Journal of Dental Research
2016, Vol. 95(10) 1084–1092

DOI: 10.1177/0022034516653743
jdr.sagepub.com

Painful Temporomandibular Disorder: Decade of Discovery from OPPERA Studies

G.D. Slade[1,2,3], R. Ohrbach[4], J.D. Greenspan[5,6], R.B. Fillingim[7], E. Bair[1,8,9], A.E. Sanders[1,2], R. Dubner[5], L. Diatchenko[10], C.B. Meloto[10], S. Smith[11], and W. Maixner[11]

Abstract

In 2006, the OPPERA project (Orofacial Pain: Prospective Evaluation and Risk Assessment) set out to identify risk factors for development of painful temporomandibular disorder (TMD). A decade later, this review summarizes its key findings. At 4 US study sites, OPPERA recruited and examined 3,258 community-based TMD-free adults assessing genetic and phenotypic measures of biological, psychosocial, clinical, and health status characteristics. During follow-up, 4% of participants per annum developed clinically verified TMD, although that was a "symptom iceberg" when compared with the 19% annual rate of facial pain symptoms. The most influential predictors of clinical TMD were simple checklists of comorbid health conditions and nonpainful orofacial symptoms. Self-reports of jaw parafunction were markedly stronger predictors than corresponding examiner assessments. The strongest psychosocial predictor was frequency of somatic symptoms, although not somatic reactivity. Pressure pain thresholds measured at cranial sites only weakly predicted incident TMD yet were strongly associated with chronic TMD, cross-sectionally, in OPPERA's separate case-control study. The puzzle was resolved in OPPERA's nested case-control study where repeated measures of pressure pain thresholds revealed fluctuation that coincided with TMD's onset, persistence, and recovery but did not predict its incidence. The nested case-control study likewise furnished novel evidence that deteriorating sleep quality predicted TMD incidence. Three hundred genes were investigated, implicating 6 single-nucleotide polymorphisms (SNPs) as risk factors for chronic TMD, while another 6 SNPs were associated with intermediate phenotypes for TMD. One study identified a serotonergic pathway in which multiple SNPs influenced risk of chronic TMD. Two other studies investigating gene-environment interactions found that effects of stress on pain were modified by variation in the gene encoding catechol *O*-methyltransferase. Lessons learned from OPPERA have verified some implicated risk factors for TMD and refuted others, redirecting our thinking. Now it is time to apply those lessons to studies investigating treatment and prevention of TMD.

Keywords: chronic pain, psychological stress, pain threshold, human COMT protein, gene-environment interaction, cohort studies

[1]Center for Pain Research and Innovation, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
[2]Department of Dental Ecology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
[3]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
[4]Department of Oral Diagnostic Sciences, University at Buffalo, Buffalo, NY, USA
[5]Department of Neural and Pain Sciences, University of Maryland School of Dentistry, Baltimore, MD, USA
[6]Brotman Facial Pain Clinic, University of Maryland School of Dentistry, Baltimore, MD, USA
[7]Department of Community Dentistry and Behavioral Science, University of Florida, Gainesville, FL, USA
[8]Department of Endodontics, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
[9]Department of Biostatistics, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
[10]The Allan Edwards Centre for Research on Pain, McGill University, Montreal, Canada
[11]Center for Translational Pain Medicine, Duke University, Durham, NC, USA

A supplemental appendix to this article is published electronically only at http://jdr.sagepub.com/supplemental.

Corresponding Author:
G.D. Slade, Koury Oral Health Sciences, UNC School of Dentistry, 385 South Columbia Street, CB#7455, Room 4501E, Chapel Hill, NC 27599-7455, USA.
Email: gary_slade@unc.edu

Introduction

In 2004, the National Institutes of Health (NIH) sought proposals for a prospective cohort study to "identify the incidence of craniofacial pain and dysfunction and its risk factors." Referring to the existing cross-sectional evidence, the NIH cited numerous factors that "may be implicated" in the etiology of temporomandibular disorder (TMD), including age, sex, stress, depression, somatic symptoms, orthodontic treatment, occlusal or masticatory dysfunction, extraction of third molars, facial trauma, and degenerative arthritis. The funding opportunity was effectively a rallying call to apply the full expanse of the biopsychosocial model (Engel 1977) to an epidemiologic study of painful TMD. In moving beyond prevailing biomechanical explanations of TMD, the funding opportunity responded to a call that research shift away "from chasing occlusal contacts" and toward "vulnerability alleles" (Stohler 2004). Controlling risk factors for TMD is a first step toward reducing health care costs, which are 60% greater for TMD patients than for primary health care patients (White et al. 2001).

The NIH subsequently funded a project entitled Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA), which enrolled its first study participant in 2006. A wide array of putative risk factors was measured, ranging from genotypes to intermediate phenotypes of psychological distress and pain amplification to environmental influences and clinical aspects of TMD itself. One decade later with 4,346 participants enrolled, the project has produced a wealth of evidence about TMD in adults—verifying some previously implicated risk factors, refuting others, and casting new light on TMD etiology. This review summarizes selected findings from OPPERA's 35 papers published to date and considers directions for future epidemiologic research into TMD.

Overview of OPPERA's Component Studies and Methods

The OPPERA study population comprised community-based volunteers aged 18 to 44 y living at 4 US locations: Baltimore, MD; Buffalo, NY; Chapel Hill, NC; and Gainesville, FL. Between 2006 and 2013, 4,346 subjects were recruited through advertisements, emails, and flyers, yielding a sample that broadly reflected the United States' main sociodemographic groups (Appendix Table 1). There were 3 study designs: a prospective cohort study, a case-control study, and a nested case-control study.

The prospective cohort study aimed to determine the incidence rate of first-onset TMD. At the baseline visit, the 3,258 enrollees were examined with the Research Diagnostic Criteria for TMD (Dworkin and LeResche 1992) to exclude any participants with clinical TMD. Participants completed an extensive array of psychosocial questionnaires; autonomic function and sensitivity to experimental pain were measured; and a blood sample was collected (Appendix Table 2). Follow-up occurred over a median 2.8-y period after enrollment when participants completed quarterly health questionnaires to screen for symptoms of TMD. Those reporting symptoms were asked to return to research clinics where examiners repeated the orofacial examination, yielding 260 incident cases of first-onset TMD myalgia and/or arthralgia through May 2011 (Bair, Brownstein, et al. 2013).

Realizing that the prospective cohort study would require several years of follow-up, a case-control study of chronic TMD was undertaken by additionally recruiting 1,088 participants with chronic TMD (Slade et al. 2011). The case classification required a history of facial pain for at least 5 d per month in the preceding 6 mo, together with examiner-verified myalgia and/or arthralgia. Chronic TMD cases completed the same baseline data collection procedures as enrollees in the prospective cohort study.

