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General Health Status and Incidence of First-Onset Temporomandibular Disorder: The OPPERA Prospective Cohort Study

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Abstract: **Temporomandibular disorder (TMD) overlaps with other health conditions, but no study has examined which of these conditions increase the risk of developing first-onset TMD. The authors prospectively evaluated the relationship between health status at enrollment and subsequent incidence of TMD in 2,722 men and women. Participants aged 18 to 44 years had no history of TMD and were clinically free of TMD when enrolled in 2006 to 2008 at 4 U.S. study sites in the Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) prospective cohort study. First-onset examiner-classified TMD developed in 260 people over a median 2.8 years of follow-up. Cox regression estimated the association between health conditions and TMD incidence while accounting for potential confounders. Incidence of first-onset TMD was 50% higher for people with low back pain (adjusted hazard ratio [AHR] = 1.50, 95% confidence limits [CLs]: 1.08, 2.10) and 75% higher for people with genital pain symptoms (AHR = 1.75, 95% CLs = 1.04, 2.93) than people without a history of these pain disorders. Digit ratio, a marker of intrauterine exposure to sex hormones, was significantly associated with TMD incidence. Other independent predictors of first-onset TMD were sleep disturbance and cigarette smoking. These findings reveal multiple influences of health status on incidence of first-onset TMD.**

Perspective: ***This article examines health conditions that commonly overlap with TMD to determine which ones predict first-onset TMD. A history of low back pain and genital pain conditions at baseline were important predictors. Novel findings were that disrupted sleep and conditions in utero may increase incidence of first-onset TMD.***

Key words: *Temporomandibular disorder, prospective cohort studies, comorbidity, epidemiology.*

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The observation, made 30 years ago, that temporomandibular disorder (TMD) coexists with other health conditions in some individuals[33] challenged the assumption that these conditions were clinically distinct phenotypes. Today evidence from clinical and epidemiologic studies shows that TMD coexists with numerous regional and systemic disorders including fibromyalgia,[1,27] low back pain/spinal pain,[35,50] vulvar lichen sclerosus,[5] chronic fatigue syndrome,[11] irritable bowel syndrome (IBS),[2] sleep disorders,[47] nonulcerative interstitial cystitis/painful bladder syndrome,[40] tension-type and migraine headaches,[9,20,21] allergy conditions,[44] and somatoform disorders.[18] What is

striking about this evidence is not so much the diversity of these conditions that span autonomic, atopic, and sensory disorders but rather the homogeneity among them, which is defined by 3 clinical features. First, most of these disorders share an idiopathic basis in which the pathophysiologic mechanisms are poorly understood.[12,29] Second, the clinical presentation of most of these disorders exhibits a disproportionate level of symptom severity, including pain and fatigue, compared to examination findings. Third, most share demographic, social, behavioral, and psychological features. The presence of shared features, including possibly etiology as well, in these joint relationships has prompted use of the term *overlapping* conditions, and many studies have quantified the extent of this overlap.[1,2,10,36,42,45]

Evidence of pain disorders overlapping with TMD was demonstrated in the Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) baseline case-control study of chronic TMD in adults aged 18 to 44 years.[38] In that study, 1,633 asymptomatic controls, examined using Research Diagnostic Criteria for TMD[15] (RDC/TMD) and found not to have TMD, were compared with 185 adults meeting RDC/TMD criteria for chronic painful TMD. In chronic TMD cases compared to controls, odds of IBS were 2.7 times as high (95% confidence limits [CLs] = 1.4, 5.1), odds of chronic pain in the body other than the face were 5.1 times as high (95% CLs = 3.6, 7.3), and odds of any headache in the last year were 8.8 times as high (95% CL = 3.8, 20.1) after statistically adjusting for the potential confounding effects of age, gender, and race/ethnicity.[38] Moreover, some effects were dose dependent. For example, using an ordinal count of different types of headache experienced in the previous year, adjusted odds of one type of headache relative to no type of headache were 3.9 times as high (95% CLs = 1.6, 9.7) for TMD cases compared to controls. Odds of 2 headache types relative to none were 7.8 times as high (95% CLs = 3.3, 18.6) for TMD cases, and odds of 3 headache types relative to none were 15.0 times as high (95% CLs = 6.1, 36.6) in TMD cases as for controls.[35]

On one level, this constellation of relationships poses challenges for the identification of pathophysiologic mechanisms and the development of multimodal treatment strategies. Another challenge is to distinguish cause and effect: which clinical conditions are preexisting experiences that contribute to development of TMD and which, such as sleep disorders or mood disorders, may be consequences of the disorder.

Until now longitudinal studies have not established which overlapping conditions predispose an individual to greater risk of first-onset TMD. To address that question, this paper reports findings from the OPPERA prospective cohort study. The aim of this analysis was to determine prospectively which clinical conditions observed at baseline in TMD-free individuals were associated with higher risk of developing first-onset TMD.

Methods

The OPPERA study is a prospective cohort study designed to investigate the etiology of first-onset TMD. The OPPERA cohort comprised 3,263 adults with no history of TMD and were enrolled at 4 U.S. study sites and followed for a median 2.8 years, during which time 260 of them developed first-onset, examiner-classified TMD.

Institutional review boards at each study site granted approval for study procedures, and signed, informed consent was obtained from each subject. Full details of enrollment, follow-up, and statistical analyses are provided elsewhere in this issue[4] and are summarized here.

