Psychological Factors Associated With Development of TMD: The OPPERA Prospective Cohort Study

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Abstract: Case-control studies have consistently associated psychological factors with chronic pain in general and with temporomandibular disorder (TMD) specifically. However, only a handful of prospective studies have explored whether preexisting psychological characteristics represent risk factors for first-onset TMD. The current findings derive from the prospective cohort study of the Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) cooperative agreement. For this study, 3,263 TMD-free participants completed a battery of psychological instruments assessing general psychological adjustment and personality, affective distress, psychosocial stress, somatic symptoms, and pain coping and catastrophizing. Study participants were then followed prospectively for an average of 2.8 years to ascertain cases of first-onset of TMD, and 2,737 provided follow-up data and were considered in the analyses of TMD onset. In bivariate and demographically adjusted analyses, several psychological variables predicted increased risk of first-onset TMD, including reported somatic symptoms, psychosocial stress, and affective distress. Principal component analysis of 26 psychological scores was used to identify latent constructs, revealing 4 components: stress and negative affectivity, global psychological and somatic symptoms, passive pain coping, and active pain coping. In multivariable analyses, global psychological and somatic symptoms emerged as the most robust risk factor for incident TMD. These findings provide evidence that measures of psychological functioning can predict first onset of TMD. Future analyses in the OPPERA cohort will determine whether these psychological factors interact with other variables to increase risk for TMD onset and persistence.

Perspective: This article reports that several premorbid psychological variables predict first-onset TMD in the OPPERA study, a large prospective cohort study designed to discover causal determinants of TMD pain. Measures of somatic symptoms were most strongly associated with TMD onset, but perceived stress, previous life events, and negative affect also predicted TMD incidence.

The association of psychological factors with clinical pain has been well documented. Numerous cross-sectional studies demonstrate that people with chronic pain conditions show greater levels of psychological distress, environmental stress, catastrophizing, and somatic symptoms compared with pain-free controls.[19,34,42] Temporomandibular disorder (TMD) represents a group of orofacial pain conditions that are highly prevalent in the population and are associated with considerable morbidity.[20,21,41] Similar to the above findings, in other chronic pain conditions, people with chronic TMD pain exhibit greater psychological maladjustment, on average, compared to healthy controls.[23,73] For example, in studies conducted in the United States and Europe, people with chronic TMD reported higher mean levels of affective distress, somatic awareness, psychosocial stress, and pain catastrophizing than pain-free individuals.[11,30,54,57,70] In other cross-sectional studies, personality characteristics, such as neuroticism, differed for chronic TMD cases versus controls.[29,66] Related findings are that psychological dysfunction is associated with greater severity and persistence of TMD-related clinical symptoms. For example, in cross-sectional studies, scores on measures of psychological distress were positively correlated with reported TMD pain and pain-related disability.[9,57,90] Further, in studies involving patients with existing TMD, psychological factors, such as somatic symptoms and depression, predict long-term persistence of TMD pain.[25,33,61]

Because the preceding associations were observed in studies of people with existing TMD, they do not establish whether psychological factors were premorbid risk factors for the development of TMD. In a precursor to the present study, Slade and colleagues[81] showed that several psychological factors associated with experimental pain sensitivity, including depression, perceived stress, and mood state, predicted new-onset TMD pain in a cohort of females followed over a 3-year period. Subsequently, Aggarwal et al[2] reported that baseline levels of health anxiety (ie, concern regarding bodily symptoms) predicted risk for development of chronic orofacial pain over the following 2-year period. More recently, depression and anxiety were found to predict new onset of TMD-related joint and muscle pain, respectively.[44] Thus, the limited available data from prospective studies implicate psychological variables as potential etiologic risk factors for TMD.

The Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) prospective cohort study endeavors to discover etiologic influences on TMD pain. Although previous research has identified multiple psychological variables that confer increased risk for development of chronic pain, few studies have incorporated a broad-based assessment of psychological functioning in order to identify risk factors for development of TMD. To overcome this potential limitation, OPPERA administered an extensive battery of psychological instruments to a cohort who did not have TMD when enrolled in the study. The goal was to assess psychological functioning, prior to onset of TMD, across several domains that previously were associated with chronic pain, including TMD. We recently reported psychological findings from the OPPERA baseline case-control study, in which a cohort of participants meeting diagnostic criteria for chronic TMD was compared to a control cohort composed of individuals who did not have TMD.[30,78] Chronic TMD cases reported higher levels of psychological symptoms, affective distress, somatic symptoms, and pain catastrophizing compared to TMD-free controls.

Below we present findings from the OPPERA prospective cohort study in which people who initially were found not to have TMD when examined were observed for up to 5.2 years in order to detect first-onset TMD. The primary aim of this study was to identify psychological characteristics at enrollment that were associated with development of first-onset TMD. A secondary aim of the study was to explore the extent to which psychological variables interact with demographic factors as well as with other psychological variables in predicting risk for TMD onset.

Methods

Institutional review boards at each study site approved study procedures and participants provided signed, informed consent. Full details of enrollment, follow-up, and statistical analyses are provided elsewhere in this issue[79] and are summarized here.

Recruitment, Eligibility Criteria, and Enrollment

This paper reports findings from the OPPERA prospective cohort study of 2,737 people who were enrolled in 2006 to 2008 and observed for up to 5.2 years in order to identify those who developed TMD. OPPERA used advertisements, e-mails, flyers, and word of mouth to recruit participants between May 2006 and November 2008 from communities in and around academic health centers at 4 U.S. study sites: Baltimore, MD; Buffalo, NY; Chapel Hill, NC; and Gainesville, FL. When they were enrolled, the sample of community-based volunteers at 4 study U.S. sites was aged 18 to 44 years and did not have painful TMD when examined using Research Diagnostic Criteria for TMD (RDC/TMD).[21] The average age of the sample was 27.1 years (SD = 7.8), and the sample was composed of 1,630 women (59.6%) and 1,448 non-Hispanic whites (52.9%), 766 African Americans (28%), and 523 (19.1%) participants from other ethnic/racial groups. At enrollment, study participants

also completed questionnaires, autonomic function and sensitivity to sensory stimuli were evaluated, and a blood sample was collected for genotyping. This paper focuses on contributions of baseline measurements of psychological functioning (ie, those recorded at enrollment) to subsequent risk of developing TMD. Additional methodological detail is available elsewhere in this issue.[79]

Psychological Instruments

In order to strike a balance between thoroughness and participant burden, the selection of psychological instruments for the OPPERA study was based on the following criteria: 1) we emphasized constructs identified in the previously proposed OPPERA heuristic model, including mood/affect, stress, somatic symptoms[16,56]; 2) we prioritized constructs previously associated with TMD in either case-control or prospective studies; and 3) we endeavored to include constructs assessing both general psychological function (eg, personality, psychological symptoms) and more specific pain-related constructs (eg, pain coping, somatic symptoms). The psychological questionnaires administered are described below. For all instruments, participants had the option to complete the questionnaire via paper form or electronic PDF version. Through self-selection, slightly more than one-third of participants (ranged from 36.2 to 39.5% depending on the questionnaire) completed the instruments on paper and just under two-thirds completed them electronically, and mode of administration had minimal effect on any of the reported outcomes. To distribute participant burden, most of the questionnaires were completed before the baseline clinic visit (preclinic), whereas state-based measures (the State Anxiety Inventory and the Profile of Mood States–Bipolar) were completed in-clinic immediately before the baseline clinical examination. Missing questionnaire items were imputed using the expectation-maximization (EM) algorithm as described previously.[30] In general, if a subject skipped at least 1 but less than half the items in a questionnaire, the missing items were imputed. If they failed to complete at least half of the items in the questionnaire, we treated their summary score as missing.