The third study design captured more detailed information from the 260 incident cases and from a sample of participants in the prospective cohort study who remained TMD free (n = 196). In this nested case-control study design, controls were matched to incident cases according to time since enrollment, study site, and sex (Slade et al. 2014). Incident cases and selected controls repeated most of the data collection procedures performed at enrollment. Six months later, they were asked to return to research clinics for a third visit where clinical TMD examinations were repeated, along with most of the data collection procedures performed at preceding visits.

The study was reviewed and approved by the Institutional Review Boards of the OPPERA study sites.

Selected Findings

4% Annual Incidence: Just the Tip of the Iceberg

In the prospective cohort study, the incidence rate of first-onset TMD was 3.9% per annum (Slade, Bair, et al. 2013). In other words, for every 100 TMD-free people enrolled, nearly 4 individuals per year developed the condition. Their pain event was not fleeting: the threshold for incident case classification was ≥5 d with TMD pain symptoms per month in ≥1 mo during a 3-mo reporting period. Incident cases rated their average pain unpleasantness as "slightly annoying" and pain intensity as "very mild" or "mild," using verbal descriptor scales (Gracely et al. 1978). Often, the condition persisted: when reexamined 6 mo after TMD first developed, almost half (49%) of incident cases still had TMD.

Facial pain symptoms occurred early and often for many study participants, including some who never developed clinical TMD (Slade, Sanders, et al. 2013). Overall, one-third of cohort members reported ≥1 symptom episodes (i.e., facial pain for ≥5 d per month for ≥1 mo during a 3-mo reporting period). Initial symptom episodes occurred at a rate of 18.8% per annum. The rate doubled during follow-up of those who had an initial episode, and it doubled again in follow-up of those with recurrent symptoms. The sheer number of symptom episodes represents a "symptom iceberg" in the community, so named because it represents subclinical suffering that rarely comes to the attention of health care providers, yet it portends substantially elevated risk for future symptoms.

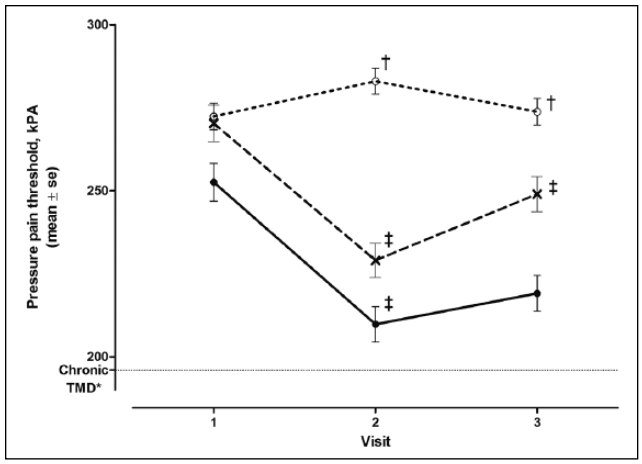

Figure 1. Pressure pain thresholds fluctuate with, but do not predict, onset and persistence of painful temporomandibular disorder (TMD). Reprinted from Slade et al. (2014). Adjusted mean pressure pain thresholds pooled from 5 anatomic locations measured at 3 visits in each of 3 study groups: OPPERA nested case-control study of TMD incidence. After enrollment (visit 1), the first follow-up (visit 2) occurred when TMD first developed or the matched control was selected, varying from 0.2 to 4.5 y after visit 1. The second follow-up (visit 3) occurred approximately 8 mo after visit 2 (range = 6 to 15 mo). Data are from 72 persistent TMD cases who developed first-onset TMD at visit 2 that persisted at visit 3 (●), 75 transient TMD cases who developed first-onset TMD at visit 2 that remitted at visit 3 (X), and 126 TMD-free controls (○). Symbols represent *P* values testing the null hypothesis that the adjusted mean threshold at one visit is equal to the adjusted mean threshold at the preceding visit in the same study group: ‡$P < 0.01$; †$0.01 < P < 0.05$. *Reference values for chronic TMD are from Greenspan et al. (2011). OPPERA, Orofacial Pain: Prospective Evaluation and Risk Assessment.

Demographics: Sex and Race Paradoxes

There were some unexpected demographic patterns in the distribution of orofacial pain. The rate of TMD symptoms was no greater in women than in men. Likewise, the incidence rate of clinically verified TMD was only marginally greater in women than men (hazard ratio = 1.3, $P = 0.06$). This contrasted with US population estimates from the National Health Interview Survey, where prevalence of TMD symptoms in women was twice that of men (Maixner et al. in press).

OPPERA's findings of racial differences in incidence were also unexpected. The rate of TMD symptoms in African Americans was twice that of whites, and the rate of clinically verified TMD was 52% greater (hazard ratio = 1.5, $P = 0.01$). Yet, in the National Health Interview Survey, prevalence of facial pain symptoms in African Americans was half that of whites (Maixner et al. in press).

These seemingly discrepant findings are due in part to prevalence-incidence bias (Friedman et al. 1966), a form of selection bias affecting cross-sectional study designs. Because they measure health status at only 1 point in time, cross-sectional studies are more likely to record disease in incident cases whose disease persists than in those whose condition resolves quickly. The bias, in turn, affects demographic associations when persistence varies according to demographics. This was seen in the nested case-control study: 6 mo after TMD onset, 54% of females versus 41% of males had persistent TMD. Also, TMD persisted in 61% of whites versus 35% of African Americans.

Somatic Symptoms: The Most Important Psychosocial Predictor of TMD Incidence

Frequency of somatic symptoms was the strongest psychosocial predictor of TMD incidence (Fillingim et al. 2013). The Pennebaker Inventory of Limbic Languidness asks about frequency of multiple somatic symptoms—for example, running nose, fatigue, and dizziness. Participants with scores in the upper tercile (i.e., symptoms occurring at least monthly, on average) had approximately twice the incidence rate of TMD as participants with less frequent somatic symptoms. The finding that a high score was the most important predictor was based on results from a random forest modeling procedure that evaluated all 26 psychosocial measures, quantifying the contribution of each one to the accuracy of predicting incident TMD. Much smaller contributions were made from measures of psychological stress, anxiety, obsessive-compulsive feelings, and pain-coping strategies (Fillingim et al. 2013). It was noteworthy, however, that reactivity to sensory stimuli, assessed with the Kohn Reactivity Scale, was not a significant univariate predictor of TMD.