Recruitment, Eligibility Criteria, and Enrollment

Between May 2006 and November 2008, potential study participants were recruited using advertisements, e-mails, and flyers at 4 U.S. study sites: Baltimore, MD; Buffalo, NY; Chapel Hill, NC; and Gainesville, FL. Eligibility criteria were age 18 to 44 years, good health, no history of facial injury or surgery, no significant symptoms of TMD pain, no previous diagnosis of TMD, and an absence of TMD myalgia and TMD arthralgia on clinical examination. On enrollment, participants completed a telephone interview and self-administered questionnaires assessing hypothesized risk factors for TMD. During a 3-hour clinical visit, autonomic function was monitored and quantitative sensory tests measured sensitivity to painful stimuli. Study examiners recorded clinical characteristics of muscles and joints of the head, neck, and body and they verified absence of TMD.

Scope of This Analysis

This analysis examined clinical conditions that may be potential putative risk predictors of first-onset TMD. Because very little is known about clinical predictors, we included a wide range of baseline clinical characteristics summarized as pain disorders, clinical status indicators, sleep quality, and anthropometric indicators. These were selected on an a priori basis of theoretical relevance or evidence of their association with TMD. Their measurement is described below. Conditions involving face or jaw symptoms are reported elsewhere in this issue.[37] Further information about the measures and forms used in OPPERA are available online at the Journal of Pain as part of the supplement to the Ohrbach et al 2011 publication.[38]

Pain Disorders

Symptoms of pain disorders were evaluated using batteries of items in the OPPERA Comprehensive Pain and Symptom Questionnaire (CPSQ) published in OPPERA baseline supplementary material.[38] This analysis draws on pain symptoms related to headache, low back pain, IBS, and genital symptoms. Headache was classified according to the second edition of the *International Classification of Headache Diseases*[23] developed by the International Headache Society (ICHD-2). We examined 3 types of primary headache: probable tension-type, tension-type, and migraine headache. Although the headache symptoms (OPPERA CPSQ questions 37 through 41) were classified algorithmically according to ICHD-2 decision rules into the various subtypes (eg, episodic

tension-type, chronic tension-type, probable migraine), only the main types listed here were considered for the present analyses. Past or current low back pain symptoms were assessed in the OPPERA CPSQ question 51. These items evaluated the constancy of pain symptoms, the frequency of episodes in the last 12 months, the duration of episodes, and whether pain symptoms extended into the buttocks or legs. Assessment of IBS symptoms was based on Rome III criteria[14] in CPSQ questions 52 and 53. The IBS questions asked about bowel movements and the experience of discomfort or pain in the abdomen that lasted at least 1 day a week during the previous 3 weeks. Genital symptoms were assessed with CPSQ questions 54 through 57 that asked about the presence of genital pain on contact but absence of genital itching during the last 3 months (CPSQ question 54).

Health Status

A subjective assessment of health status obtained in the medical history questionnaire asked participants to describe their health overall as excellent, good, fair, or poor. A checklist of medical conditions asked respondents to indicate conditions they had now or in the past. Conditions were grouped as 1) endocrine (diabetes, hypothyroid disease, hyperthyroid disease), 2) cardiovascular (mitral valve prolapse, high blood pressure, angina, heart attack, heart failure, pacemaker/defibrillator, stroke), 3) hematologic (anemia, bleeding disorder, leukemia), 4) neural and sensory (earache; ringing in ears; hearing loss; fainting or dizzy spells; epilepsy, seizures, or convulsions; psychiatric treatment); and 5) respiratory (sinus trouble, allergies or hives, asthma, tuberculosis, breathing difficulties). Finally, a binary response (yes/no) was used for each of sleep apnea and history of being hospitalized for any surgical operation or serious illness. A count of 11 currently used medications was computed.

Pittsburgh Sleep Quality Index (PSQI)

The PSQI[7] investigated whether disturbances in sleep play a role in the development of first-onset TMD. Participants rated their sleep quality and disturbances over a 1-month reference period. Scores for the 7 PSQI components—subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction—were summed to yield one global score. Sleep disorders are associated with headache,[43] and primary insomnia is associated with TMD.[47]

Anthropometric Status

In the physical examination, weight and height were measured using standardized equipment to compute body mass index (BMI = weight/height^2). In a U.S. population health survey, a strong dose-response positive relationship was observed between BMI and pain experienced during the previous day for "a lot of the day."[48]

Examiners used photocopied images of participants' hands to measure the length of the second digit [2D] and the fourth digit [4D]. The 2D:4D ratio was calculated and averaged for both hands. A high 2D:4D ratio is a marker of greater estrogen relative to testosterone exposure toward the end of the first trimester in utero.[30]

Cigarette Smoking

People who reported having smoked fewer than 100 cigarettes in their lives were classified as nonsmokers, and the remainder were asked whether they were current or former smokers. In the Kentucky Women's Health Registry, daily smoking showed a dose-response relationship with at least 1 pain syndrome among fibromyalgia, sciatica, chronic neck pain, chronic back pain, joint pain, chronic head pain, nerve problems, and pain all over the body.[32] In that study, former smoking showed a weaker effect than daily smoking but remained a significant risk factor. Previously we reported a strong association between cigarette smoking and chronic TMD.[44]

Short Form 12 Health Survey v2 (SF-12v2)

General health status was evaluated using the SF-12v2. This analysis used the weighted summary scores that comprise the physical component (PCS-12) and the mental component (MCS-12) derived using the standard SF-12v2 scoring algorithm. Like self-rated health, this measure was excluded from multivariable models since it is considered to be a consequence of health conditions, rather than an independent determinant.