Global Measures of Psychological Function

Symptom Checklist 90–Revised (SCL 90R)

This 90-item instrument evaluates a broad range of psychological symptoms by having 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). The SCL 90R provides measures of psychological distress across the following 9 subscales: Somatization, Obsessive-Compulsive, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation, and Psychoticism.[16] Some evidence suggests a unitary factor structure for the SCL 90R,[24] whereas other findings indicate a multiple factor structure, overlapping to some

extent with the subscales originally reported by Derogatis.[65,77] Given this mixed evidence and consistent with the preponderance of studies using this instrument to investigate chronic pain, we chose to use the original scoring to optimize comparisons with existing literature. This instrument has demonstrated good internal consistency (Cronbach's alpha for subscales in our sample ranged from .78 to .88) and test-retest reliability, which ranged from .78 to .90.[15] The SCL 90R has been widely used in research with numerous pain conditions,[3,13,67,69,76] including TMD.[43,48,63,87]

Eysenck Personality Questionnaire–Revised (Short Form, EPQ-R)

This 57-item true-false instrument assesses 3 personality dimensions: Extraversion, Neuroticism, and Psychoticism. The EPQ-R also includes a Lie scale, which reflects an effort to present oneself in the most positive light. Factor analysis of the EPQ-R supports the 4 scales, and internal consistency of each of the scales is acceptable, with Cronbach's alpha in our sample ranging from .62 to .82, similar to that previously reported for the full scale.[28] Scales derived from the 57-item EPQ-R Short Form were found to correlate highly with scale scores from the original EPQ-R, with correlation coefficients ranging from .89 to .96.[27] Based on previous research in chronic pain populations,[7,14,38,85] including TMD,[45,46] our analyses focused on the Extraversion and Neuroticism scales.

Measures of Affective Distress

State-Trait Anxiety Inventory

The State-Trait Anxiety Inventory includes two 20-item questionnaires, the State Anxiety Inventory and the Trait Anxiety Inventory.[82] For each item, participants are asked to indicate either how they "generally feel" (trait anxiety) or how they "feel right now" (state anxiety) using a 4-category scale (not at all, somewhat, moderately so, extremely so). Test-retest reliability for the Trait Anxiety Scale has been adequate, ranging from .73 to .86 over intervals of 20 to 104 days.[82] As expected, State Anxiety is significantly less stable over time, given the transitory nature of anxiety states. In our sample, internal consistencies for both scales were high, with Cronbach's alphas of greater than .91.

The Profile of Mood States–Bipolar (POMS-Bi)

This instrument 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 4-category scale (much unlike this, slightly unlike this, slightly like this, much like this). This questionnaire assesses both positive and negative affective dimensions. It yields 6 subscale scores (Agreeable-Hostile, Elated-Depressed, Confident-Unsure, Energetic-Tired, Clearheaded-Confused, Composed-Anxious), as well as global indices of Positive Affect and Negative Affect, which were the focus of our analyses. Internal consistency in our sample was high

for both Positive Affect (.91) and Negative Affect (.94). The POMS has been well validated with other mood measures and is sensitive to subtle differences in affective state.[53]

Measures of Psychosocial Stress

The Perceived Stress Scale

This 10-item scale assesses the perception of stress, that is, the degree to which an individual appraises situations as stressful, and the extent to which an individual perceives himself or herself capable of coping with the situations.[12] For each item, participants indicate how often they felt or thought that way in the past month using a 5-category scale (never, almost never, sometimes, fairly often, very often). The Perceived Stress Scale yields a single overall perceived stress score by summing the numerical weights of each item, after reverse scoring 4 of the items. Internal consistency was good, with Cronbach's alpha of .86 in our sample, and construct validity has been demonstrated, as the Perceived Stress Scale correlates significantly with other measures of stress appraisal.[12]

The Life Experiences Survey (LES)

This 57-item instrument assesses the frequency of life events that have occurred over the past year, as well as the impact of these events.[75] Impact ratings range from −3 (extremely negative) to +3 (extremely positive), with 0 indicating "no impact." There are multiple approaches to scoring the LES, which generally yield measures of frequency of positive, negative, and total events as well as positive, negative, and total impact of events. The test-retest reliability of positive impact was reported as low (.10 and .53 across 2 samples), whereas reliabilities for negative and total impact were adequate, ranging from .56 to .88. Therefore, we report the number and impact of negative events. Cronbach's alpha for the number of negative events in our sample was .93. Previous research indicated that scoring of impact based on individualized weights (ie, each respondent's rating of impact) was the best predictor of psychological distress[91]; therefore, we report negative impact scores based on individualized weights in the included tables. For the LES, subjects who endorsed 40 or more items were excluded on the grounds that they likely misunderstood the instructions for the questionnaire. Others were excluded from LES scoring if their answers were inappropriate based on their gender. (For example, male respondents who reported a pregnancy in the previous year were discarded.)

The Lifetime Stressor List/PTSD Checklist–Civilian Version

The Lifetime Stressor List presents a checklist of 15 different traumatic events, and participants indicate which (if any) of these events they have experienced. For participants who endorse at least 1 item, they are then asked to identify the most significant stressor, and they complete the remaining 17-items regarding the extent to which they experience post-traumatic stress disorder (PTSD) symptoms (eg, repeated, disturbing memories of the experience) related to the selected traumatic event. Each item is endorsed on a 5-category scale (not at all, a little bit, moderately, quite a bit, extremely). A total score is derived by summing the scores from each of the 17 symptoms. Test-retest reliability is high (.96), and internal consistency has ranged from .89 to .92.[88] Internal consistency in our sample was .93. For participants who did not endorse any traumatic events, PTSD Checklist–Civilian Version scores were set to a minimum score of 17.

Measures of Somatic Symptoms and Reactivity

People with chronic pain often report multiple somatic symptoms across different bodily systems (eg, nausea, fatigue, dizziness), and varied terminology has been applied to this phenotypic domain, including somatization, hypochondriasis, hypervigilance, and somatic awareness.[30,31,59] These terms imply underlying cognitive or psychological processes that are not directly assessed in most instruments. Therefore, we use the term *somatic symptoms*, which we believe accurately reflects the construct assessed by the 2 primary measures included in the OPPERA study, the Pennebaker Inventory of Limbic Languidness (PILL) (described below) and the SCL 90R Somatization Scale (described above).

The PILL assesses the frequency with which individuals experience 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). A single summary score is derived by summing each of the individual item responses, and PILL scores are related to the construct of somatic awareness or the general tendency to endorse physical symptoms. High internal consistency (alpha = .88) and adequate test-retest reliability (.70 over 2 months)[68] have been reported. Internal consistency in our sample was .93. The PILL has been used as a measure of general somatic symptomatology in fibromyalgia patients, who demonstrated higher scores on the PILL compared to arthritis patients and pain-free controls.[59]

The Kohn Reactivity Scale[47] consists of 24 items that assess an individual's level of reactivity or central nervous system arousability to sensory stimuli. Individuals respond to each item on a 5-category scale ranging from "disagree strongly" to "agree strongly." The Kohn yields a single summary score created by summing all of the items after reverse scoring half of the items. This measure has been reported to have adequate internal consistency, ranging from alphas of .73 to .83 in previous studies[47] and .81 in our sample. The Kohn has been shown to correlate negatively with pain tolerance[17] and it has been used as a measure of the construct of hypervigilance.[59]

Measures of Coping/Catastrophizing

The Coping Strategies Questionnaire–Revised (CSQ-R)

The CSQ-R is a revised version of the original CSQ,[74] 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 numerical 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 showed adequate internal consistency, with Cronbach's alpha ranging from .82 to .92 in our sample. The CSQ-R has been shown to have stable factor structure in people with chronic pain[72] and in healthy populations.[36] Because the catastrophizing scale from the CSQ-R is identical to the Helplessness scale from the PCS (see below), the CSQ-R's catastrophizing scale was excluded from all analyses.

