CSQ-R: Catastrophizing (0–6)	0.63 (0.05), 248	0.86 (0.08), 177	1.05 (0.11), 109	1.14 (0.14), 69	1.78 (0.25), 32	2.64 (0.36), 11
CSQ-R: Ignoring pain (0–6)	2.65 (0.10), 248	2.47 (0.11), 177	2.80 (0.14), 109	2.60 (0.19), 69	2.68 (0.23), 32	2.02 (0.35), 11
CSQ-R: Distancing (0–6)	1.01 (0.09), 248	1.01 (0.11), 177	1.10 (0.13), 109	1.20 (0.18), 69	1.74 (0.32), 32	2.00 (0.32), 11
CSQ-R: Coping statements (0–6)	3.55 (0.10), 248	3.52 (0.11), 177	3.84 (0.13), 109	3.53 (0.17), 69	3.95 (0.23), 32	4.20 (0.34), 11
CSQ-R: Praying and hoping (0–6)	2.13 (0.14), 248	2.40 (0.16), 177	1.86 (0.19), 109	1.99 (0.26), 69	2.99 (0.40), 32	3.52 (0.56), 11

Data are reported as mean (standard error), number of unweighted participants. PILL = Pennebaker Inventory of Limbic Languidness; SCL-90-R = Symptom Checklist 90-Revised; PSS = Perceived Stress Scale; MPSS = Modified Posttraumatic Stress Disorder Symptom Scale; LES = Life Experiences Survey; CSQ-R = Coping Strategies Questionnaire-Revised.

regression analyses, all COPCs independently predicted somatic symptom burden, but only a subset of COPCs were independently associated with the other psychologic measures. For example, LBP, IBS, and TMD each showed independent associations with depression, and LBP and IBS were also related to perceived stress. LBP was independently associated with more psychologic variables than any other COPC. Random forest analyses that evaluated contributions of all psychologic factors also found that somatic symptoms were the strongest predictors of case status, particularly for fibromyalgia and TMD.

Regarding the count of COPCs, univariate analyses showed that most psychologic measures differed significantly when comparing individuals with no COPCs to those with one or more COPCs, and the magnitude of association generally increased incrementally with each additional COPC. Similarly, multiple psychologic variables were linearly related to the count of COPCs. Thus, in general, deterioration in psychologic functioning was proportionate to the number of COPCs experienced by an individual. This is consistent with prior research demonstrating that the presence of multiple pain conditions is associated with greater psychologic symptomatology.[52,53] The current findings extend these results to suggest that the presence of multiple COPCs increases the propensity for greater psychologic symptoms, with the increase in psychologic symptoms generally proportionate to the increased number of COPCs.

One conclusion based on this pattern of results is that similar psychologic processes appear to be associated with different COPCs. This is not particularly surprising given prior work examining the

Table 5 Estimates of Linear Associations and Pairwise Comparisons Between Number of COPCs and *z* Scores for Psychologic Measures, Adjusted for Study Site and Demographics