Follow-Up and Case Classification of First-Onset TMD

At 3-month intervals after enrollment through May 2011, study participants were asked to complete a questionnaire that screened for TMD pain symptoms. Those who reported TMD pain symptoms were asked to attend a clinical examination that determined presence or absence of painful TMD according to OPPERA's adaptation of the RDC/TMD criteria.[15] In this adaptation, classification of first-onset TMD required 2 criteria: 1) $\geq$5 days/month of pain in TMD locations specified by examiner and 2) examiner findings of arthralgia (ie, pain in temporomandibular joint(s) during jaw maneuver or digital palpation) or myalgia (ie, pain during jaw maneuver or digital palpation in $\geq$3 of 8 muscle groups, each assessed bilaterally: temporalis, masseter, lateral pterygoid, submandibular) or both.

All examiners underwent annual training and calibration in the RDC/TMD protocol. In blinded, replicated examinations, Kappa statistics for interexaminer reliability of TMD case classification ranged from .87 to 1.0, signifying excellent reliability.

Statistical Analysis

All analyses were conducted with SAS version 9 statistical software (SAS Institute, Inc, Cary, NC). The follow-up period for each study participant was computed as the time from enrollment to the first of 3 possible events: 1) examiner-classification of first-onset TMD, 2) loss to follow-up, or 3) the census date used for this analysis (ie, May 2011). Incidence 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 (equivalent to the number of incident cases per 100 years of follow-up). For descriptive purposes, an adjusted, average annual incidence of first-onset TMD was computed using a Poisson regression model that adjusted for study site. Buffalo was selected as the referent from among the 4 study sites.

To test hypotheses about associations between baseline risk factors and TMD incidence, hazard ratios (HRs) were computed as approximations of the rate ratio. HRs represent the relative difference in hazard rates between 2 groups. Although the hazard rate is a theoretical construct, representing the instantaneous probability of an event as the duration of follow-up approaches zero, it is a good approximation of the average rate ratio in a cohort study. Furthermore, the Cox proportional hazards models used to estimate HRs require fewer statistical assumptions than other modeling methods. Hereafter, we use the term "incidence" when referring to the annual incidence rate and the hazard rate. We report *P* values unadjusted for multiple tests. However, a strict Bonferroni correction that took account of the 26 variables reported in univariate results (Tables 1–3) would revise the critical *P* value to $P < .002$.

For the Cox models, incident cases of TMD were regarded as an event; otherwise they were censored. Each person's follow-up period was used as the time-to-event. When the baseline risk factor was categorical, one category was nominated as the referent and dummy variables represented each of the other categories. For continuous variables, scores were transformed to unit-normal deviates (mean = 0, standard deviation [SD] = 1). This transformation to standardized values permits a comparison of the magnitudes of effect of the risk factors when these are measured on different continuous scales, although not when measured categorically. When calculating univariate HRs and 95% CLs, a hierarchical approach was used in which models initially adjusted only for study site, and subsequently additionally adjusted for demographic characteristics, that is, age in years, gender, race/ethnicity (white, African American/black, Hispanic, Asian, and other/unstated), and lifetime U.S. residence (no and yes/unstated).

HRs were also computed using multiple imputation to account for 2 sources of potential bias associated with 1) nonexamination of 243 people with symptoms and 2) a higher than expected incidence of TMD classification for 1 examiner who conducted 75 examinations. As described in detail elsewhere,[4] findings for 318 examinations were imputed in 3 steps. First, an algorithm predicting probability of TMD was created using binary logistic regression analysis of quarterly screening questionnaire data among people who were reexamined. Predictor variables in the algorithm were study site, time since enrollment, and number of nonspecific orofacial symptoms reported in the quarterly health update. The algorithm was then used to generate 100 imputed, binary case classifications for each person who was not examined or whose examination findings were discarded. Finally, the imputed case classifications and 100 replicates of observed case classifications were analyzed in a Cox regression model using multiple imputation to estimate an average HR and corresponding 95% confidence interval. The imputed analysis adjusted for OPPERA study and demographic characteristics described above. When fitting the random forest models, the 318 people used for imputation were given missing censoring indicators and imputed using adaptive tree imputation.

Variables found to be significantly associated with TMD onset in the demographically adjusted, imputed analysis were evaluated for their combined effects in successive multivariable models. The first model considered only the sociodemographic characteristics, the second model added painful conditions, and the third model added nonpainful conditions. All variables were retained in the model, regardless of their statistical significance. Instead, the focus was on the degree to which estimated HRs were altered by addition of new blocks of variables, signifying likely confounding. Subjective health status and medication usage were not included in multivariable models since they were considered to reflect consequences of having one or more overlapping conditions and might therefore mask statistical associations attributable to the conditions themselves.

A second strategy of multivariable analysis used random forest modeling[25] to analyze potential contributions of all 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. The model produced importance scores, 1 for each variable, representing the decrease in the predictive accuracy of the model when the variable is measured incorrectly. 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.[28]

The 2 strategies were selected in favor of other approaches for multivariable analysis for several reasons. The first strategy is a conventional approach that adjusts for potential confounding effects of variables identified a priori, based on conceptual relevance and univariate association with TMD incidence. However, it does not take advantage of information about the excluded variables. Thus, a random forest model was used to evaluate contributions of all variables. Random forests have several other advantages compared to conventional linear regression models. Specifically, random forests can impute for missing data and handle large numbers of correlated predictor variables without decreasing the accuracy of the model.[22]

Table 1. Univariate Associations Between Baseline Pain Disorders as Etiologic Risk Factors Measured Categorically and Incidence Rate of First-Onset TMD: OPPERA Prospective Cohort Study, 2006–2011