The Pain Catastrophizing Scale (PCS)

This instrument consists of 13 items rated on a 5-point scale ranging from 0 (not at all) to 4 (all the time). Participants indicate the degree to which they have specified thoughts and feelings when experiencing pain. The measure assesses 3 dimensions of catastrophizing—Rumination, Magnification, and Helplessness—and a total score is calculated by summing the 3 subscales. Internal consistency was very good, with coefficient alphas ranging from .74 to .91 across subscales in the current sample. The PCS has been validated for both clinical and nonclinical samples.[64,84] For nonclinical samples, respondents are asked to respond to the questionnaire based on their thoughts when they experience common pain events (eg, headache, toothache).

Follow-Up and Case-Classification of First-Onset TMD

At 3-month intervals after enrollment, study participants were asked to complete questionnaires that screened for TMD pain symptoms. Specifically, participants responded to questions about "headaches or pain in your face, jaw, temples, in front of the ear, or in the ear" (hereafter "orofacial pain") during the reporting period. Those reporting symptoms were contacted by the study site by telephone and/or e-mail and asked to return for an examination that determined presence or absence of painful TMD using the same RDC/TMD criteria. Specifically, to be classified as incident cases, study participants had to meet 2 criteria: 1) symptoms of orofacial pain reported for ≥5 days in the prior 30 days and 2) examiner findings of TMD myalgia, arthralgia, or both. Of the 3,263 participants enrolled into the inception cohort, 2,737 (84%) completed one or more quarterly follow-up questionnaires, with a median of 10 follow-up questionnaires over a median 2.8-year follow-up period. Additional details regarding follow-up rates are provided in Bair et al.[5]

Statistical Analysis

A multistage analytic approach was developed to identify psychological characteristics that predicted TMD onset and to determine which psychological variables interacted with demographic factors and with other psychological variables in predicting risk for TMD onset. As is common in epidemiologic studies of TMD,[1,46] the first stage of analysis examined univariate associations to test which individual psychological variables predicted TMD onset. This univariate approach provides information regarding which individual psychological measures are associated with risk for development of TMD and provides a basis for readers to compare findings across studies using the same variable. The limitation of this approach is that, not surprisingly, some of the individual variables are intercorrelated, and findings from the univariate approach should be interpreted with the knowledge that some of the associations are not independent.

The second stage of the analysis involved a series of multivariable Cox regression models in which the entered psychological variables were derived from a principal component analysis (PCA), which was performed in order to reduce the number of psychological variables by identifying putative latent constructs. The goal of Cox multivariable modeling was to assess independent contributions of each latent construct to TMD incidence. In this context, an "independent" contribution is one that is not confounded by the other latent constructs. Hazard ratios (HRs) for the associations were estimated in a single Cox regression model that included all latent constructs as predictor variables, together with study site and sociodemographic characteristics. First, all factors were entered into a multivariable Cox regression model simultaneously in order to identify the factors that independently predicted development of TMD. Second, interactions of each factor score with demographic variables in predicting TMD development were examined in Cox regression models. Third, all possible 2-way interactions between factor scores were examined in regression models. This more traditional multivariable approach allowed us to examine whether psychological variables, either alone or via interactions with other variables, predicted TMD onset.

The third stage of the analysis involved a different multivariable approach, random forest modeling, to analyze potential contributions of all measured psychological variables, not merely the reduced set of latent constructs. This novel method of data mining was used to achieve 2 goals: 1) to identify the most important risk factors for first-onset TMD and 2) to generate plots depicting adjusted association between each variable and TMD incidence, with adjustment for the effects of other variables and with latitude in generating the plots that permitted departure from a

straight-line association. Random forest modeling represents a machine learning technique based on a series of decision tree models.[40] Decision trees predict outcomes by recursively partitioning predictor variables, and these trees are superior to regression-based models in identifying nonlinear effects and handling missing data. Random forests improve the accuracy of individual decision trees by averaging over a series of decision trees. In recent years, random forests have been increasingly applied to classification problems in biomedical research, including predicting several pain-related outcomes.[39,71,89] The random forest model computed importance scores for each variable, representing the decrease in the predictive accuracy of the model when the variable is removed from the analysis. The most important variable was assigned a score of 100, and all other importance scores have lower values that could range to a negative value if the variable worsened prediction. The random forest model was used also to compute the expected rate of first-onset TMD that would be observed at several values of the variable after averaging over the values of all other variables in the model. Partial dependence plots were then generated and LOESS smoothing was used to help visualize the association.[52]

The 2 multivariable strategies were selected in favor of other approaches for several reasons. The first strategy builds on findings from our baseline case-control studies that identified meaningful latent constructs from among the multitude of psychological measures used in OPPERA.[30] The relatively small number of latent constructs meant that all 4 of them could be used in a single Cox regression model, thereby adjusting for potential confounding effects between constructs. This avoided arbitrary choices and potential bias that occur commonly when stepwise procedures and related variable selection methods are used to select a restricted set of potential confounders.[35] However, regression using principal component scores can mask effects on TMD incidence of single items that do not fit well within the latent constructs. Furthermore, it does not provide information about the relative importance of the variables that contribute to each score, and variable selection methods used to exclude variables from a large candidate set of predictors do not provide information about the excluded variables. Also, variable selection regression methods produce *P* values and confidence intervals that are unreliable.[1,35] Thus, a random forest model was used to address these shortcomings.[8,40] Random forests have other advantages compared to conventional linear regression models. For example, random forests can impute for missing data and handle large numbers of correlated predictor variables without decreasing the accuracy of the model.[37]

For descriptive purposes, the rate of first-onset TMD was calculated as the number of people with first-onset TMD divided by the sum of follow-up periods, and the result was expressed as the percentage of people per annum. To test hypotheses about associa-

tions between baseline characteristics and the TMD incidence rate, univariate HRs were first computed using Cox proportional hazard regression. For each variable, scores were transformed to unit-normal deviates (mean = 0, standard deviation [SD] = 1), which allows HRs to be compared meaningfully when original psychological scores were computed using different scales. HRs were computed with adjustment for study site and with additional adjustment for age, gender, race/ethnicity, and lifetime U.S. residence. Univariate HRs were also computed using multiple imputation to assess 2 sources of potential biases associated: 1) nonexamination of 243 people with symptoms (because of their unwillingness or inability to return to the study site for reexamination; see Bair et al[5] for further detail) and 2) a higher-than-expected rate of TMD classification for 1 examiner who conducted 75 examinations. Additional details regarding the multiple imputation approach are provided in Bair et al.[5] Briefly, the multiple imputation procedure used logistic regression to estimate the probability of examiner-verified TMD for all symptomatic episodes that were followed by an examination, excluding examinations conducted by the examiner in question. The parameters from this regression were then applied to symptomatic episodes that were not followed by an examination and to all episodes that were classified by the examiner in question, yielding a predicted probability of first-onset TMD for such episodes.

