Journal of Dental Research

Sleep Apnea Symptoms and Risk of Temporomandibular Disorder : OPPERA Cohort

A.E. Sanders, G.K. Essick, R. Fillingim, C. Knott, R. Ohrbach, J.D. Greenspan, L. Diatchenko, W. Maixner, R. Dubner, E. Bair, V.E. Miller and G.D. Slade

The online version of this article can be found at:

Additional services and information for *Journal of Dental Research* can be found at:

Email Alerts: http://jdr.sagepub.com/cgi/alerts

Subscriptions: http://jdr.sagepub.com/subscriptions

Reprints: http://www.sagepub.com/journalsReprints.nav

Permissions: http://www.sagepub.com/journalsPermissions.nav

>> Version of Record - Jun 17, 2013

OnlineFirst Version of Record - May 20, 2013

What is This?

ORIGINAL REPORT

Sleep Apnea Symptoms and Risk of Temporomandibular Disorder: OPPERA Cohort

A.E. Sanders[1]*, G.K. Essick[1], R. Fillingim[2], C. Knott[3], R. Ohrbach[4], J.D. Greenspan[5], L. Diatchenko[1], W. Maixner[1], R. Dubner[5], E. Bair[1], V.E. Miller[6], and G.D. Slade[7]

Abstract: *The authors tested the hypothesis that obstructive sleep apnea (OSA) signs/symptoms are associated with the occurrence of temporomandibular disorder (TMD), using the OPPERA prospective cohort study of adults aged 18 to 44 years at enrollment (n = 2,604) and the OPPERA case-control study of chronic TMD (n = 1,716). In both the OPPERA cohort and case-control studies, TMD was examiner determined according to established research diagnostic criteria. People were considered to have high likelihood of OSA if they reported a history of sleep apnea or ≥ 2 hallmarks of OSA: loud snoring, daytime sleepiness, witnessed apnea, and hypertension. Cox proportional hazards regression estimated hazard ratios (HRs) and 95% confidence limits (CL) for first-onset TMD. Logistic regression estimated odds ratios (OR) and 95% CL for chronic TMD. In the cohort, 248 individuals developed first-onset TMD during the median 2.8-year follow-up. High likelihood of OSA was associated with greater incidence of first-onset TMD (adjusted HR = 1.73; 95% CL, 1.14, 2.62). In the case-control study, high likelihood of OSA* was associated with higher odds of chronic TMD (adjusted OR = 3.63; 95% CL, 2.03, 6.52). Both studies supported a significant association of OSA symptoms and TMD, with prospective cohort evidence finding that OSA symptoms preceded first-onset TMD.

Key Words: chronic pain, epidemiology, cohort studies, case-control studies, sleep-disordered breathing, autonomic effect.

Introduction

Thirty percent of US adults have pain persisting for 6 mos or longer (Johannes *et al.*, 2010). Experimental studies involving humans have established that pain and sleep disruption occur in reciprocal, bidirectional relations. Experimentally reducing total sleep and disrupting slow-wave and rapid-eye-movement stages of sleep evoke musculoskeletal pain (Moldofsky, 2008), decreased pain thresholds, increased pain sensitivity (Onen *et al.,* 2001), and lowered antinociceptive potency of morphine (Skinner *et al.,* 2011). Reciprocally, when individuals with excessive daytime sleepiness due to sleep deprivation extended their sleep, their finger withdrawal latency to noxious heat increased by 25% (Roehrs *et al.*, 2012).

Sleep extension, however, does not restore sleep quality in sleep-disordered breathing. During sleep, neuronal activation of dilator muscles that maintain airway patency during wakefulness is reduced. In individuals with excess pharyngeal fat deposits or structural anatomic abnormalities that encroach on airway diameter, this loss of compensatory tonic input results in repetitive episodes of upper airway collapse. In people with obstructive sleep apnea (OSA), the upper airway obstruction causes respiratory hypopneas (reductions) or apneas (pauses), despite persisting respiratory efforts that terminate when central nervous system arousal restores airway patency. The immediate effects are oxyhemoglobin desaturation, blood pressure and heart rate fluctuations, sustained sympathetic excitation, cortical arousal, and sleep fragmentation. Long-term effects include neurocognitive impairment (Lal *et al.,* 2012), metabolic syndrome (Hasan *et al.,* 2012), systemic hypertension (Peppard *et al.,* 2000), and cardiovascular diseases (Redline *et al.,* 2010).