Pain Disorders	Category	N	Site-Adjusted* TMD Incidence Rate (% of People per Annum)	Study Site-Adjusted Effect†	Site, Demographic-Adjusted Effect‡	P Value	Imputed Values for Loss to Follow-Up§
Current low back pain	Yes	341	5.92	2.02 (1.49, 2.72)	1.91 (1.41, 2.58)	<.001	1.89 (1.38, 2.57)
	No (ref)	2,379	2.92				
Low back pain episodes in last year	≥11	236	5.26	2.04 (1.38, 2.99)	1.92 (1.30, 2.83)	<.001	2.01 (1.35, 3.00)
	5–10	293	6.19	2.40 (1.71, 3.36)	2.33 (1.65, 3.27)		2.20 (1.54, 3.14)
	2–4	592	3.06	1.20 (.85, 1.67)	1.16 (.82, 1.61)		1.24 (.87, 1.74)
	1	237	2.63	1.04 (.63, 1.69)	.98 (.59, 1.59)		.99 (.60, 1.63)
	0 (ref)	1,347	2.59				
Rome IBS classification	Yes	74	9.16	3.00 (1.85, 4.84)	2.84 (1.75, 4.62)	<.001	2.27 (1.35, 3.79)
	No (ref)	2,632	3.07				
Count of 10 IBS symptoms	≥6	182	7.04	2.95 (2.00, 4.34)	2.66 (1.79, 3.93)	<.001	2.35 (1.57, 3.50)
	3–5	446	4.53	1.89 (1.37, 2.60)	1.77 (1.28, 2.44)		1.68 (1.20, 2.33)
	1–2	574	3.27	1.37 (.98, 1.89)	1.26 (.90, 1.74)		1.15 (.81, 1.62)
	0 (ref)	1,507	2.39				
Genital pain symptoms	Yes	84	9.11	3.06 (1.93, 4.84)	2.78 (1.74, 4.44)	<.001	2.31 (1.41, 3.77)
	No (ref)	2,570	2.99				
No. of headache types in last year	≥3	496	5.54	2.23 (1.55, 3.19)	2.05 (1.42, 2.95)	<.001	1.94 (1.33, 2.81)
	2	681	3.38	1.37 (.94, 1.98)	1.25 (.85, 1.82)		1.29 (.88, 1.89)
	1	836	2.43	.98 (.67, 1.43)	1.00 (.68, 1.47)		.97 (.66, 1.42)
	0 (ref)	696	2.47				
Headache intensity at baseline	Mostly severe	218	5.70	2.33 (1.51, 3.57)	2.07 (1.34, 3.18)	.004	2.13 (1.37, 3.28)
	Mostly mild	1,732	3.35	1.37 (.99, 1.88)	1.32 (.95, 1.82)		1.26 (.90, 1.75)
	None (ref)	696	2.45				
Migraine headache(s)	Yes	894	3.84	1.32 (1.03, 1.70)	1.28 (.99, 1.64)	.057	1.26 (.97, 1.62)
	No (ref)	1,827	2.91				
Tension-type headache(s)‖	Yes	206	5.31	1.75 (1.20, 2.53)	1.74 (1.18, 2.53)	.004	1.69 (1.12, 2.53)
	No (ref)	2,515	3.04				
Probable tension-type headache(s)‖	Yes	1,271	3.17	1.00 (.77, 1.27)	.98 (.76, 1.25)	.860	1.01 (.77, 1.29)
	No (ref)	1,450	3.24				

*Adjusted rates computed using Poisson regression controlling for study site (categorical variable, 4 levels). Estimated rate is for reference study site (University of Buffalo).
†Rate ratio represents relative increase in incidence rate of TMD relative to reference group. Calculated using Cox proportional hazards regression model controlling for study site (categorical variable, 4 levels).
‡As for footnote †, with additional adjustment for age in years, gender (categorical, 2 levels), race/ethnicity (categorical, 2 levels), and lifetime U.S. residence (categorical, 2 levels).
§As for footnote ‡, with inclusion of imputed TMD rates for subjects lost to follow-up and imputed data for values missing at baseline.
‖Both tension-type headache and probable tension-type headache are evaluated in a single Cox model. Other variables in this Table are evaluated as univariate predictors in separate Cox models.

Sample Size Considerations

OPPERA was designed with a target sample size of 3,200 enrolled study participants expected to yield 196 cases of first-onset TMD during a 3-year follow-up period, assuming 30% loss to follow-up. These targets were based on incidence and cohort retention rates observed in a previous study conducted at the North Carolina study site[13] and were sufficient to provide statistical power of 80% to detect risk ratios of at least 1.8 for risk predictors with as few as 15% in the high risk category, consistent with the magnitude of effect seen for genetic predictors seen in the previous North Carolina study.

Results

In 7,368 person-years of follow-up, 260 people developed first-onset TMD, yielding an average annual incidence of 3.5%. Two-thirds (70.4%) of the 260 incident cases reported having experienced TMD symptoms for 1 or 2 months in the 3-month period prior to the examination at which TMD-onset was determined, and 65% said that their symptoms occurred in recurrent bouts.

Virtually all pain disorders assessed at enrollment were associated with greater TMD incidence (Table 1) and the relationship showed a dose-response pattern.