Pain Thresholds: A Consequence of TMD, Not a Predictor of It

Many cross-sectional studies have reported greater sensitivity to experimental pain in TMD cases as compared with controls, even when sensitivity is measured at noncranial sites. This has been variously attributed to alterations in sensory, endocrine, inflammatory, and psychological processes (Lautenbacher et al. 1994), with greatest credence given to central sensitization (Woolf 2011). The OPPERA case-control study likewise found that chronic TMD cases had greater sensitivity to pressure pain, heat, and pinprick stimuli than controls (Greenspan et al. 2011). The strongest associations with chronic TMD were seen for pressure pain, with odds ratios ranging from 2.6 to 3.7 ($P < 0.001$) for thresholds measured at the trapezius and temporalis muscles, respectively. However, only a few of those measures were also significant predictors of TMD incidence, and effect estimates were weak (i.e., hazard ratios ranging from 1.1 to 1.2; Greenspan et al. 2013).

The puzzle was at least partly resolved by analyzing repeated measurements of pressure pain thresholds in the nested case-control study (Slade et al. 2014). In persistent TMD cases, mean thresholds reduced by 17% between enrollment and TMD onset and did not change significantly thereafter (Fig. 1). In transient TMD cases, mean thresholds initially reduced by 15% ($P < .001$) between enrollment and the TMD onset but increased by 9% ($P < .001$) once clinical TMD had resolved. Thresholds in controls did not change significantly over time. In other words, pressure pain thresholds fluctuated in response to onset and remission of TMD but did not usefully predict such changes. We speculated that painful TMD represents a trigger that increases synaptic efficacy of neurons in

Table 1. Tests for Genetic Association between SNPs and TMD-Related Outcome Measures.

Gene	Definition	SNP	Minor Allele	Effect Estimate[a]	*P* Value
			Outcome: Chronic TMD[b]		
NR3C1	Glucocorticoid receptor	rs2963155	G	OR = 0.63	6.2E-05
HTR2A	Serotonin 2A receptor	rs9316233	G	OR = 0.64	3.4E-04
CHRM2	Muscarinic cholinergic receptor 2	rs7800170	A	OR = 0.72	6.2E-04
CAMK4	Calcium/calmodulin-dependent protein kinase 4	rs3756612	G	OR = 1.51	6.4E-04
IFRD1	Interferon-related developmental regulator 1	rs728273	G	OR = 1.38	1.2E-03
GRK5	G protein–coupled receptor kinase 5	rs12415832	A	OR = 2.4	1.3E-03
			Outcome: Nonspecific orofacial symptoms[c]		
SCN1A	Voltage-gated sodium channel, type 1	rs6432860	A	OR = 1.43	2.8E-05
ACE2	Angiotensin I–converting enzyme 2	rs1514280	A	OR = 1.32	4.9E-05
			Outcome: Global psychological symptoms[c]		
PTGS1	Prostaglandin-endoperoxide synthase 1	rs3842803	C	$\beta = -0.22$	2.8E-06
			Outcome: Stress and negative affectivity[c]		
APP	Amyloid beta (A4) precursor protein	rs466448	A	$\beta = 0.11$	4.3E-05
			Outcome: Heat pain temporal summation[c]		
MPDZ	Multiple PDZ domain protein	rs10809907	C	$\beta = 0.16$	3.1E-05

SNP, single-nucleotide polymorphism; TMD, temporomandibular disorder.
[a]OR, odds ratio for codominant test for association with binary outcome measure. β, linear regression parameter estimate of change in *z* score transformation of outcome measure associated with each copy of the minor allele.
[b]Smith et al. (2011).
[c]Smith et al. (2013).

nociceptive pathways, including pathways that participate in enhanced central nervous system sensitization.

Genetic Associations: SNPs and Biological Pathways of Their Combined Effects

The OPPERA case-control study evaluated genetic associations with chronic TMD using a panel of 2,924 single-nucleotide polymorphisms (SNPs) representing 358 genes involved in biological systems relevant to pain perception. Six SNPs had stronger-than-expected associations within the distribution of *P* values for all tested SNPs (Table 1). One SNP was in the glucocorticoid receptor gene, suggesting a contribution of the hypothalamic-pituitary-adrenal system to chronic TMD. Another SNP was in the serotonin receptor gene, supporting other studies indicating that the gene influences nociceptive and affective pathways. The other 4 SNPs had not previously been associated with pain in humans and therefore represented novel findings implicating yet other biologic processes involved in chronic TMD.

The prospective cohort of initially TMD-free individuals provided an opportunity to investigate genetic associations with intermediate phenotypes, defined as "measurable components unseen by the unaided eye along the pathway between disease and distal genotype" (Gottesman and Gould 2003). Four SNPs had associations that exceeded the false discovery rate (Smith et al. 2013). One was in the gene encoding the alpha subunit of the voltage-gated sodium channel Nav1.1, which influences action potentials in sensory nerves. It was associated with nonspecific orofacial symptoms such as jaw stiffness and fatigue. The same intermediate phenotype was associated with variation in a gene, angiotensin I–converting enzyme, which is implicated in hypertension. Meanwhile, global psychological and somatic symptoms were associated with an SNP in the prostaglandin-endoperoxide synthase 1 gene, also known as COX-1, which regulates nociception and inflammatory response. Psychological stress and negative affectivity were associated with variation in the gene encoding APP, amyloid beta (A4) precursor protein, which affects synapse formation and neuronal plasticity. Finally, heat pain temporal summation was associated with an SNP in the multiple PDZ domain protein gene, which influences G protein–coupled receptors involved in nociception and analgesia.

While individual SNPs provide important insights into etiology, complex conditions such as TMD are likely influenced by combined effects of multiple SNPs operating through specific biological pathways. Pathway analysis is a bioinformatics procedure that combines gene-disease association signals from several sets of genes that regulate predefined cellular pathways (Elbers et al. 2009). OPPERA was 1 of 2 cohorts in a discovery-and-replication strategy to identify genetically regulated pathways relevant to TMD. Two subtypes of chronic TMD cases were defined according to the presence or absence of additional widespread body palpation pain (Slade, Smith, et al. 2013). Relative to controls, cases of TMD without widespread pain had enrichment of genetic associations in a serotonergic signaling pathway, a finding that remained statistically significant when replicated in the OPPERA cohort (Fig. 2). The specificity of the association for localized TMD suggested that the pathway elicited local hyperalgesia through activation of peripheral serotonin receptors but was counteracted by an adequate central serotonergic response mechanism that limits potential for more widespread pain.