	Linear association	Estimated mean difference (SE), *P*				
Psychologic measure	β (SE), *P*	1 vs 0 COPCs	2 vs 0 COPCs	3 vs 0 COPCs	4 vs 0 COPCs	5 vs 0 COPCs
Somatic symptoms						
PILL score	0.39 (0.04), < .01	0.42 (0.10), < .01	0.78 (0.12), < .01	0.94 (0.14), < .01	1.39 (0.34), .01	2.82 (0.32), < .01
SCL-90-R: Somatization subscale	0.46 (0.04), < .01	0.31 (0.07), < .01	0.87 (0.11), < .01	1.15 (0.27), < .01	1.80 (0.16), .01	3.26 (0.36), < .01
Mood/affect						
SCL-90-R: Depression	0.32 (0.05), < .01	0.18 (0.12), .13	0.50 (0.12), < .01	0.81 (0.21), < .01	1.83 (0.50), < .01	1.57 (0.26), < .01
POMS: Negative affect	0.23 (0.04), < .01	0.12 (0.13), .32	0.47 (0.15), < .01	0.65 (0.15), < .01	0.74 (0.28), < .01	1.68 (0.30), < .01
POMS: Positive affect (reverse scoring)	0.16 (0.04), < .01	0.21 (0.14), .13	0.40 (0.15), < .01	0.54 (0.18), < .01	0.65 (0.16), < .01	0.28 (0.27), .28
STAI: Trait anxiety	0.28 (0.04), < .01	0.27 (0.12), .02	0.54 (0.15) , < .01	0.73 (0.15), < .01	1.13 (0.27), < .01	1.68 (0.19), < .01
Psychosocial stress						
PSS	0.28 (0.04), < .01	0.26 (0.13), .03	0.58 (0.14), < .01	0.85 (0.14), < .01	1.01 (0.21), < .01	1.63 (0.27), < .01
MPSS	0.26 (0.04), < .01	0.40 (0.14), < .01	0.38 (0.13), < .01	0.73 (0.17), < .01	1.28 (0.28), < .01	1.30 (0.35), < .01
LES: Sum of negative life events	0.24 (0.05), < .01	0.08 (0.13), .55	0.43 (0.17), .01	0.43 (0.22), .05	1.51 (0.36), < .01	1.14 (0.33), < .01
Pain coping						
CSQ-R: Distraction	0.09 (0.04), .03	0.01 (0.12), .95	0.03 (0.15), .84	0.05 (0.15), .74	0.64 (0.16), < .01	1.22 (0.26), < .01
CSQ-R: Catastrophizing	0.21 (0.05), < .01	0.32 (0.13), .01	0.28 (0.12), .01	0.41 (0.15), < .01	1.00 (0.51), .05	1.71 (0.32), < .01
CSQ-R: Ignoring pain	0.00 (0.05), .92	−0.27 (0.13), .03	0.04 (0.14), .80	−0.17 (0.17), .33	0.50 (0.40), .20	−0.26 (0.20), .19
CSQ-R: Distancing	0.14 (0.06), .02	0.11 (0.15), .45	0.24 (0.16), .13	0.17 (0.16), .29	1.00 (0.50), .04	0.55 (0.35), .11
CSQ-R: Coping statements	0.02 (0.05), .63	−0.15 (0.13), .24	0.00 (0.15), .98	−0.26 (0.17), .12	0.37 (0.31), .22	0.75 (0.26), < .01
CSQ-R: Praying and hoping	0.08 (0.03), .01	0.23 (0.11), .04	0.00 (0.10), .98	0.14 (0.16), .40	0.51 (0.16), < .01	0.68 (0.21), < .01

SE = standard error; PILL = Pennebaker Inventory of Limbic Languidness; SCL-90-R = Symptom Checklist 90-Revised; POMS = Profile of Mood States-Bipolar; STAI = State-Trait Anxiety Inventory; PSS = Perceived Stress Scale; MPSS = Modified Posttraumatic Stress Disorder Symptom Scale; LES = Life Experiences Survey; CSQ-R = Coping Strategies Questionnaire-Revised.

relationship between psychologic factors and individual COPCs.[9,54,55] However, this study is among the first to explore a broad array of psychologic variables within a single cohort in which multiple COPCs have been characterized. While the statistical models used did not specifically test whether the magnitude of association between psychologic measures and case status differed across COPCs, inspection of the ORs and means suggests that the strength of association was generally similar across COPCs, with some exceptions (eg, somatic symptoms were more strongly associated with TMD, fibromyalgia, and LBP than with IBS or headache).

While these findings show that multiple psychologic factors are associated with each individual COPC and with the number of COPCs, the strongest associations clearly emerged for measures of somatic symptom burden. This is consistent with prior findings related to TMD, in which a greater number of somatic symptoms was associated with chronic TMD[9] as well as with risk of new-onset TMD[18] more strongly than any other psychologic variable. Other investigators have also reported that somatic symptoms are strongly associated cross-sectionally with COPCs[56,57] and that somatic symptoms predict increased risk for development or persistence of COPCs, including widespread pain,[58] TMD,[59] LBP,[54,60] and abdominal pain.[61] Also, recent findings show an association of generalized sensory sensitivity with the number of comorbid pain conditions