Table 2. Univariate Associations Between Baseline Clinical Conditions and Conditions as Etiologic Risk Factors Measured Categorically and Incidence Rate of First-Onset TMD: OPPERA Prospective Cohort Study, 2006–2011

Putative Risk Factor	Category	N	Site-Adjusted* TMD Incidence Rate (% of People per Annum)	Study Site-Adjusted Effect†	Site, Demographic Adjusted Effect‡	P Value	Imputed Values for Loss to Follow-Up§
Count of 20 comorbidities	≥2	424	7.53	3.20 (2.41, 4.23)	2.87 (2.15, 3.81)	<.001	2.70 (2.02, 3.59)
	1	505	3.26	1.40 (.99, 1.95)	1.39 (.98, 1.94)		1.42 (1.00, 2.01)
	Zero (ref)	1,773	2.33				
History of 3 endocrine conditions	≥1	78	5.65	1.82 (1.01, 3.25)	1.78 (.98, 3.20)	.056	1.41 (.75, 2.64)
	Zero (ref)	2,659	3.18				
History of 7 cardiovascular conditions	≥1	139	4.68	1.47 (.90, 2.37)	1.10 (.67, 1.80)	.710	1.05 (.63, 1.73)
	Zero (ref)	2,598	3.18				
History of 4 hematologic conditions	≥1	225	4.13	1.29 (.85, 1.94)	1.15 (.75, 1.75)	.520	1.11 (.71, 1.72)
	Zero (ref)	2,512	3.18				
History of 4 neurosensory conditions	≥1	626	4.44	1.52 (1.16, 1.98)	1.51 (1.15, 1.97)	.003	1.52 (1.15, 2.00)
	Zero (ref)	2,110	2.92				
History of 5 respiratory conditions	≥1	931	4.20	1.50 (1.17, 1.92)	1.47 (1.14, 1.88)	.002	1.44 (1.11, 1.85)
	Zero (ref)	1,805	2.78				
Sleep apnea	Yes	47	4.36	1.37 (.60, 3.09)	1.13 (.50, 2.56)	.760	1.15 (.51, 2.56)
	No (ref)	2,678	3.24				
Past use of 11 medications	3 ore more	427	4.92	1.41 (.96, 2.05)	1.35 (.90, 2.00)	.009	1.52 (1.00, 2.28)
	2	954	2.85	.82 (.57, 1.16)	.82 (.56, 1.18)		.91 (.61, 1.33)
	1	790	2.66	.76 (.52, 1.09)	.76 (.52, .09)		.87 (.59, 1.25)
	Zero (ref)	560	3.49				
Cigarette smoking history	Current	415	5.34	2.07 (1.48, 2.88)	1.74 (1.22, 2.47)	<.001	1.61 (1.13, 2.30)
	Former	210	5.69	2.26 (1.54, 3.30)	2.12 (1.43, 3.14)		1.86 (1.23, 2.79)
	Never (ref)	2,058	2.55				
Ever hospitalized for surgery/serious illness	Yes	1,010	3.38	1.07 (.82, 1.37)	.95 (.73, 1.23)	.720	1.07 (.82, 1.39)
	No (ref)	1,714	3.17				
Self-rated general health	Fair or poor	127	7.47	2.93 (1.86, 4.60)	2.55 (1.60, 4.05)	.000	2.60 (1.64, 4.11)
	Good	1,410	3.55	1.40 (1.07, 1.82)	1.35 (1.03, 1.76)		1.37 (1.04, 1.80)
	Excellent (ref)	1,185	2.53				

*Adjusted rates computed using Poisson regression controlling for study site (categorical variable, 4 levels). Estimated rate is for reference study site (University of Buffalo).
†Rate ratio represents relative increase in incidence rate of TMD relative to reference group. Calculated using Cox proportional hazards regression model adjusted for study site (categorical variable, 4 levels).
‡As for footnote †, with additional adjustment for age in years, gender (categorical, 2 levels), race/ethnicity (categorical, 2 levels), and lifetime U.S. residence (categorical, 2 levels).
§As for footnote ‡, with inclusion of imputed TMD rates for subjects lost to follow-up and imputed data for values missing at baseline.

For example, a simple count of the number of low back pain episodes in the year prior to enrollment revealed a dose-response relationship of increasing incidence of first-onset TMD with higher number of episodes, peaking at 5 to 10 episodes (HR = 2.01, 95% CLs = 1.35, 3.00). Among the 341 people with low back pain at enrollment, the incidence of first-onset TMD (site adjusted rate = 5.52% per annum) was twice the incidence seen in 2,379 people without low back pain (2.92% per annum). The corresponding site-adjusted HR (2.02, 95% CLs = 1.49, 2.72) was only slightly attenuated after adjustment for demographic characteristics (HR = 1.91, 95% CLs = 1.42, 2.58), and back pain remained a significant predictor of TMD after further adjustment for loss to follow-up (HR = 1.89, 95% CLs = 1.38, 2.57).

Stronger effects were observed with IBS (Table 1). Incidence of first-onset TMD was 3 times as high in people with IBS on enrollment as in people without IBS. Again the effect diminished on adjustment for demographic characteristics (HR = 2.84, 95% CLs = 1.75, 4.62) and for loss to follow-up (HR = 2.27, 95% CLs= 1.35, 3.79; P = .002) but IBS symptoms remained a significant predictor. As the count of IBS symptoms increased, so did incidence of first-onset TMD, such that people with 6 or more symptoms had 2.35 times greater rate of developing TMD than people with no IBS symptoms, in the fully adjusted model.

Incidence of first-onset TMD was 3 times higher in the 84 people with genital pain symptoms on enrollment than in 2,632 people without genital pain symptoms, and incidence remained elevated in the fully adjusted model (HR = 2.31, 95% CLs = 1.41, 3.77).