The variables included in the PCA were selected based on both our previous case-control findings and the OPPERA conceptual model.[30] For purposes of predicting first-onset TMD, we expanded the variables included in the PCA model in order to ensure that all important predictors were represented. All variables in Table 1 were included in the PCA, except for the 2 LES variables, which were excluded because of high rates of missingness. Consistent with our previous approach,[30] PCA models were fit using the R statistical computing platform. All variables were normalized to have mean 0 and SD 1 prior to fitting the models. Eigenvalues from the initial, unrotated solution were inspected using a scree plot. To help determine the optimal number of eigenvectors, a parallel analysis was performed to determine the number of components that exceeded what would be expected due to chance alone. Parallel analysis estimates the number of components to include in a PCA model by generating random data sets with the same numbers of observations and predictor variables as the original data.[86] The eigenvalues are computed for each random data set and averaged over all the data sets. When the average eigenvalue from these randomly generated data sets is larger than the corresponding eigenvalue of the original data, then the principal component associated with that eigenvalue is likely to be random noise (see Supplementary e-Figure 1). After calculating the PCA eigenvectors, a promax rotation was applied to increase the interpretability of the resulting PCA loadings. The promax rotation produced loadings that were easier to interpret than the loadings resulting from orthogonal

Table 1. Univariate Associations of Psychological Characteristics and Incidence Rate of First-Onset TMD: OPPERA Prospective Cohort Study, 2006–2011

Psychological Measure	Units and Potential Range	Distribution of Risk Factor at Enrollment			Site-Adjusted* TMD Incidence Rate (% of People per Annum) According to Tercile of Risk Factor			Standardized HRs (95% CI) Adjusted for			Imputed Estimates With Adjustment for Study Site + Demographics†		
		N	Mean (SD) [1st; 2nd Tercile]		Lower	Mid	Upper	Study Site‡	Study Site + Demographics§	P Value	N	HR (95% CI)	P Value¶
PILL Global Score	(1–270 scale)	2,597	88.8 (21.1) [77.0; 95.0]		2.43	2.56	6.17	1.52 (1.36, 1.68)	1.55 (1.39, 1.72)	<.001	2,733	1.44 (1.29, 1.60)	<.001
SCL 90R Depression	(0–4 scale)	2,693	.4 (.4) [.0; .3]		2.98	2.87	5.68	1.35 (1.23, 1.47)	1.35 (1.23, 1.46)	<.001	2,729	1.31 (1.19, 1.42)	<.001
SCL 90R Somatization Full	(0–4 scale)	2,699	.2 (.3) [.0; .2]		2.58	2.60	5.84	1.44 (1.32, 1.55)	1.42 (1.30, 1.53)	<.001	2,729	1.38 (1.27, 1.49)	<.001
SCL 90R Anxiety	(0–4 scale)	2,699	.2 (.3) [.0; .2]		–	–	–	1.33 (1.22, 1.43)	1.31 (1.20, 1.41)	<.001	2,729	1.29 (1.19, 1.39)	<.001
SCL 90R Obsessive-Compulsive	(0–4 scale)	2,705	.4 (.5) [.1; .5]		2.64	3.36	5.33	1.35 (1.23, 1.48)	1.36 (1.24, 1.49)	<.001	2,729	1.32 (1.20, 1.44)	<.001
SCL 90R Interpersonal Sensitivity	(0–4 scale)	2,703	.3 (.4) [.1; .3]		3.07	3.10	5.13	1.26 (1.14, 1.38)	1.28 (1.16, 1.40)	<.001	2,729	1.25 (1.14, 1.37)	<.001
SCL 90R Hostility	(0–4 scale)	2,719	.3 (.4) [.0; .1]		–	–	–	1.25 (1.14, 1.35)	1.25 (1.15, 1.36)	<.001	2,729	1.23 (1.13, 1.33)	<.001
SCL 90R Phobia	(0–4 scale)	2,702	.1 (.2) [.0; .0]		–	–	–	1.22 (1.14, 1.30)	1.22 (1.13, 1.30)	<.001	2,729	1.19 (1.11, 1.27)	<.001
SCL 90R Paranoid	(0–4 scale)	2,716	.3 (.4) [.0; .3]		–	–	–	1.32 (1.20, 1.43)	1.31 (1.19, 1.42)	<.001	2,729	1.28 (1.16, 1.39)	<.001
SCL 90R Psychotic	(0–4 scale)	2,704	.2 (.3) [.0; .1]		–	–	–	1.22 (1.12, 1.33)	1.21 (1.10, 1.31)	<.001	2,729	1.31 (1.19, 1.42)	<.001
PTSD Checklist for Civilians	(17–85 scale)	2,631	22.0 (9.8) [17.0; 19.0]		–	–	–	1.38 (1.25, 1.50)	1.34 (1.21, 1.46)	.000	2,669	1.34 (1.21, 1.46)	.000
EPQ-R Extraversion	(0–12 scale)	2,695	8.4 (3.2) [7.0; 11.0]		3.97	4.25	3.57	.97 (.85, 1.09)	1.00 (.88, 1.12)	.970	2,726	1.02 (.89, 1.15)	.790
EPQ-R Neuroticism	(0–12 scale)	2,704	4.2 (3.2) [2.0; 6.0]		3.00	3.26	5.18	1.28 (1.13, 1.43)	1.29 (1.14, 1.45)	<.001	2,726	1.24 (1.09, 1.39)	.001
Perceived Stress Scale	(0–40 scale)	2,690	14.4 (6.3) [11.0; 17.0]		2.65	3.05	5.43	1.34 (1.18, 1.51)	1.35 (1.19, 1.51)	<.001	2,734	1.31 (1.16, 1.48)	<.001
LES Number of Negative Events	(0–50 scale)	2,394	3.0 (3.2) [1.0; 3.0]		3.71	2.56	5.67	1.32 (1.19, 1.45)	1.30 (1.17, 1.43)	<.001			
LES Negative Impact	(0–150 scale)	2,394	5.4 (6.9) [2.0; 6.0]		3.23	3.09	5.93	1.30 (1.19, 1.41)	1.27 (1.16, 1.39)	<.001			
State Anxiety Inventory	(20–80 scale)	2,679	30.5 (9.3) [24.0; 33.0]		2.88	3.42	4.95	1.22 (1.09, 1.36)	1.23 (1.10, 1.37)	<.001	2,725	1.23 (1.09, 1.37)	<.001
Trait Anxiety Inventory	(20–80 scale)	2,674	35.2 (9.2) [30.0; 38.0]		2.30	3.44	5.53	1.40 (1.25, 1.57)	1.42 (1.26, 1.59)	<.001	2,733	1.35 (1.20, 1.51)	<.001
POMS-Bi Positive Affect	(30–120 scale)	2,604	87.5 (15.4) [82.0; 95.0]		5.11	3.30	3.23	.80 (.70, .89)	.80 (.71, .89)	<.001	2,720	.80 (.71, .90)	<.001
POMS-Bi Negative Affect	(30–120 scale)	2,645	49.2 (15.5) [39.0; 54.0]		3.08	3.51	4.89	1.24 (1.10, 1.38)	1.26 (1.12, 1.41)	<.001	2,720	1.22 (1.08, 1.36)	.001
PCS Helplessness	(0–24 scale)	2,716	3.3 (3.9) [1.0; 4.0]		3.78	3.53	4.31	1.11 (.99, 1.24)	1.10 (.98, 1.23)	.086	2,734	1.12 (1.00, 1.25)	.036
PCS Magnification	(0–12 scale)	2,727	1.8 (2.1) [.0; 2.0]		–	–	–	1.06 (.94, 1.19)	1.06 (.94, 1.18)	.340	2,734	1.09 (.97, 1.22)	.140
PCS Rumination	(0–16 scale)	2722	4.2 (3.9) [1.0; 5.0]		4.30	3.26	4.27	1.07 (.95, 1.20)	1.05 (.93, 1.18)	.390	2734	1.07 (.94, 1.20)	.270
CSQ Coping Statements	(0–6 scale)	2715	3.6 (1.3) [3.0; 4.2]		3.99	3.67	3.93	.98 (.86, 1.10)	1.00 (.88, 1.12)	1.000	2734	.98 (.86, 1.10)	.750
CSQ Reinterpreting Pain	(0–6 scale)	2727	1.2 (1.3) [.0; 1.5]		–	–	–	1.00 (.88, 1.13)	1.02 (.89, 1.15)	.810	2734	1.04 (.91, 1.17)	.550
CSQ Distraction	(0–6 scale)	2715	2.4 (1.5) [1.6; 3.0]		4.23	3.22	4.21	1.01 (.89, 1.13)	.99 (.87, 1.12)	.890	2734	1.01 (.88, 1.14)	.940
CSQ Ignoring Pain	(0–6 scale)	2714	2.6 (1.4) [2.0; 3.2]		4.36	3.46	3.98	.93 (.82, 1.05)	.96 (.84, 1.08)	.530	2734	.94 (.82, 1.06)	.300
CSQ Praying & Hoping	(0–6 scale)	2723	2.3 (2.0) [.6; 3.0]		3.69	3.62	4.34	1.07 (.94, 1.20)	.98 (.85, 1.11)	.720	2734	1.03 (.90, 1.18)	.630
Kohn Global Score	(24–120)	2643	71.5 (11.8) [67.0; 77.0]		3.38	3.73	4.61	1.15 (1.02, 1.30)	1.09 (.94, 1.24)	.240	2727	1.12 (.97, 1.28)	.120