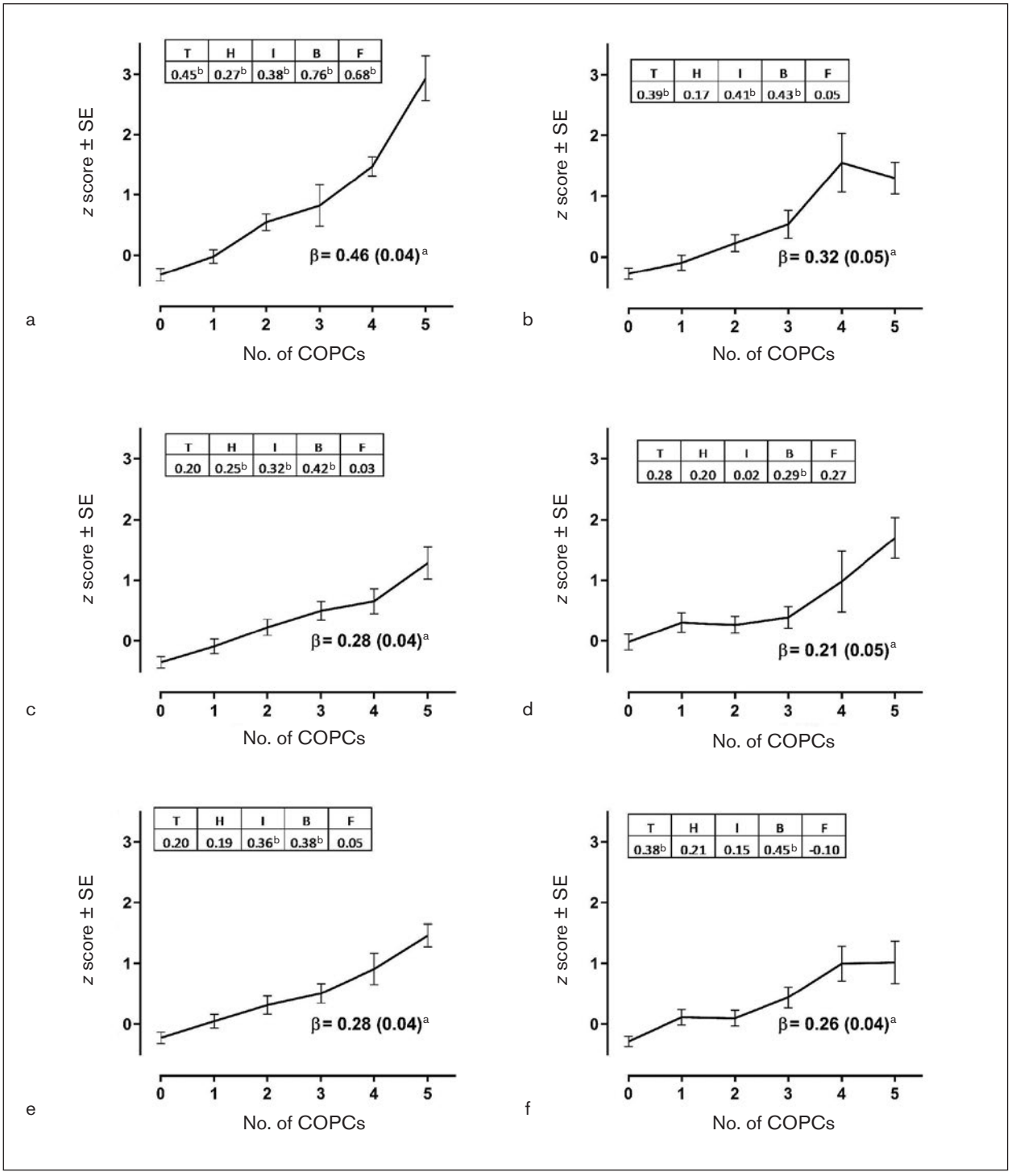

Fig 3 Relationships between number of COPCs and psychologic measures in OPPERA-2 (n = 655 participants). **(a)** SCL-90-R: Somatization. **(b)** SCL-90-R: Depression. **(c)** Perceived Stress Scale. **(d)** Coping Strategies Questionnaire-Revised: Catastrophizing. **(e)** State-Trait Anxiety Inventory: Trait anxiety. **(f)** Modified Posttraumatic Stress Disorder Symptom Scale. Each psychologic measure was the dependent variable in separate linear regression models that used weighted estimates from generalized estimating equations with robust error variance calculation. Each model was adjusted for study site, age, gender, and race/ethnicity. Each plot summarizes results from three linear regressions: *(1)* Plotted values are adjusted means of the *z*-transformed health measure ± standard error from models in which the number of COPCs was the categorical predictor variable. *(2)* The beta (b) estimate (standard error [SE]) represents the amount of change in the dependent variable associated with a one-unit increase in number of COPCs, modeled as a continuous variable. [a]*P* < .05 for the null hypothesis that b = 0. *(3)* In the micro-table, each COPC was modeled as a separate binary predictor in a multivariable linear regression model to show independent contributions of COPCs to each psychologic measure. Tabulated numbers are parameter estimates for COPCs denoted as T = temporomandibular disorders, H = headache, I = IBS, B = low back pain, and F = fibromyalgia. [b]*P* < .05 for the null hypothesis that parameter estimate for the dummy variable equals 0.

among individuals with pelvic pain.[53] Generalized sensory sensitivity was driven primarily by somatic symptoms, similar to the measures of somatic symptoms used here. One might argue that somatic symptoms should be considered physical rather than psychologic factors; however, as in the current study, somatic symptom burden as typically measured generally includes both a somatic component (eg, the symptom itself) and an evaluative appraisal component, in that the symptom is unpleasant or concerning. The mechanisms linking somatic symptoms with chronic pain conditions remain inadequately understood; however, excessive somatic symptoms likely emerge from perturbations of biologic pathways subserving somatic perception and cognitive-affective processes. For example, inducing systemic inflammation via endotoxemia produces somatic symptoms, increases anxiety, enhances pain sensitivity, and alters pain-related cerebral function.[62–64] Thus, the self-report measures of somatic symptom burden may reflect dysregulation of such peripheral and/or central processes, which could mediate their association with COPCs. Whether this putative dysregulation represents a cause or a consequence of the development of one or more COPCs cannot be determined by the present cross-sectional design.