COMT Genotype Modifies Effects of Stress on Sensitivity to Noxious Stimuli and Incidence of TMD

Two analyses focused on the gene catechol *O*-methyltransferase (*COMT*) because of its previously reported association with

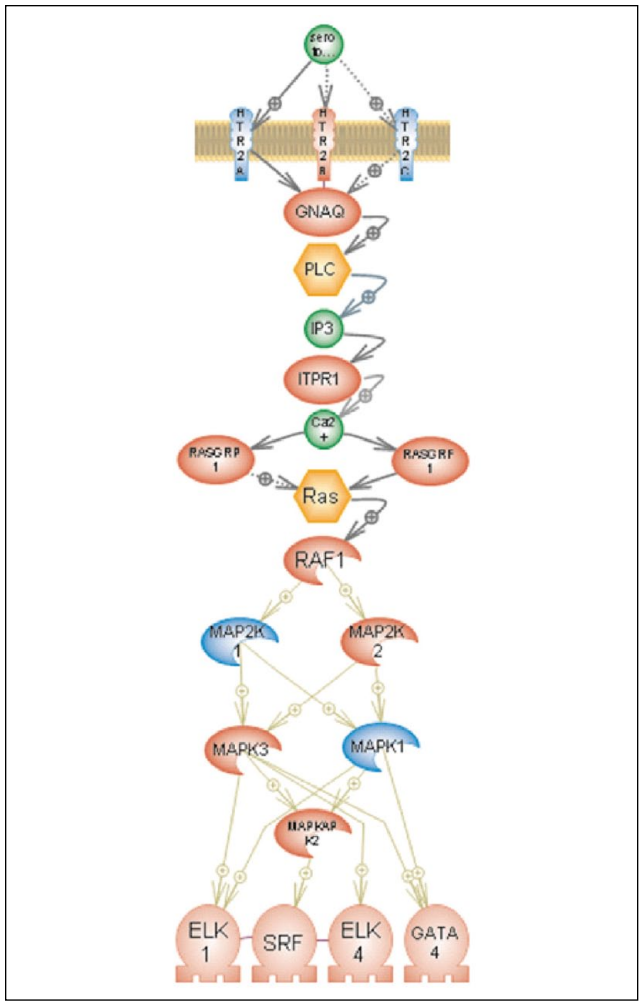

Figure 2. Cellular pathways associated with localized temporomandibular disorder. From Slade, Smith, et al. (2013). Genes shown in blue are significantly associated with case status ($P < 0.05$). *HTR2A*, 5-hydroxytryptamine receptor 2A (OMIM 182135); *HTR2C*, 5-hydroxytryptamine receptor 2C (OMIM 312861); *MAPK1*, mitogen-activated protein kinase 1 (OMIM 176948); *MAP2K1*, mitogen-activated protein kinase 1 (OMIM 176872).

experimental pain (Diatchenko et al. 2006) and clinical TMD (Diatchenko et al. 2005). Gene-environment interactions with psychological stress were investigated because of the known role of COMT in regulating catechol neurotransmitter catabolism, a process critical to the stress response. While the 2 studies had noteworthy differences in pain and stress phenotypes selected for analysis, the findings were consistent in demonstrating potential for COMT to modify the effect of psychological stress on pain.

One study using experimental pain as the dependent variable evaluated cross-sectional associations of COMT haplotype, experimental stress, and the 2-way interactions (Meloto et al. 2015). Experimental pain was evoked through repeated thermal stimuli applied to the arm, and stress was reported on a rating scale of 0 to 100. Summary variables of overall pain and maximum pain rating were both positively associated with stress. Pain ratings were also greater in participants with haplotypes coding for low-activity COMT, signifying impaired catabolism of catecholamines. Significant interaction also occurred whereby the genetic association with pain was more pronounced in participants who experienced lower levels of stress.

The other study investigated contributions of COMT haplotypes to incidence of first-onset TMD in the prospective cohort study. The Perceived Stress Scale (Cohen et al. 1983) measured response to common psychological stressors at enrollment and once every 3 mo during follow-up (Slade et al. 2015). Stress increased to a greater degree in incident cases as compared with those who remained TMD free, although this effect was limited to participants with haplotypes coding for low-activity COMT (Fig. 3). A Cox model with stress as a time-varying covariate revealed a significant genetic interaction such that a postbaseline increase in stress more than doubled the rate of TMD in participants with low-activity COMT haplotypes but not in participants with high-activity COMT haplotypes.

Oral Parafunction and TMJ Derangements: Patients Know Best

The clinical examination included assessments of tooth wear (an indicator of oral parafunction) and TMJ noises during jaw movement (indicators of internal joint derangement). In the case-control study, both indicators were associated with chronic TMD, with corresponding odds ratios of 2.3 and 3.4, respectively (Ohrbach et al. 2011). However, associations were markedly stronger with participant-reported measures. Participants reporting multiple parafunctional behaviors in the Oral Behaviors Checklist questionnaire (Markiewicz et al. 2006) had 16 times the odds of chronic TMD as participants who reported only a few. Likewise, the odds ratio associated with self-reported TMJ noises was 30.2. We commented, however, that these double-digit measures of effect were almost certainly biased, probably due to differential recall by TMD cases versus controls.

Greater emphasis was therefore given to findings from the prospective cohort study, which eliminated any effects of recall bias by assessing parafunction and joint noises at enrollment, before TMD developed. It turned out that effect measures were not only smaller but also statistically nonsignificant for both examiner-assessed measures of tooth wear and joint derangement (Ohrbach et al. 2013). However, self-reported temporomandibular joint noises remained a significant predictor of TMD incidence. To underscore the value of self-reported measures, the Oral Behaviors Checklist scale emerged as the strongest predictor of incident TMD among all clinical variables—both examiner assessed and self-reported. There was a clear threshold effect such that risk of TMD was elevated only in participants who reported multiple behaviors that occurred frequently. We speculated that this density of parafunctional behavior in initially TMD-free participants probably signified some form of central dysregulation, such as heightened motor

activation, diminished motor inhibition, reduced proprioception, or persistent psychophysiologic reactivity.

Comorbid Conditions: Nonpainful Ones Also Matter

Another of the strongest risk factors for developing TMD was also one of the simplest to assess: a checklist of 20 health conditions (e.g., abdominal pain, depression, ringing in the ears). In random forest modeling that considered multiple health status measures, the checklist was the most important predictor of incident TMD (Sanders, Slade, et al. 2013). In some respects, this was not surprising, given good evidence from other studies that pain elsewhere in the body strongly predicts TMD (Von Korff et al. 1993; John et al. 2003). However, the checklist was a significant predictor after controlling for more specific, validated measures of similar constructs, such as the ROME measure of irritable bowel syndrome (Longstreth et al. 2006) and SCL-90-R depression scale (Derogatis 1994). Moreover, the majority of checklist items were not primarily painful and instead represent ill-defined "comorbid" conditions (Valderas et al. 2009), suggesting that they are consequences of underlying mechanisms contributing to TMD and the comorbid conditions. There was evidence that cigarette smoking might be one such risk factor. In multivariable modeling, it was associated with increased risk of TMD, even after adjusting for painful and nonpainful health conditions. Overall, the findings point to the importance of general indicators of poor health in predicting TMD incidence, filling a gap identified in an earlier systematic review of TMD etiology that found insufficient evidence regarding the potential effects of comorbidities on TMD (Macfarlane et al. 2001).