*Adjusted rates computed using Poisson regression controlling for study site (categorical variable, 4 levels). Estimated rate is for reference study site (University at Buffalo).

†As for footnote §, with inclusion of imputed TMD rates for subjects who were not examined as intended.

‡HRs represent relative increase in incidence of TMD associated with an increase of 1 SD in risk factor. Computed using Cox proportional hazard regression model controlling for study site (categorical variable, 4 levels) controlling for study site (categorical variable, 4 levels).

§As for footnote ‡, with additional adjustment for age (in years as a continuous variable), gender (categorical, 2 levels), race/ethnicity (categorical, 5 levels) and lifetime U.S. residence (categorical, 3 levels).

¶P value evaluating null hypothesis that the HR equals 1.

Table 2. Component Loadings for PCA Model: OPPERA Prospective Cohort Study, 2006–2011

	COMPONENT 1	COMPONENT 2	COMPONENT 3	COMPONENT 4
Kohn Global Score	−.16	.23	.48*	−.28
PILL Global Score	.42*	.06	.11	.07
POMS-Bi Positive Affect	.15	−.89*	.09	.05
POMS-Bi Negative Affect	.21	.64*	−.05	.07
Perceived Stress Scale	.08	.72*	.08	.01
SCL 90R Depression	.75*	.22	.01	−.01
SCL 90R Somatization	.79*	.03	.02	.03
SCL 90R Anxiety	.92*	−.01	−.01	−.03
SCL 90R Obsessive Compulsive	.80*	.11	−.03	.06
SCL 90R Hostility	.82*	−.01	−.03	−.04
SCL 90R Phobia	.85*	−.13	.02	−.06
SCL 90R Paranoid	.82*	−.03	.02	.03
SCL 90R Psychotic	.86*	−.01	.02	.00
CSQ Distraction	−.16	.01	.35	.65*
CSQ Ignoring Pain	.06	.02	−.33	.81*
CSQ Distancing	−.03	.12	.03	.72*
CSQ Coping	.04	−.10	−.01	.80*
CSQ Praying	−.10	−.08	.57*	.27
State Anxiety Inventory	.08	.81*	−.09	.00
Trait Anxiety Inventory	.12	.78*	.05	.01
PCS Rumination	.01	−.06	.89*	−.07
PCS Magnification	.06	−.01	.79*	.01
PCS Helplessness	.06	.01	.84*	−.06
EPQ-R Extraversion	.14	−.56*	.11	−.03
EPQ-R Neuroticism	.11	.56*	.19	−.01
PTSD Checklist for Civilians	.57*	−.06	.18	−.01
Cumulative Variance	.25	.40	.51	.60

*Numbers reflect the highest loading for each variable.

rotations, and other nonorthogonal rotations produced similar results. The rotated loadings are presented unless otherwise noted.

Results

During the follow-up period, 721 orofacial symptom episodes were reported, 478 (66%) of which resulted in RDC examinations. These examinations classified 235 participants as TMD onset cases. In addition, 338 participants who did not report orofacial symptom episodes were selected at random for examination, and 25 of these examinations (7%) were classified with TMD onset. Thus, a total of 260 examiner-verified cases of TMD onset were ascertained (see Bair et al[5] for further detail).

Univariate Findings

Measures of Global Psychological and Somatic Function, Stress, and Mood (See Table 1)

Among the psychological characteristics reported in Table 1, the highest HR for predicting TMD onset emerged for the PILL (imputed HR = 1.55), a measure of somatic symptoms. The effect was statistically significant, as demonstrated by the associated 95% confi-

dence interval (1.33 to 1.66) that excluded the null of 1. Also, greater scores on all SCL 90R subscales were associated with increased incidence of TMD, with HRs ranging from 1.22 (for the Phobia and Paranoid scales) to 1.44 for the Somatization scale. For both the PILL and SCL 90R scales, the rate of TMD was highest for people in the upper tercile of the scales' distributions, whereas the lower- and mid-terciles differed to a smaller degree.

A greater degree of PTSD symptoms, as measured by the PTSD Checklist for Civilians, was associated with statistically significantly greater TMD incidence (HR = 1.38). Regarding personality as measured by the EPQ-R, neuroticism was associated with increased rates of TMD onset, with an HR of 1.28, whereas extraversion was not associated with statistically significant variation in TMD incidence. Higher scores on the Perceived Stress Scale predicted increased incidence of TMD (HR = 1.34), and a greater number (HR = 1.30) and impact (HR = 1.27) of negative events reported on the LES predicted increased rates of TMD onset. Both trait and state anxiety were associated with increased incidence of TMD, with HRs of 1.4 and 1.22, respectively. Negative affect (HR = 1.24) and positive affect (HR = .8), measured with the POMS-Bi, were associated with increased and decreased rates of TMD onset, respectively. Across most measures, HRs and their 95% confidence intervals were only slightly lower when using imputed versus nonimputed data.

Measures of Active and Passive Coping and Reactivity (See Table 1)

None of the subscales of the Pain Catastrophizing Scale (Rumination, Magnification, Helplessness) predicted TMD onset to a statistically significant degree, although the Helplessness scale was weakly significant when using imputed data (HR = 1.12). Likewise, no subscales from the Coping Strategies Questionnaire were statistically significant predictors of TMD incidence. The Kohn Reactivity Scale also was not a significant predictor of TMD onset.