In addition to somatic symptoms, measures of perceived stress and negative mood and affect were also associated with individual COPCs as well as with the number of COPCs for a given individual. These findings are consistent with considerable prior research that has linked stress and negative affect with different chronic pain conditions.[9,16,52,65–67] In addition, univariate associations emerged between pain catastrophizing and most of the COPCs, and catastrophizing increased with the number of COPCs, which parallels prior research linking pain catastrophizing with many different chronic pain conditions.[8,68] Notably, other measures of pain coping were not consistently associated with COPCs in this analysis.

The extent to which the multiple psychologic variables included in this analysis represent distinct vs overlapping constructs deserves consideration. In univariate analyses, most of the psychologic variables were significantly associated with each COPC; however, associations between COPCs and psychologic factors were fewer and less robust in the multivariable approach. Perhaps this should not be surprising, since there is a considerable amount of prior work suggesting significant intercorrelations among many of these variables; for example, somatic symptoms are associated with measures of negative mood, including anxiety and depression.[69–71] Similarly, pain catastrophizing shows significant correlations with both anxiety and depression,[72–74] as does perceived stress.[39,75] In a prior work by the authors, a factor analysis that included many of these measures revealed two major symptom components: *(1)* general psychologic symptoms, which included somatic symptoms and depression from the SCL-90-R; and *(2)* stress and negative affectivity, which included perceived stress, trait anxiety, and negative affect.[9] Two additional pain coping factors emerged, one for passive coping (pain catastrophizing, praying and hoping) and one for active coping (eg, distraction, coping statements). Thus, the multiple psychologic variables included in the current analysis are likely reducible to a smaller number of higher-order constructs, suggesting that these psychologic processes likely share underlying mechanisms, and these shared mechanisms may be relevant to multiple COPCs. One resulting implication is that psychologic interventions that address these shared underlying mechanisms may show clinical efficacy across COPCs. Indeed, cognitive behavioral treatment, the most commonly applied psychologic intervention for pain, has shown efficacy for all of the COPCs examined as part of this study.[19–24] Likewise, mindfulness meditation and acceptance-based therapies appear to be effective across these COPCs.[76–80]