When headache types were examined separately, clear differences emerged, with tension-type headache most strongly associated with TMD incidence (Table 1). Among the 206 people with tension-type headache at enrollment, TMD incidence was 69% greater than people who did not have tension-type headache (HR = 1.69, 95% CLs = 1.12, 2.53). Although TMD incidence was

Table 3. Univariate Associations Between Continuous Measures of Etiologic Risk Factors Reporting and Incidence Rate of First-Onset TMD HRs With 95% CLs: OPPERA Prospective Cohort Study, 2006–2011

	Distribution of Risk Factor at Enrollment		Site-Adjusted* TMD Incidence Rate in Each Tercile of Risk Factor (% of People per Annum)			Standardized HRs (95% CLs)† Adjusted for:			Standardized HRs (95% CLs) Adjusted for Study Site + Demographics With Imputation‡		
Putative Risk Factor	n	Mean (SD), 1st, 2nd Tercile	Lower	Mid	Upper	Study Site§	Demographic‖	P Value	N	Loss to Follow-Up¶	P Value#
BMI (kg/m^2)	2,705	26.1 (6.1), 22.8, 26.9	3.19	3.14	5.15	1.23 (1.11, 1.37)	1.13 (1.00, 1.26)	.038	2,705	1.09 (.97, 1.23)	.140
Average of RD2:RD4 ratio left and right hands	2,723	96.3 (3.3), 94.7, 97.5	3.23	3.57	4.81	1.18 (1.04, 1.33)	1.21 (1.06, 1.37)	.003	2,723	1.15 (1.01, 1.30)	.026
PSQI global score (0–21)	2,559	4.7 (2.8), 3.0, 5.0	2.16	2.84	5.46	1.47 (1.32, 1.63)	1.40 (1.25, 1.55)	<.001	2,732	1.32 (1.18, 1.47)	<.001
SF-12v2 Physical component summary score	2,597	52.7 (4.3), 51.9, 54.3	4.52	3.06	3.81	.83 (.73, .93)	.86 (.76, .97)	.016	2,597	.85 (.74, .95)	.008
SF-12v2 Mental component summary score	2,597	51.6 (10.4), 49.2, 58.3	6.18	2.80	2.63	.71 (.64, .79)	.71 (.63, .79)	<.001	2,597	.74 (.66, .82)	<.001

*Adjusted rates computed using Poisson regression controlling for study site (categorical variable, 4 levels). Estimated rate is for reference study site (University of Buffalo).
†Values are standardized HRs (95% CLs), which express the risk per SD increase in the putative risk factor.
‡Imputed for loss to follow-up and missing values at baseline.
§Rate ratio represents relative increase in incidence rate of TMD associated with an increase of 1 SD in risk factor. Computed using Cox proportional hazards regression model adjusting for study site (categorical variable, 4 levels).
‖As for footnote †, with additional adjustment for age in years, gender (categorical, 2 levels), race/ethnicity (categorical, 5 levels), and lifetime U.S. residence (categorical, 2 levels).
¶As for footnote ‡, with inclusion of imputed TMD rates for subjects lost to follow-up and imputed data for values missing at baseline.
#*P* value is for HR adjusted for study site and demographic characteristics, evaluating null hypothesis that the HR equals 1.

Table 4. Multivariable-Adjusted Associations in Development of First-Onset TMD: OPPERA Prospective Cohort Study, 2006–2011

	*Model 1** *Demographics* *HR (95% CLs)*	*Model 2** *Pain Disorders* *HR (95% CLs)*	*Model 3** *Other Health Conditions* *HR (95% CLs)*
Female gender (ref = male)	1.37 (1.04, 1.80)	1.28 (.96, 1.69)	1.22 (.91, 1.62)
Age (in decades)	1.20 (1.01, 1.43)	1.17 (.98, 1.39)	1.07 (.88, 1.28)
Asian race (ref = white)	.66 (.31, 1.40)	.67 (.32, 1.43)	.71 (.33, 1.50)
Black race (ref = white)	1.33 (.97, 1.84)	1.36 (.99, 1.88)	1.47 (1.05, 2.05)
Hispanic ethnicity (ref = white)	1.17 (.63, 2.14)	1.19 (.64, 2.18)	1.22 (.66, 2.26)
Other race (ref = white)	.96 (.45, 2.07)	1.04 (.48, 2.25)	1.08 (.49, 2.34)
Nonlifetime U.S. residence (ref = lifetime)	.46 (.27, .78)	.47 (.28, .79)	.51 (.30, .86)
Current low back pain (ref = no)		1.80 (1.30, 2.48)	1.50 (1.08, 2.10)
Rome IBS classification (ref = no)		1.92 (1.12, 3.30)	1.62 (.94, 2.81)
Genital symptoms (ref = no)		1.92 (1.15, 3.19)	1.75 (1.04, 2.93)
Genital symptoms not stated (ref = no)		1.84 (1.04, 3.27)	1.68 (.94, 3.00)
Tension-type headache (ref = no)		1.57 (1.04, 2.35)	1.46 (.97, 2.20)
Neurologic conditions (ref = no)			1.25 (.93, 1.68)
Respiratory conditions (ref = no)			1.28 (.98, 1.67)
PSQI (z-score)			1.18 (1.05, 1.33)
RD2:RD4 ratio average both hands (z-score)			1.15 (1.00, 1.31)
Current smoker (ref = never smoked)			1.55 (1.08, 2.25)
Former smoker (ref = never smoked)			1.84 (1.22, 2.78)
Smoking status unstated (ref = never smoked)			1.39 (.63, 3.04)

*All models are adjusted for study site.

positively associated with migraine at enrollment, the HR attenuated to statistical nonsignificance after adjustment for demographic characteristics (HR = 1.28, 95% CLs = .99, 1.64). Meanwhile, probable tension-type headache at enrollment was not associated with TMD incidence. In a simple count of number of self-reported types of headaches, first-onset TMD incidence increased in monotonic fashion in accordance with the counts. Similarly, incidence of first-onset TMD increased with increasing intensity of headache.