PCA

As in our original PCA,[30] a 4-component solution emerged based on the scree plot and parallel analysis (see Supplementary e-Figure 1). The loadings for the PCA model are shown in Table 2. The 4 components, which are consistent with our previous PCA, are labeled as follows: 1) Global Psychological and Somatic Symptoms (high loadings from all SCL 90R scales, the PILL, and the Lifetime Stressor List/PTSD Checklist–Civilian Version PTSD symptom scale); 2) Stress and Negative Affectivity (high loadings from both State and Trait Anxiety, Perceived Stress, POMS Negative Affect, and EPQ-R Neuroticism; negative loadings for POMS Positive Affect and EPQ-R Extraversion); 3) Passive Pain Coping (positive loading from all 3 PCS subscales, the Praying and Hoping subscale of the CSQ-R, and the Kohn score); and 4) Active Pain Coping (positive loadings from the

Table 3. Demographically Stratified Associations of Principal Component Scores and Incidence Rate of First-Onset TMD: OPPERA Prospective Cohort Study, 2006–2011

	STRESS AND NEGATIVE AFFECTIVITY	GLOBAL PSYCHOLOGICAL SYMPTOMS	ACTIVE PAIN COPING	PASSIVE PAIN COPING
STRATUM	*Stratum-Specific HR (95% CI) Relating QST Principal Component to Rate of First-Onset TMD**			
Age				
18–24 years	1.33 (1.11, 1.60)	1.45 (1.26, 1.67)	1.04 (.83, 1.29)	1.01 (.82, 1.25)
25–34 years	1.66 (1.34, 2.06)	1.65 (1.42, 1.92)	1.26 (1.02, 1.56)	.86 (.69, 1.08)
35–44 years	1.16 (.93, 1.45)	1.23 (1.04, 1.44)	1.08 (.88, 1.33)	1.12 (.92, 1.37)
Interaction *P* value†	.070	.030	.374	.224
Gender				
Female	1.42 (1.22, 1.64)	1.39 (1.26, 1.54)	1.10 (.94, 1.27)	1.08 (.93, 1.26)
Male	1.27 (1.05, 1.55)	1.45 (1.23, 1.71)	1.17 (.95, 1.44)	.87 (.71, 1.07)
Interaction *P* value	.383	.706	.593	.105
Race/ethnicity				
White	1.77 (.95, 3.32)	1.51 (.99, 2.30)	1.30 (.71, 2.37)	.60 (.30, 1.20)
Black/African American	1.20 (.97, 1.48)	1.27 (1.11, 1.45)	1.11 (.93, 1.33)	1.10 (.92, 1.32)
Asian	1.66 (1.02, 2.73)	2.02 (1.24, 3.30)	.85 (.50, 1.47)	1.00 (.61, 1.65)
Hispanic	1.37 (.68, 2.77)	1.96 (.94, 4.11)	1.31 (.56, 3.09)	.75 (.35, 1.60)
Other	1.41 (1.21, 1.65)	1.54 (1.36, 1.75)	1.15 (.95, 1.39)	.96 (.80, 1.16)
Interaction *P* value	.568	.135	.845	.422
Lifetime U.S. residency				
Yes	1.99 (1.32, 2.98)	2.28 (1.65, 3.14)	.97 (.62, 1.53)	.74 (.47, 1.15)
No/not stated	1.32 (1.16, 1.49)	1.37 (1.25, 1.51)	1.13 (1.00, 1.29)	1.03 (.90, 1.17)
Interaction *P* value	.057	.003	.522	.160

*Multivariable proportional hazards models of time-to-event for first-onset TMD for n = 2,737 people in the OPPERA inception cohort. Separate models for each principal component that includes interaction between stratum variable and principal component. Other covariates in each model are the remaining stratification variables.
†*P* value is from Wald chi-square test (2 degrees of freedom) of interaction term in the multivariable model, evaluating null hypothesis that stratum-specific HRs are equivalent.

remaining CSQ-R subscales). These 4 components were used in further univariate and multivariable analyses presented below.

Univariate Analyses of PCA Components as Predictors of First-Onset TMD

In univariate analyses of single PCA scores, high levels of Global Psychological and Somatic Symptoms (imputed HR = 1.37) and Stress and Negative Affectivity (imputed HR = 1.31) predicted increased TMD incidence in both the unimputed and imputed analyses, whereas Passive Pain Coping was a weaker, though statistically signifi-

cant, predictor of TMD incidence (imputed HR = 1.16; see Supplementary e-Table 1 for detailed information).

Table 3 presents the outcomes of analyses examining PCA components as predictors of TMD onset, stratified separately by age, gender, and race/ethnicity. In general, PCA components did not interact with demographic factors in predicting TMD onset, such that HRs were similar across age groups, gender, and race/ethnicity. However, Global Psychological and Somatic Symptoms was the exception, showing a modest interaction with age group (*P* = .03), such that this component was a stronger predictor of TMD incidence in the 2 younger age groups compared to the 35- to 44-year-old group.

Table 4. Multivariable Associations of Principal Component Scores and Incidence Rate of First-Onset TMD: OPPERA Prospective Cohort Study, 2006–2011

	SITE- AND DEMOGRAPHICALLY ADJUSTED*		MULTIPLY IMPUTED, SITE- AND DEMOGRAPHICALLY ADJUSTED†	
PRINCIPAL COMPONENT	HR (95% CI)	P VALUE	HR (95% CI)	P VALUE
Stress and Negative Affectivity	1.17 (1.01, 1.35)	.040	1.12 (.97, 1.30)	.1333
Global Psychological Symptoms	1.37 (1.22, 1.55)	<.001	1.33 (1.18, 1.50)	<.001
Passive Pain Coping	.89 (.77, 1.02)	.096	.96 (.83, 1.11)	.5698
Active Pain Coping	.97 (.86, 1.10)	.659	.95 (.84, 1.08)	.4285

*Multivariable proportional hazards models of time-to-event for first-onset TMD for n = 2,737 people in the OPPERA inception cohort. Covariates are all principal components shown here as well as study site (3 dummy variables), age (continuous variable), gender (1 dummy variable), country of birth (4 dummy variables), and lifetime U.S. residency (2 dummy variables).
†As for footnote * with additional imputation for subjects who were not examined as intended.

Multivariable Analyses of PCA Components as Predictors of First-Onset TMD

In fully adjusted models (ie, including study site and demographic factors) that examined main effects of multiple PCA components predicting TMD incidence after controlling for the other components, Global Psychological and Somatic Symptoms remained the only strong predictor (imputed HR = 1.33, Table 4). The Stress and Negative Affectivity component was a weakly significant predictor in the unimputed analysis but did not significantly predict TMD onset in the analysis using imputed data (HR = 1.12).

The next multivariable analyses examined the 2-way interactions among PCA components. The findings indicated that Global Psychological and Somatic Symptoms interacted with each of the other components in predicting TMD onset (all P's < .01). The pattern of findings was similar for all factors. Specifically, when Psychological and Somatic Symptom scores were low, the other components significantly predicted TMD onset. This pattern of results is depicted for Global Psychological and Somatic Symptoms and Stress and Negative Affectivity. After controlling for study site and demographic factors, the 2-way interaction was statistically significant (P = .004; see imputed model in Supplementary e-Table 2). As shown in Fig 1, the interaction indicated that Stress and Negative Affectivity significantly predicted TMD onset when Global Psychological and Somatic Symptoms were low (HR for Stress and Negative Affectivity = 1.30), but not when Global Psychological and Somatic Symptoms were moderate or high (HR for Stress and Negative Affectivity = .96).