While the present study focused on COPCs, for which there is no clear biomedical pathology, psychologic factors have also been associated with chronic pain in disease-related conditions. For example, patients with pain due to osteoarthritis and rheumatoid arthritis show higher levels of psychologic distress than individuals without such pain.[81–85] Moreover, cancer-related pain has been associated with psychologic factors, including psychosocial stress and higher levels of affective distress.[86–89] Thus, psychosocial functioning appears to be significantly related to the experience of chronic pain, whether that pain is disease-related or of unknown pathogenesis.

Because this study was cross-sectional, it was not possible to determine the direction of association between psychologic factors and COPCs. Indeed, previous research provides evidence for bidirectional relationships between pain and psychologic functioning. For example, the presence of chronic pain conditions is a risk factor for adverse psychologic outcomes, including stress, anxiety, and depression.[90–92] Moreover, multiple studies have demonstrated that psychologic symptoms represent premorbid risk factors for future development of COPCs.[14,18,93,94] In a recent long-term observational study, it was reported that psychologic symptoms changed in parallel with changes in TMD status.[95] Specifically, over a roughly 7-year period, individuals who transitioned from being TMD free to experiencing TMD showed significant increases in psychologic symptoms, while those who transitioned from having TMD to being TMD free showed significant decreases in such symptoms.

Taken together, existing evidence suggests that psychologic symptoms both predict and reflect the onset and remission of COPCs.

These findings should be interpreted in light of several study limitations. First, as noted above, the cross-sectional nature of this study prohibits causal inferences regarding the associations between psychologic factors and COPCs. Second, the convenience sample recruited for this study may not be representative of the general population. Third, while the sample was relatively large, the number of individuals with fibromyalgia and the number experiencing five COPCs were small, which limited the statistical power for comparisons involving these groups. Finally, while the authors had a large battery of psychologic measures, not all relevant psychologic factors could be measured. In particular, this battery included very few measures of psychologic resilience, which restricted the ability to address this important aspect of psychologic functioning.[96,97]

These limitations notwithstanding, individuals with each of the COPCs showed poorer psychologic functioning compared to pain-free individuals, and psychologic symptoms were generally linearly related to the number of COPCs an individual experienced. Both univariate and multivariable analyses demonstrated that measures of somatic symptom burden were the psychologic variables most strongly associated with COPCs. These findings further highlight the importance of considering psychologic functioning in the assessment and management of chronic pain conditions. Specifically, future prospective studies are needed to characterize the temporal unfolding of the relationships among COPCs and psychosocial functioning and to determine why multiple COPCs are associated with greater psychologic dysfunction. For example, does psychosocial adjustment to a single COPC predict risk for or resilience against the development of additional COPCs? Similarly, it would be interesting to know whether early psychologic intervention in patients with a single COPC could protect against the emergence of multiple COPCs. Alternatively, one might speculate that the increased organismic burden of multiple vs single COPCs is the primary driver of greater psychologic distress. These findings also have implications for clinical care pathways, as patients often experience compartmentalized care that addresses a single COPC at a time. It would likely be more effective to provide more integrative treatment that addresses higher-order biologic and psychosocial mechanisms contributing to multiple COPCs. Future research that further explicates the findings presented in this manuscript will advance both scientific understanding and clinical management of COPCs.

Acknowledgments

This work was supported by National Institutes of Health grants U01DE017018 (NIDCR) and UL1TR001427 (NCATS). The OPPERA program also acknowledges resources provided for this project by the participating institutions: Battelle Memorial Institute; University at Buffalo; University of Florida; University of Maryland; and University of North Carolina. Drs Fillingim and Maixner have equity ownership in Algynomics Inc. The authors have nothing else to disclose.