Sleep and Sleep Breathing: The Relationship with TMD

It is well established that the relationship between pain and sleep is bidirectional: pain disturbs sleep, and poor sleep exacerbates pain. Only in recent years have more nuanced study designs determined that sleep impairment is a stronger predictor of pain, rather than the converse (Finan et al. 2013). To explore sleep quality in OPPERA, the Pittsburgh Sleep Quality Index was administered at enrollment in the prospective cohort study. Analysis showed that for each standard deviation decrement in sleep quality, the rate of first-onset TMD increased 40% (Sanders, Slade, et al. 2013). Sleep quality was also monitored over time when participants completed a sleep quality rating scale of 0 to 10 every 3 mo throughout follow-up. In those who developed TMD, sleep quality deteriorated progressively leading up to TMD onset, independent of psychosocial stress and other major TMD predictors. By contrast, sleep quality remained stable in participants who remained TMD free (Fig. 4). We then examined the possibility, demonstrated elsewhere (Onen et al. 2001; Smith et al. 2007), that disturbed sleep induces pain development via increased sensitivity to experimental pain. We indexed the latter in the nested case-control study using pressure pain threshold and average

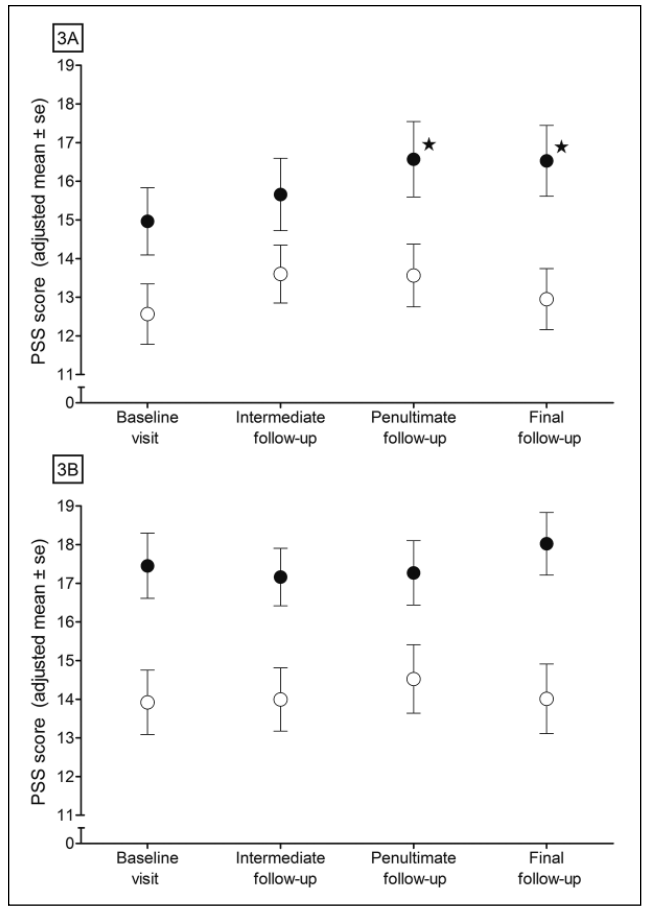

Figure 3. Psychological stress increases in participants with low-activity catechol *O*-methyltransferase (COMT) diplotypes who develop first-onset temporomandibular disorder (TMD) but not in other groups. From Slade et al. (2015). Adjusted mean Perceived Stress Scale (PSS) scores at 4 time points for incident cases of first-onset TMD (●) and TMD-free controls (○), stratified according to diplotypes of the gene encoding COMT: (**A**) incident cases (n = 96) and TMD-free controls (n = 90) with low-activity COMT diplotypes (HPS-APS, HPS-HPS, APS-APS, or HPS-LPS); (**B**) incident cases (n = 84) and TMD-free controls (n = 63) with high-activity COMT diplotypes (LPS-LPS or LPS-APS). The 4 periods were as follows: the day of the baseline visit, when all participants were TMD free; intermediate follow-up, the quarterly periods after enrollment but before the penultimate quarter; the penultimate follow-up, the quarterly period preceding the final quarter; and the final follow-up, the quarterly period that coincided with the clinical visit at which incident TMD was determined. Error bars represent ±1 standard error (se) of the adjusted mean. Data points denoted by a star (★) represent PSS scores that differ significantly (P < 0.05) from baseline for participants with the same case classification within the same stratum of COMT diplotype. low (LPS), average (APS), and high pain sensitive (HPS).

pinprick pain sensation at baseline as well as changes in each measure during follow-up. The findings of formal mediation analysis were null, meaning that sensitivity to pain did not mediate the relationship between sleep quality and first-onset TMD.

Another intriguing aspect of the sleep and pain relationship is sleep-disordered breathing. A loss of muscle tonicity during sleep leads to partial or complete closure of the upper airway and disordered sleep breathing. Obstructive sleep apnea is a

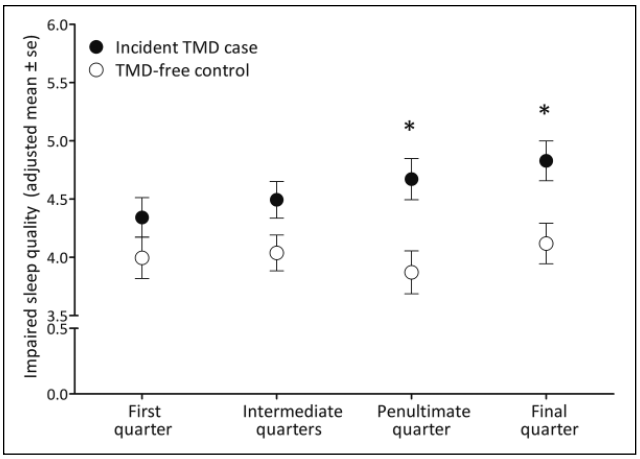

Figure 4. Sleep quality worsens prior to onset of temporomandibular disorder (TMD) in incident cases while remaining unchanged for matched controls. Reproduced from Sanders et al. (2016). Sleep quality was rated on a scale of 0 to 10 (0 = worst sleep, 10 = best sleep) in questionnaires completed once every quarter during follow-up of first-onset TMD cases (n = 220) and controls (n = 193) in the OPPERA nested case-control study. The 4 periods on the horizontal axis refer to the following: the first quarter (i.e., 3 mo) after enrollment; the intermediate quarters, between the first and penultimate quarters; the penultimate quarter, 3 mo before the final quarter; and the final quarter, the 3-mo interval prior to the follow-up visit at which presence or absence of TMD was determined. Error bars represent ±1 standard error (se) of the adjusted mean. Estimates are adjusted for study site, sex, age in years, and race/ethnicity. Asterisk (*) signifies a statistically significant difference ($P < 0.05$) as compared with the first quarter in the same study group. OPPERA, Orofacial Pain: Prospective Evaluation and Risk Assessment.