Using the second multivariable approach of random forest models, the PILL emerged as the most important predictor of TMD incidence, based on its variable importance score (VIS) of 100. The second most important predictor, the Perceived Stress Scale, contributed much less to the predictive accuracy of the model (VIS = 14.3), as did the SCL 90R Anxiety (VIS = 8.9) and Obsessive-Compulsive (VIS = 7.5) scores, the CSQ Ignoring Pain score (VIS = 5.2), the State Anxiety Inventory (VIS = 5.0), the SCL 90R Somatization Scale (VIS = 4.8), and the LES Sum of Negative Events score (VIS = 3.1).

Three partial dependence plots from the random forest model were selected to illustrate effects from different constructs showing relatively high variable importance scores (see Fig 2). These variables were chosen for presentation from among the variables with the highest variable importance scores to illustrate different nonlinear patterns and to present examples of findings from multiple psychological domains. Different ranges for the y-axis scales were used to illustrate the full degree of variation in TMD incidence across variables that differed in importance. For PILL scores, the predicted TMD incidence remained at a constant low level below a score of approximately 95, at which time there was a linear increase in risk up to a score of approximately 140, at which time further increases in PILL scores did not confer additional risk. In contrast, for Perceived Stress Scores, a somewhat U-shaped function emerged, such that risk of TMD
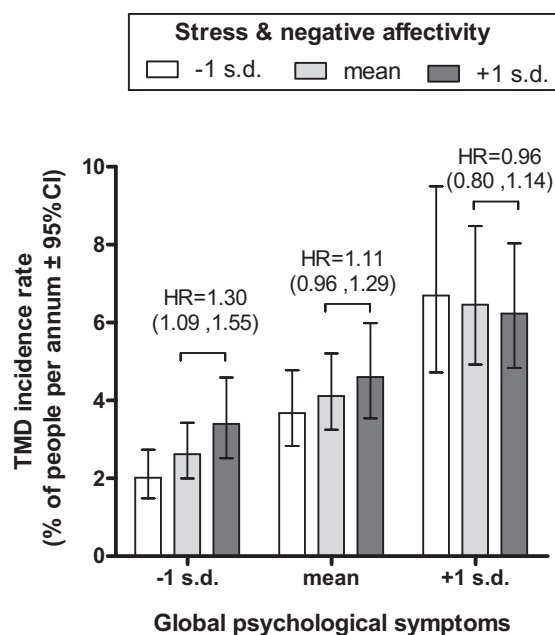

Figure 1. Imputed TMD incidence rates and HRs for stress and negative affectivity for 3 levels of Global Psychological and Somatic Symptoms. Each vertical bar depicts the TMD incidence rate for participants in the bottom (open bar), middle (light gray bar), and upper (dark gray bar) terciles of Stress & Negative Affectivity scores at each tercile (from left to right) of Global Psychological and Somatic Symptoms scores. Incidence rates of first-onset TMD were computed using multivariable Poisson regression models with multiple imputation to account for subjects who were not examined as intended. Covariates were study site (categorical variable, 4 levels), age (in years, with rates estimated for 3 selected age groups: 20, 30, and 40 years), race/ethnicity (5 categories: rates not shown for "other/unknown" race category) and lifetime U.S. residence (2 categories), Global Psychological and Somatic Symptoms principal component, Stress and Negative Affectivity principal component, and the interaction of the 2 principal components. For the interaction, P = .0004. HRs represent the effect of 1 SD increase in the stress and negative affectivity on TMD incidence. They were calculated using multivariable Cox regression models with the same covariates described for the Poisson models.

onset was slightly higher at a score of zero than at a score of 15, above which the risk of TMD onset increased in linear fashion through the remainder of the scale range. For the CSQ Ignoring Pain Sensations scale, TMD incidence was greatest at a score of 0 and decreased in linear fashion until a score of approximately 2, beyond which incidence increased slightly.

Discussion

These findings identify several psychological variables that represent premorbid risk factors for first onset of TMD. Based on univariate analyses, psychological variables that predicted TMD incidence include measures of somatic symptoms, general psychological symptoms, negative mood, and multiple measures of stress, including PTSD symptoms, perceived stress, and recalled life events. Measures of catastrophizing and active pain coping, well-established constructs associated with chronic pain, were not significant predictors of TMD
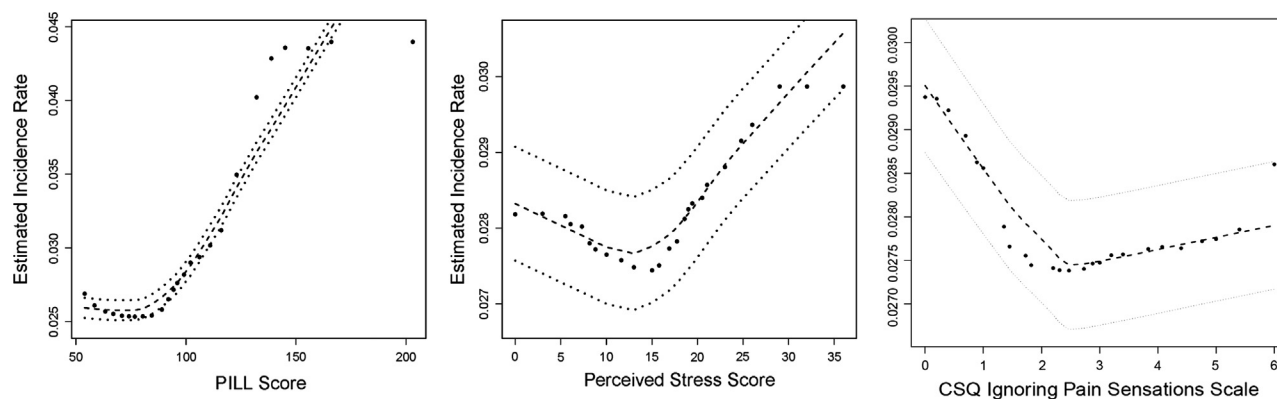
Figure 2. Partial dependence plots for the PILL, the Perceived Stress Scale, and the Coping Strategies Questionnaire (CSQ) Ignoring Pain Sensations scale. The plots depict the estimated TMD incidence rate that would be observed at several values of the variable after averaging over the values of all other variables in the model. TMD incidence rates, expressed as cases per 100 person-years, were generated from random forest models that predicted TMD onset using study site, demographic variables, and psychosocial variables presented in Table 1. Predicted values (●) are plotted together with LOESS-smoothed estimates (- - -) and their 95% confidence intervals (⋯⋯). Note that the *y*-axis scales vary across the 3 figures.

first onset. The largest HRs emerged for measures of somatic symptoms. These findings are consistent with the recently reported outcomes from our OPPERA case-control study, in which measures of somatic symptoms were the psychological variables that differed most markedly between TMD cases and TMD-free controls,[30] whereas measures of negative mood and stress showed more modest, albeit significant, associations with chronic TMD in that study. The generally consistent findings of the prospective and case-control studies are notable, because the designs differ in at least 2 important dimensions. First, the case-control study recruited chronic TMD cases, whereas the first-onset TMD cases captured by the prospective study exhibit more acute symptoms by definition. The findings of generally similar psychological risk factors for chronic TMD and first-onset, typically acute, TMD suggest that these psychological factors are associated with both onset and chronicity of TMD. Second, the case-control study ascertained case status and psychological function concurrently, whereas in the prospective study psychological assessment was completed months or years before case classification. This implies that the influence of these psychological factors extends over a long time period.