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Appendices

Appendix 1 Independent Contribution of Each COPC to Standardized Mean (Standard Error) of Psychologic Measure, Adjusted for Study Site and Demographics

Psychologic measure	TMD Est (SE), *P*	Headache Est (SE), *P*	IBS Est (SE), *P*	LBP Est (SE), *P*	Fibromyalgia Est (SE), *P*
Somatic symptoms					
PILL score	0.31 (0.22), .16	0.38 (0.10), < .01	0.34 (0.10), < .01	0.46 (0.17), < .01	0.65 (0.23), < .01
SCL-90-R: Somatization	0.45 (0.15), < .01	0.27 (0.09), < .01	0.38 (0.11), < .01	0.76 (0.15), < .01	0.68 (0.22), < .01
Mood/affect					
SCL-90-R: Depression	0.39 (0.17), .02	0.17 (0.13), .19	0.41 (0.14), < .01	0.43 (0.15), < .01	0.05 (0.22), .83
POMS: Negative affect	0.20 (0.15), .18	0.21 (0.12), .09	0.22 (0.14), .13	0.38 (0.13), < .01	−0.05 (0.25), .84
POMS: Positive affect (reverse scoring)	0.23 (0.20), .24	0.15 (0.11), .18	0.11 (0.12), .37	0.34 (0.13), .01	−0.53 (0.24), .02
STAI: Trait anxiety	0.20 (0.13), .11	0.19 (0.11), .09	0.36 (0.12), < .01	0.38 (0.13), < .01	0.05 (0.29), .85
Psychosocial stress					
PSS	0.20 (0.13), .13	0.25 (0.12), .04	0.32 (0.14), .02	0.42 (0.14), < .01	0.03 (0.25), .90
MPSS	0.38 (0.17), .03	0.21 (0.16), .19	0.16 (0.12), .21	0.45 (0.18), .01	−0.10 (0.21), .64
LES: Negative affect	0.20 (0.18), .27	0.05 (0.11), .61	0.31 (0.15), .03	0.32 (0.14), .03	0.33 (0.23), .16
Pain coping					
CSQ: Distraction	0.33 (0.19), .09	−0.12 (0.12), .33	0.00 (0.12), 1.00	0.11 (0.12), .36	0.48 (0.24), .05
CSQ: Catastrophizing	0.28 (0.23), .22	0.20 (0.16), .21	0.02 (0.13), .87	0.29 (0.13), .03	0.27 (0.37), .46
CSQ: Ignoring pain	−0.01 (0.14), .94	0.02 (0.12), .89	−0.01 (0.12), .96	0.03 (0.15), .83	0.00 (0.22), 1.00
CSQ: Distancing	0.35 (0.20), .09	0.20 (0.14), .16	−0.07 (0.13), .59	0.12 (0.20), .54	0.01 (0.32), .98
CSQ: Coping statements	−0.04 (0.14), .81	−0.02 (0.13), .89	−0.01 (0.13), .93	0.08 (0.13), .54	0.34 (0.22), .12
CSQ: Praying and hoping	0.26 (0.18), .16	0.08 (0.12), .52	−0.06 (0.12), .63	−0.03 (0.14), .81	0.19 (0.23), .42

Est = estimated mean difference; SE = standard error.

Appendix 2 Summary Measures of Model Fit for Random Forest Models

Metric	TMD	Headache	IBS	LBP	Fibromyalgia
Observed % of cases	0.278	0.412	0.241	0.212	0.079
Area under precision-recall curve	0.622	0.676	0.438	0.569	0.321
Area under receiver operator characteristic curve	0.815	0.769	0.723	0.785	0.830
Brier score	0.163	0.193	0.191	0.164	0.134
Mutual information index	0.113	0.074	0.034	0.071	0.045
Proportion of variance explained	0.218	0.170	0.129	0.177	0.213
Maximum variable importance factor: Predicting cases	0.386	0.249	0.213	0.400	0.555
Maximum variable importance factor: Predicting controls	0.008	0.047	0.006	0.008	0.003
Maximum variable importance factor: All	0.027	0.043	0.008	0.022	0.001