severe form of sleep-disordered breathing. OPPERA asked questions at baseline about 4 cardinal obstructive sleep apnea signs/symptoms: loud snoring, daytime sleepiness, witnessed apnea, and hypertension. Compared with participants with none or 1 of these characteristics, participants with ≥2 symptoms had a 73% greater hazard of developing TMD (Sanders, Essick, et al. 2013).

Putting It All Together: Finding the Forest among the Trees

The prospective cohort study evaluated 202 phenotypic risk factors from 6 domains: sociodemographic, general health status, pain sensitivity, cardiac autonomic function, and psychological and clinical orofacial characteristics. This called for novel methods of multivariable modeling that could identify independent contributions of each risk factor and rank their importance in predicting TMD (Bair, Ohrbach, et al. 2013). One approach used penalized Cox regression, and the other used random forest models. Both overcome bias arising in regular regression models when selecting or ranking variables. Random forest models have the additional benefit of modeling nonlinear effects of continuous variables on the rate of TMD. Findings from both methods were consistent in finding that health status variables made the greatest contribution to TMD, followed closely by variables from psychological and clinical orofacial domains (Table 2). There were much smaller independent contributions from the sociodemographic, pain sensitivity, and autonomic function domains.

Table 2. Putative Temporomandibular Disorder Risk Factors with the Largest Importance Scores.

Domain: Variable	Importance Score	Rank
Autonomic		
HRV: total power (color-word Stroop)	19.1	15
Average mean arterial pressure (pain-affect Stroop)	16.2	17
Average mean arterial pressure (color-word Stroop)	15.8	19
Average heart rate—ECG (pain-affect Stroop)	12.6	22
HRV: total power (pain-affect Stroop)	10.8	28
Clinical		
Count of nonspecific orofacial symptoms	92.9	2
Oral parafunction sum score (OBC)	66.0	5
Could not open mouth wide in the last month	54.1	6
No. of palpation sites with pain (right masseter)	50.0	8
Ever had orthodontic procedures	29.3	12
Demographic		
Age	51.6	7
Marital status	44.7	9
Race	25.1	13
Lifetime US residence	12.4	23
Satisfaction with financial situation	5.5	58
Health status		
Count of 20 comorbid conditions	100.0	1
Bodily pain (SF-12v2)	80.6	4
General health (SF-12v2)	31.8	11
No. of different types of headaches in the last year	16.1	18
Sleep latency (PSQI)	12.7	21
Pain sensitivity		
Pressure pain threshold (masseter)	5.8	53
Heat pain ratings of 10 stimuli: area under curve (48 °C)	4.2	62
Pressure pain threshold (trapezius)	3.7	66
Thermal pain single stimulus rating (46 °C)	3.6	67
Thermal pain single stimulus rating (48 °C)	3.5	68
Psychosocial		
Somatic symptom reporting (PILL)	42.4	10
Catastrophizing—magnification (PCS)	10.4	30
EPQ Lie scale	9.9	31
Anxiety (SCL-90-R)	9.7	32
Mood—clearheaded/confused (POMS-Bi)	6.5	46

Reproduced from Bair, Ohrbach, et al. (2013).
ECG, electrocardiogram; EPQ, Eysenck Personality Questionnaire; HRV, heart rate variability; OBC, Oral Behaviors Checklist; PCS, Pain Catastrophizing Scale; PILL, Pennebaker Inventory of Limbic Languidness; POMS-Bi, Profile of Mood States: Bi-polar Form; PSQI, Pittsburgh Sleep Quality Index; SCL-90-R, Symptom Checklist-90-R; SF-12v2, Medical Outcomes Study Short Form 12 Item Version 2.

A different method of multivariable data analysis was then applied to create a clinically applicable tool to classify people with or at risk of TMD (Bair et al. 2016). This called for data reduction so that prediction could be achieved through only a few measures that are feasible in clinical practice. Another requirement was that individuals be reliably and unambiguously classified into meaningful categories based on their risk profiles. The method

was supervised cluster analysis, and it reliably identified 3 clusters based on distinctive risk factor profiles in each group—"adaptive," "pain sensitive," and "global symptoms." Cluster membership was strongly associated with odds of chronic TMD and with risk of developing first-onset TMD, thereby providing good evidence of predictive validity. Nearest centroid models were then fit with only 4 variables, providing promise that individuals could be classified into clusters by a relatively small number of variables.

Limitations and Future Directions

Findings summarized here are limited to adults aged 18 to 44 y who have been followed for no more than 5 y, with TMD representing the primary pain outcome. Inevitably, loss to follow-up produced some problems with missing data, although analytic methods were identified to control bias (Bair, Brownstein, et al. 2013). Genetic association studies to date have been limited to targeted genes, although a genome-wide association study is now underway, and a second wave of studies that began in 2013 has broadened the scope of biomarkers to include RNA and protein expression. Those studies will also investigate other idiopathic pain conditions that overlap with TMD. Other limitations have been discussed elsewhere (Slade, Fillingim, et al. 2013).

Conclusion

The decade of research discoveries summarized above endorses the premise underlying the National Institute of Dental and Craniofacial Research's call for studies of TMD etiology—namely, that TMD is a complex disorder resulting from an interplay of causes from multiple genetic and environmental domains. Time adds another dimension, with several risk factors exerting influences for some years before TMD manifests and with some fluctuating as the condition develops and either progresses or remits.

This complex etiology can seem overwhelming when considering the clinical implications of these findings. However, we see several general themes that should be applied judiciously to guide patient care. First, it is clear that TMD develops at a disproportionately high rate in people with relatively poor health, whether in the form of comorbid disease, other pain conditions, poor sleep quality, or cigarette smoking. Efforts to promote general health should therefore be supported as a method of primary prevention for TMD. Second, it is noteworthy that some of the strongest predictors of developing TMD are also the easiest to assess, including simple participant-completed checklists. Third is the encouraging finding that even hundreds of risk factors can be distilled by rigorous application of cluster analysis to reliably categorize participants into a few clinically relevant subgroups.