The prospective nature of the OPPERA study identifies these psychological factors as predisposing risk factors for the development of TMD pain. Few previous studies investigating psychological factors related to TMD have employed a prospective design. Members of this research group reported that premorbid measures of depression, perceived stress, and mood state obtained at baseline were significant predictors of new-onset TMD in a sample of healthy young females.[81] Also, Aggarwal and colleagues[2] showed that health anxiety predicted future development of chronic orofacial pain in adults and that depression, somatization, and life satisfaction predicted TMD onset in adolescents.[18,49] Additional studies implicate psychological variables as premorbid risk factors for development of other chronic pain conditions, including chronic widespread pain,[58]

regional musculoskeletal pain,[60] and low back pain.[50,51,60]

As in our previous report,[30] PCA revealed that our psychological instruments assessed 4 psychological domains, Global Psychological and Somatic Symptoms, Stress and Negative Affectivity, Passive Coping, and Active Coping. Not surprisingly, the Global Psychological and Somatic Symptoms component, on which measures of somatic symptoms loaded, was the strongest predictor of TMD onset. In univariate analyses, Stress and Negative Affectivity also predicted incident TMD; however, this association became weak or nonsignificant in multivariable analyses that adjusted for the other principal components. Interestingly, in individuals with moderate to high Global Psychological and Somatic Symptoms, Stress and Negative Affectivity did not significantly predict TMD onset; however, when Global Psychological and Somatic Symptoms were low, Stress and Negative Affectivity significantly predicted TMD incidence. This suggests that Stress and Negative Affectivity does not additively contribute to TMD risk over and above Global Psychological and Somatic Symptoms; rather, in the absence of global symptomatology, stress/negative affect emerges as a potentially important risk factor. This interaction was modest in magnitude and should be interpreted cautiously; however, based on these results, future studies designed to examine psychological risk factors for TMD may benefit from assessing both of these domains.

Passive Pain Coping failed to predict first-onset TMD in our prospective study, which contrasts with previous case-control findings reported from the OPPERA Study[30]; additionally, other studies indicated higher levels of pain catastrophizing, a component of passive pain coping, among people with TMD.[10,70] However, that passive pain coping failed to predict first onset of TMD pain is not particularly surprising given the method of assessment of this construct. In assessing catastrophizing, for example, individuals with pain are asked to report how they respond to their existing pain condition. However, TMD-free individuals, such as

the participants at enrollment in our prospective cohort, were asked to indicate how they respond to pain in general when it does occur, which represents a more hypothetical construct. Indeed, in pain-free adults, such measures of general catastrophizing have not consistently predicted responses to experimental pain, whereas post hoc assessments of individuals' catastrophic cognitions when they were experiencing experimental pain have been associated with laboratory pain responses.[10,22] Thus, measures of catastrophizing, and perhaps other forms of pain coping, may be associated with pain in a context-dependent manner. In addition, catastrophizing may increase risk for transition from acute to chronic pain rather than predicting pain onset.

Analyses stratified by demographic factors revealed that psychological risk factors for first-onset TMD were generally similar across age, sex, and racial and ethnic groups. One exception was that Global Psychological and Somatic Symptoms predicted TMD incidence more strongly in the 2 younger age groups (18–24, 25–34 years) versus the older age group (35–44 years). Interestingly, this older group had the highest incidence of first-onset TMD (see[79]), and the present findings suggest that either unmeasured psychological variables or nonpsychological factors confer this increased risk of TMD onset in this age group. However, it should be noted that the interaction of age with Global Psychological and Somatic Symptoms in predicting TMD onset, though statistically significant, was modest in magnitude and needs to be replicated.

In addition to more traditional regression-based multivariable analyses using the PCA factor scores, random forest models provided an additional, more exploratory multivariable approach that was able to accommodate the individual variables. The random forest models identified similar predictors of TMD onset as observed in the univariate analyses, with the PILL being the strongest predictor of TMD onset. Other variables with nonzero variable importance scores, suggesting at least modest predictive ability even after accounting for somatic symptoms, included the Perceived Stress Scale, State Anxiety, the SCL 90R anxiety, somatization, and obsessive-compulsive scales, and the CSQ Ignoring Pain Sensations Scale. This latter scale did not emerge as a predictor in the univariate model, suggesting that this coping strategy may provide some predictive value after adjusting for the effects of other psychological variables. The depicted partial dependence plots indicate that the association of a given predictor with TMD onset can be nonlinear, and the pattern varies across variables. For the 3 plotted variables, the nonlinear patterns generally were consistent with incidence rates reported for terciles of those variables in the univariate analysis. Given that the multivariable regression used factor scores and the random forest used individual measures, direct comparisons are not possible. However, in univariate analyses as well as both multivariable approaches, the somatic symptom construct represented the strongest predictor of TMD onset, suggesting convergence of findings regarding somatic symptoms across analytic methods.

Although multiple psychological measures predicted TMD onset in univariate analyses, results of multivariable models provide strong evidence that reported somatic symptoms represent the strongest predictor of incident TMD in this analysis. Increased somatic symptom reporting could result from altered physiological function leading to increased symptoms and/or from altered central nervous system function resulting in greater awareness of somatic and interoceptive cues. The mechanisms whereby somatic symptoms increase risk for TMD remain unknown. Perhaps somatic symptoms may reflect or be associated with health behaviors or conditions that increase risk of TMD. For example, somatic symptoms could result from parafunctional behaviors (eg, bruxism, nail-biting), or other behavioral changes (eg, sleep disturbance), which could in turn increase risk for TMD.[62] Alternatively, somatic symptoms may reflect underlying physiological perturbations, and these physiological perturbations might contribute directly to the pathogenesis of TMD. Indeed, enhanced responses in immune and inflammatory systems have been associated with somatic symptoms,[4,26,55] and these biological pathways have also been implicated in TMD in cross-sectional studies.[80] Similarly, brain imaging findings suggest that overlapping neural alterations may contribute to somatization and chronic pain states.[32,83] Hence, it seems plausible that in our cohort, high somatic symptom reporting at baseline could reflect alterations in biological pathways that may increase risk for TMD onset. In any event, increased reporting of somatic symptoms represents a strong risk factor for development of TMD, and additional investigation of this construct is warranted.

The findings of this study should be interpreted in light of its limitations. First, some variables identified as significant risk factors in univariate analyses would not remain significant in a related multivariable analysis (eg, the PILL score and the SCL 90R Somatization score likely share predictive variance). This is supported by findings that both measures load onto a single principal component and by results from random forest models showing that the variable importance ranking of the SCL 90R Somatization score was considerably lower in the random forest model than in the univariate analysis. Second, although we examined some of the potential interactions among factors (eg, demographic measures and PCA components), many other possible interactions were not tested (eg, between individual psychological measures) because of the exceedingly large number of statistical tests this would require, and we chose to remain conservative in our explorations. Third, the analyses herein do not examine potentially important associations between psychological variables and other phenotypic measures, such as those presented in other papers in this issue. Instead, cross-domain analyses are presented elsewhere in this issue.[6]

These limitations notwithstanding, the current findings verify etiologic influences of several psychological

variables that have been implicated as possible risk factors for TMD in previous cross-sectional studies. The strongest predictors of TMD incidence were measures of somatic symptoms and their associated latent construct of Global Psychological and Somatic Symptoms, derived from PCA. In general, these psychological influences were similar across demographic categories. Future analyses will examine associations of these psychological variables with transition from acute to chronic pain, and changes in psychological functioning that accompany onset of TMD will also be explored.

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Supplementary Data

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