Among other clinical conditions and characteristics reported at enrollment (Table 2), those significantly associated with increased incidence of TMD were a higher number of comorbid conditions, a history of neural conditions, a history of respiratory conditions, usage of 3 or more medications, current and former cigarette smoking, and a poorer than "excellent" self-rating of general health status. Strongest effects were observed for 2 or more comorbidities and poor/fair self-rated health. None of the potential putative risk factors emerged as being protective against first-onset TMD. Equally noteworthy were the conditions found not associated with TMD incidence: endocrine, cardiovascular or hematologic, sleep apnea, and lifetime hospitalization for surgery or serious illness. However, the low frequencies of endocrine conditions (n = 78) and sleep apnea (n = 47 for) diminished the study's power to detect a true association if one exists.

The standardized hazard ratios (SHRs) for continuous variables (Table 3) are interpreted as the change in incidence of first-onset TMD associated with a 1 SD change in the risk factor. For example, for each 1 SD increase in PSQI score, denoting poorer sleep quality, incidence of first-onset TMD increased by 32% (adjusted SHR = 1.32, 95% CLs = 1.18, 1.47). A 1 SD increase in finger length ratio (RD2:RD4) was associated with a 15% increased incidence of developing first-onset TMD (adjusted SHR = 1.15, 95% CLs = 1.01, 1.30), implying greater risk for people with lower testosterone and higher estrogen exposure in utero. In additional analyses that stratified by gender, the effect of 2D:4D ratio was stronger in females (HR = 1.30, 95% CLs = 1.11, 1.52) than males (HR = 1.07, 95% CLs = .86, 1.32), although the effect modification of gender was not significant (P = .15) (results not tabulated). BMI was a putative risk factor for first-onset TMD in analysis that adjusted for study site and demographic characteristics (Table 3), but its effect was attenuated to statistical nonsignificance after imputation for loss to follow-up. Higher summary scores on the SF-12v2 physical and mental component reflect better health and functioning. Consistent with this coding, higher scores on both components were protective against development of first-onset TMD, and the effect was especially strong for the mental component (adjusted SHR = .74, 95% CLs = .66, .82).

The successive multivariable models (Table 4) demonstrated generally little confounding among overlapping conditions in their association with TMD incidence. For example, all 5 pain disorders were independent putative risk factors for first-onset TMD in model 2 with HRs ranging from 1.80 for low back pain to 1.92 for both IBS and genital symptoms. In model 3 that also adjusted for other health status conditions, sleep disturbances, current and former smoking, and a high 2D:4D finger length ratio were independent risk factors for first-onset TMD. Also in model 3, black race, low back pain, and genital symptoms, but not tension-type headache or IBS, remained significant predictors. There was,

however, evidence that other demographic associations were attenuated by effects of nonpainful health conditions. For example, in model 1, risk of first-onset TMD increased by 20% for each 10 years of age and the effect was attenuated only by 3% with the inclusion in model 2 of the pain disorders. However, in model 3, in the presence of other clinical conditions, the effect of age reduced by a more marked increment of 10% per decade.

In the random forest model that predicted incidence using all health status variables reported in Tables 1–3 together with study site and demographics, incidence of TMD increased sharply as the number of comorbid conditions increased from 0 to 5, and thereafter flattened out (Supplementary Fig 1A). However, there was a threshold effect of headaches: TMD incidence was low among people with up to 2 headaches, but above that threshold, there was a sharp increase in incidence (Supplementary Fig 1B). People who never smoked had markedly lower incidence of TMD compared to either current or former smokers (Supplementary Fig 1C). Although the model predicted a significantly higher rate of TMD in former smokers compared to current smokers, the absolute difference of the average predicted rates was approximately .002 cases per annum (equivalent to a net difference of .2% per annum).

Discussion

Main Findings

In this first large-scale prospective evaluation of the relationship between general health status and development of first-onset TMD, people with a history of low back pain at enrollment had a 50% greater incidence of TMD than people with no such history, after adjustment for other overlapping conditions. Similarly, a history of genital pain symptoms was associated with 75% greater incidence of developing TMD. Tension-type headache and IBS predicted first-onset TMD after adjustment for demographic characteristics and pain disorders; however, their effects were rendered statistically nonsignificant in the presence of other overlapping conditions. Some nonpainful conditions at enrollment were independently associated with increased TMD incidence, including poor sleep quality. This finding in a prospective cohort study is noteworthy by demonstrating that poor sleep is not solely a consequence of TMD pain. Another novel finding was that higher D2:D4 digit ratio was associated with greater incidence of first-onset TMD. This lifelong signature of prenatal exposure poses the intriguing possibility of organizational hormonal contributions to TMD. Finally, this study provides the first evidence that current and former cigarette smoking increased incidence of first-onset TMD.