These findings also make it clear that there are distinct pathways of TMD etiology. For example, there appears to be interplay of central and peripheral nociceptive mechanisms that contribute to some manifestations of TMD, while other mechanisms reflect gene-environment interactions. Those pathways will be understood more completely as new research is undertaken. Nonetheless, the general notion of distinct pathways—coupled with findings that biopsychosocial risk factors define distinct clusters of people with or at risk of TMD—supports the ideas underlying a precision medicine approach to treating TMD. That premise likewise requires testing through rigorous clinical research. Taken together, they represent fascinating opportunities for the next decade of TMD research.

Author Contributions

G.D. Slade, contributed to conception, design, data acquisition, analysis, and interpretation, drafted and critically revised the manuscript; R. Ohrbach, J.D. Greenspan, R.B. Fillingim, L. Diatchenko, C.B. Meloto, S. Smith, contributed to conception, critically revised the manuscript; E. Bair, contributed to data acquisition and analysis, critically revised the manuscript; A.E. Sanders, contributed to conception and design, drafted and critically revised the manuscript; R. Dubner, contributed to data interpretation, critically revised the manuscript; W. Maixner, contributed to data acquisition, critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

Acknowledgments

This work was supported by the National Institutes of Health and the National Institute of Dental and Craniofacial Research (grants U01-DE017018, R0-1DE016155, R03-DE022595, R03DE023592). Drs. Fillingim, Smith, Maixner, and Diatchenko have equity ownership in Algynomics Inc., the commercial provider of the genotyping platform used in studies summarized here. Drs. Maixner and Diatchenko are consultants to the company and on the Board of Directors. Drs. Maixner and Diatchenko are inventors on a patent application related to COMT haplotypes and pain sensitivity, which has been licensed to Proove Biosciences. These relationships have been reviewed in conjunction with this research and are under management by the University of North Carolina–Chapel Hill and Duke University. The authors declare no other potential conflicts of interest with respect to the authorship and/or publication of this article.

References

Bair E, Brownstein NC, Ohrbach R, Greenspan JD, Dubner R, Fillingim RB, Maixner W, Smith SB, Diatchenko L, Gonzalez Y, et al. 2013. Study protocol, sample characteristics, and loss to follow-up: the OPPERA prospective cohort study. J Pain. 14(12 Suppl):T2–T19.

Bair E, Gaynor S, Slade GD, Ohrbach R, Fillingim RB, Greenspan JD, Dubner R, Smith SB, Diatchenko L, Maixner W. 2016. Identification of clusters of individuals relevant to temporomandibular disorders and other chronic pain conditions: the OPPERA study. Pain. 157(6):1266–1278.

Bair E, Ohrbach R, Fillingim RB, Greenspan JD, Dubner R, Diatchenko L, Helgeson E, Knott C, Maixner W, Slade GD. 2013. Multivariable modeling of phenotypic risk factors for first-onset TMD: the OPPERA prospective cohort study. J Pain. 14(12 Suppl):T102–T115.

Cohen S, Kamarck T, Mermelstein R. 1983. A global measure of perceived stress. J Health Soc Behav. 24(4):385–396.

Derogatis L. 1994. The SCL-90-R: administration, scoring and procedures manual. Minneapolis (MN): National Computer Systems, Inc.

Diatchenko L, Nackley AG, Slade GD, Bhalang K, Belfer I, Max MB, Goldman D, Maixner W. 2006. Catechol-*O*-methyltransferase gene polymorphisms are associated with multiple pain-evoking stimuli. Pain. 125(3):216–224.

Diatchenko L, Slade GD, Nackley AG, Bhalang K, Sigurdsson A, Belfer I, Goldman D, Xu K, Shabalina SA, Shagin D, et al. 2005. Genetic basis for individual variations in pain perception and the development of a chronic pain condition. Hum Mol Genet. 14(1):135–143.

Dworkin SF, LeResche L. 1992. Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique. J Craniomandib Disord. 6(4):301–355.

Elbers CC, van Eijk KR, Franke L, Mulder F, van der Schouw YT, Wijmenga C, Onland-Moret NC. 2009. Using genome-wide pathway analysis to unravel the etiology of complex diseases. Genet Epidemiol. 33(5):419–431.

Engel GL. 1977. The need for a new medical model: a challenge for biomedicine. Science. 196(4286):129–136.

Fillingim RB, Ohrbach R, Greenspan JD, Knott C, Diatchenko L, Dubner R, Bair E, Baraian C, Mack N, Slade GD, et al. 2013. Psychological factors associated with development of TMD: the OPPERA prospective cohort study. J Pain. 14(12 Suppl):T75–T90.

Finan PH, Goodin BR, Smith MT. 2013. The association of sleep and pain: an update and a path forward. J Pain. 14(12):1539–1552.

Friedman GD, Kannel WB, Dawber TR, McNamara PM. 1966. Comparison of prevalence, case history and incidence data in assessing the potency of risk factors in coronary heart disease. Am J Epidemiol. 83(2):366–378.

Gottesman, II, Gould TD. 2003. The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry. 160(4):636–645.

Gracely RH, McGrath F, Dubner R. 1978. Ratio scales of sensory and affective verbal pain descriptors. Pain. 5(1):5–18.

Greenspan JD, Slade GD, Bair E, Dubner R, Fillingim RB, Ohrbach R, Knott C, Diatchenko L, Liu Q, Maixner W. 2013. Pain sensitivity and autonomic factors associated with development of TMD: the OPPERA prospective cohort study. J Pain. 14(12 Suppl):T63–T74.e1–e6.

Greenspan JD, Slade GD, Bair E, Dubner R, Fillingim RB, Ohrbach R, Knott C, Mulkey F, Rothwell R, Maixner W. 2011. Pain sensitivity risk factors for chronic TMD: descriptive data and empirically identified domains from the OPPERA case control study. J Pain. 12(11 Suppl):T61–T74.

John MT, Miglioretti DL, LeResche L, Von Korff M, Critchlow CW. 2003. Widespread pain as a risk factor for dysfunctional temporomandibular disorder pain. Pain. 102(3):257–263.

Lautenbacher S, Rollman GB, McCain GA. 1994. Multi-method assessment of experimental and clinical pain in patients with fibromyalgia. Pain. 59(1):45–53.

Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. 2006. Functional bowel disorders. Gastroenterology. 130(5): 1480–1491.

Macfarlane TV, Glenny AM, Worthington HV. 2001. Systematic review of population-based epidemiological studies of oro-facial pain. J Dent. 29(7):451–467.

Maixner W, Fillingim RB, Williams DA, Slade GD. In press. Chronic overlapping pain conditions: implications for diagnosis and classification. J Pain.

Markiewicz MR, Ohrbach R, McCall WD Jr. 2006. Oral behaviors checklist: reliability of performance in targeted waking-state behaviors. J Orofac Pain. 20(4):306–316.

Meloto CB, Bortsov A, Bair E, Helgeson E, Ostrom C, Smith S, Dubner R, Slade GD, Fillingim RB, Greenspan JD, et al. 2015. Modification of COMT-dependent pain sensitivity by psychological stress and sex. Pain. 157(4):858–867.

National Institutes of Health. 2004. RFA-DE-05-007: prospective studies on craniofacial pain and dysfunction. http://grants.nih.gov/grants/guide/rfa-files/RFA-DE-05–007.html [accessed 2016 May 20].

Ohrbach R, Bair E, Fillingim RB, Gonzalez Y, Gordon SM, Lim PF, Ribeiro-Dasilva M, Diatchenko L, Dubner R, Greenspan JD, et al. 2013. Clinical orofacial characteristics associated with risk of first-onset TMD: the OPPERA prospective cohort study. J Pain. 14(12 Suppl):T33–T50.

Ohrbach R, Fillingim RB, Mulkey F, Gonzalez Y, Gordon S, Gremillion H, Lim PF, Ribeiro-Dasilva M, Greenspan JD, Knott C, et al. 2011. Clinical findings and pain symptoms as potential risk factors for chronic TMD: descriptive data and empirically identified domains from the OPPERA case-control study. J Pain. 12(11 Suppl):T27–T45.

Onen SH, Alloui A, Gross A, Eschallier A, Dubray C. 2001. The effects of total sleep deprivation, selective sleep interruption and sleep recovery on pain tolerance thresholds in healthy subjects. J Sleep Res. 10(1):35–42.

Sanders AE, Akinkugbe AA, Bair E, Fillingim RB, Greenspan JD, Ohrbach R, Dubner R, Maixner W, Slade GD. 2016. Subjective sleep quality deteriorates prior to development of painful temporomandibular disorder. J Pain. 17(6):669–677.

Sanders AE, Essick GK, Fillingim R, Knott C, Ohrbach R, Greenspan JD, Diatchenko L, Maixner W, Dubner R, Bair E, et al. 2013. Sleep apnea symptoms and risk of temporomandibular disorder: OPPERA cohort. J Dent Res. 92(7):70S–77S.

Sanders AE, Slade GD, Bair E, Fillingim RB, Knott C, Dubner R, Greenspan JD, Maixner W, Ohrbach R. 2013. General health status and incidence of first-onset temporomandibular disorder: the OPPERA prospective cohort study. J Pain. 14(12 Suppl):T51–T62.

Slade GD, Bair E, By K, Mulkey F, Baraian C, Rothwell R, Reynolds M, Miller V, Gonzalez Y, Gordon S, et al. 2011. Study methods, recruitment, sociodemographic findings, and demographic representativeness in the OPPERA study. J Pain. 12(11 Suppl):T12–T26.

Slade GD, Bair E, Greenspan JD, Dubner R, Fillingim RB, Diatchenko L, Maixner W, Knott C, Ohrbach R. 2013. Signs and symptoms of first-onset TMD and sociodemographic predictors of its development: the OPPERA prospective cohort study. J Pain. 14(12 Suppl):T20–T32.e1–e3.

Slade GD, Fillingim RB, Sanders AE, Bair E, Greenspan JD, Ohrbach R, Dubner R, Diatchenko L, Smith SB, Knott C, et al. 2013. Summary of findings from the OPPERA prospective cohort study of incidence of first-onset temporomandibular disorder: implications and future directions. J Pain. 14(12 Suppl):T116–T124.

Slade GD, Sanders AE, Bair E, Brownstein N, Dampier D, Knott C, Fillingim R, Maixner WO, Smith S, Greenspan J, et al. 2013. Preclinical episodes of orofacial pain symptoms and their association with health care behaviors in the OPPERA prospective cohort study. Pain. 154(5):750–760.

Slade GD, Sanders AE, Ohrbach R, Bair E, Maixner W, Greenspan JD, Fillingim RB, Smith S, Diatchenko L. 2015. COMT diplotype amplifies effect of stress on risk of temporomandibular pain. J Dent Res. 94(9):1187–1195.

Slade GD, Sanders AE, Ohrbach R, Fillingim RB, Dubner R, Gracely RH, Bair E, Maixner W, Greenspan JD. 2014. Pressure pain thresholds fluctuate with, but do not usefully predict, the clinical course of painful temporomandibular disorder. Pain. 155(10):2134–2143.

Slade GD, Smith SB, Zaykin DV, Tchivileva IE, Gibson DG, Yuryev A, Mazo I, Bair E, Fillingim R, Ohrbach R, et al. 2013. Facial pain with localized and widespread manifestations: separate pathways of vulnerability. Pain. 154(11):2335–2343.

Smith MT, Edwards RR, McCann UD, Haythornthwaite JA. 2007. The effects of sleep deprivation on pain inhibition and spontaneous pain in women. Sleep. 30(4):494–505.

Smith SB, Maixner DW, Greenspan JD, Dubner R, Fillingim RB, Ohrbach R, Knott C, Slade GD, Bair E, Gibson DG, et al. 2011. Potential genetic risk factors for chronic TMD: genetic associations from the OPPERA case control study. J Pain. 12(11 Suppl):T92–T101.

Smith SB, Mir E, Bair E, Slade GD, Dubner R, Fillingim RB, Greenspan JD, Ohrbach R, Knott C, Weir B, et al. 2013. Genetic variants associated with development of TMD and its intermediate phenotypes: the genetic architecture of TMD in the OPPERA prospective cohort study. J Pain. 14(12 Suppl):T91–T101.e1–e3.

Stohler CS. 2004. Taking stock: from chasing occlusal contacts to vulnerability alleles. Orthod Craniofac Res. 7(3):157–161.

Valderas JM, Starfield B, Sibbald B, Salisbury C, Roland M. 2009. Defining comorbidity: implications for understanding health and health services. Ann Fam Med. 7(4):357–363.

Von Korff M, Le Resche L, Dworkin SF. 1993. First onset of common pain symptoms: a prospective study of depression as a risk factor. Pain. 55(2):251–258.

White BA, Williams LA, Leben JR. 2001. Health care utilization and cost among health maintenance organization members with temporomandibular disorders. J Orofac Pain. 15(2):158–169.

Woolf CJ. 2011. Central sensitization: implications for the diagnosis and treatment of pain. Pain. 152(3):S2–S15.