Comparison With Previous Studies

These results confirm and extend previous cross-sectional research of overlapping pain disorders. Consistent with the OPPERA baseline case-control study of chronic TMD, pain disorders in the present study were strongly associated with first-onset TMD. Also concordant with the OPPERA case-control study, the present study found that cigarette smoking was strongly predictive of TMD. Although the OPPERA case-control study found that TMD was associated with higher 2D:4D finger length ratios, the effect was nonsignificant in the fully adjusted model.[38]

An association between sleep disturbance and chronic pain is well established. Several longitudinal studies have found that persistent pain, including chronic orofacial pain, predicted onset of sleep disturbance.[8,39,41] The relationship appears reciprocal. A Finnish cohort study[26] followed industry workers for 28 years and examined 2 types of self-reported sleep disturbances as risk factors for incident hospitalization due to painful back disorders. Compared to workers with no sleep disturbances, those with 1 type of sleep disturbance had twice the risk of back disorder (HR = 2.1, 95% CLs = 1.0, 4.6) and those with 2 types of sleep disturbance had 3 times the risk (HR = 2.9; 95% CLs = 1.2, 7).[26] Another study examined sleep duration in 1 night and subsequent pain reports the following day in a representative subset of the national Midlife in the United States Survey.[16] Sleep duration of $\leq$3 hours relative to 6 to 9 hours was associated with an 81% increase in pain frequency.[3]

The finding that a history of smoking increased incidence of first-onset TMD is consistent with other prospective cohort evidence of other pain conditions. Among a cohort of high school adolescents in Montreal, Canada, smoking was predictive of low back pain incidence occurring at least once a week within the past 6 months and the effect was dose responsive.[19] Similar dose response findings were reported in the Northern Finland 1986 Birth Cohort, although the effect was inconsistent in males.[31] Among 4,472 subjects aged 18 to 30 years who were followed for 7 to 15 years in the Coronary Artery Risk Development in Young Adults (CARDIA) study, smokers had a 35% higher risk than nonsmokers of developing migraine headache (risk ratio = 1.35, 95% CLs = 1.08, 1.68).[24] In a 4-year prospective cohort study in Norway of adults aged up to 32 years, those who were smokers at enrollment had greater risk than nonsmokers of developing musculoskeletal pain in the neck, shoulder, upper back, and low back regions and reported greater pain intensity than nonsmokers.[17]

The 2D:4D digit ratio is informative of intrauterine exposure to sex hormones during the period of digit cartilage development in the 14th week of fetal life.[51] Specifically, compared with females, males are exposed to higher fetal levels of testosterone relative to estrogen, resulting in lower D2:D4 ratio. Evidence is growing that digit ratio predicts health outcomes, although the direction of the effect varies and the effect is sometimes seen in one hand only. In the left hand, higher 2D:4D ratio was associated with greater breast cancer risk,[34] but with reduced odds of amyotrophic lateral sclerosis, a neurodegenerative disease in both men and women.[49] Brabin et al[6] showed that among female adolescents, high 2D:4D ratio was associated with greater likelihood

of persistent infection with human papilloma virus and with greater occurrence of cervical intraepithelial neoplasia. The authors interpreted these findings to suggest that lower fetal androgen exposure may predispose women to develop persistent human papilloma virus with subsequent increased risk of cervical intraepithelial neoplasia.[6]

Another noteworthy finding was that nonpainful health conditions to a large degree attenuated for the association between greater age and increased TMD incidence. In the OPPERA case-control study, greater age within this 18- to 44-year range was also associated with increased odds of chronic TMD, a result that was consistent with findings from the U.S. population,[46] and which refutes views that TMD occurs most frequently in early adulthood. The current finding from multivariable modeling helps explain the age association by showing that the association is mostly attributable to nonpainful health conditions that increase with age. One implication is that TMD risk might be reduced if general health disorders could be prevented or managed early in adulthood.

Strengths and Limitations

The multisite OPPERA project is a continuing prospective cohort study purposefully designed to investigate the etiology of first-onset TMD and variation in its genetic, biological, and psychosocial determinants. It applied a rigorous methodology by using the same protocol and conditions to measure outcome and exposures in all subjects. This feature, along with the large size of the study, strengthens the validity of estimates. Findings should not be extrapolated beyond the study population or the condition studied: this was a generally healthy cohort of 18- to 44-year-olds, and most participants who developed first-onset TMD had experienced symptoms for only 1 or 2 months. There are several limitations to the interpretation of findings that merit discussion. Despite demonstrating that a history of pain conditions, sleep disturbance, digit ratio, and smoking preceded incident first-onset TMD, no finding is sufficient to infer a causal relationship. However, the new information does permit us to speculate about plausible mechanisms through which these predictors may operate. Although the PSQI is a psychometrically sound measure of sleep quality and disturbance, the subjective assessment falls short of evaluating specific sleep problems such as sleep disordered breathing, for which measures such as hypoxemia and arousal may underlie this relationship. We believe this is an important area for future research using overnight sleep monitoring. This investigation would clarify whether hypoxemia plays a role in systemic inflammation in TMD pathophysiology. Some of the health status variables examined in this study were obtained by self-report of lifetime history. Although this may introduce recall bias, there is no reason to believe that recall precision differs between with and without first-onset TMD. Hence, any misclassification would bias findings toward the null hypothesis. Loss to follow-up is an important source of bias when loss occurs more commonly in specific subgroups. The implications of this bias and our strategies for handling bias are discussed elsewhere.[4]

In conclusion, preexisting pain conditions, sleep disturbance, cigarette smoking, and high 2D:4D digit ratio were independent risk factors for first-onset TMD. This knowledge presents opportunities to explore aspects of general health and overlapping pain conditions for future therapeutic approaches to prevent TMD.

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Supplementary Data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpain.2013.06.001.

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