OSA is estimated to affect 4% of men and 2% of women (Young *et al.*, 1993) and accounts for 95% of all apneas. Nasal continuous positive airway pressure (CPAP) is effective in maintaining airway patency in OSA, as are oral appliances that hold the jaw in a forward position. Both therapies reduce blood pressure (Gotsopoulos *et al.*, 2002), and CPAP decreases pain sensitivity (Khalid *et al.*, 2011) and increases pain tolerance (Onen *et al.*, 2010).

An emergent body of evidence suggests that OSA is associated with chronic pain disorders including temporomandibular disorder (TMD) (Cunali *et al.,* 2009; Smith *et al.,* 2009). TMD is a musculoskeletal disorder characterized by persistent pain in the temporomandibular joint, periauricular region, and masticatory muscles. Current evidence of a relationship between OSA and TMD is limited to descriptive findings in clinical samples (Cunali *et al.,* 2009; Smith *et al.,* 2009) that, while suggestive of association, cannot estimate strength of association or determine the temporal order of the association between OSA and pain.

To extend this preliminary evidence, the authors estimated the strength of association between OSA signs/symptoms and chronic TMD in a population-based epidemiologic study of TMD. We tested the hypothesis that OSA sign/symptoms are associated with the occurrence of TMD and precede first-onset TMD.

Methods

Institutional review boards at each of 4 study sites and the data coordination center granted approval for study procedures, and participants provided informed consent.

Study Design and Recruitment

The Orofacial Pain Prospective Evaluation and Risk Assessment study (OPPERA) is a prospective cohort study designed to investigate the etiology of first-onset TMD. Its detailed methodology is described elsewhere (Slade *et al.,* 2011). Briefly, from 2002 to 2004, 3,263 adults were recruited by community-wide advertising at 4 US study sites: Baltimore, Maryland; Buffalo, New York; Chapel Hill, North Carolina; and Gainesville, Florida. Eligibility criteria

were: age 18 to 44 yrs, 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. The target sample size of 3,200 was expected to yield 196 cases of first-onset TMD, assuming 30% loss to follow-up, sufficient to address study aims regarding the incidence and etiology of TMD. Once enrolled, participants completed quarterly screening questionnaires to monitor the development of TMD symptoms. Symptomatic participants were recalled for examination to establish a definitive classification of incident TMD.

A case-control study of chronic TMD was embedded in OPPERA at baseline. Chronic cases were adults aged 18 to 44 yrs, with TMD symptomatic for at least 6 mos (n = 182), recruited by community-wide advertising at the same study sites. Controls were a random sample of enrollees in the cohort study (n = 1,534). All cohort and case-control participants completed health-history questionnaires and a three-hour clinical assessment that included physical examination and assessment of autonomic function. OPPERA's unique hybrid design permitted rigorous comparison of chronic TMD *vs.* incident first-onset TMD phenotypes under standardized conditions.

TMD Classification

All participants were clinically examined according to Research Diagnostic Criteria for TMD (RDC/TMD) (Dworkin and LeResche, 1992) adapted for OPPERA. TMD cases met 2 criteria: (1) ≥ 5 days/month of pain in masticatory structures, confirmed by examiner; and (2) examiner findings of arthralgia [*i.e.*, pain in temporomandibular joint(s) during jaw maneuver or digital palpation] and/or myalgia (*i.e.*, pain during jaw maneuver or digital palpation in ≥ 3 of 8 muscle groups based on bilateral assessment of temporalis, masseter, lateral pterygoid, and submandibular muscles).

Signs/Symptoms of Obstructive Sleep Apnea

From the Pittsburgh Sleep Quality Index (PSQI), we extracted responses to 3

questions that asked about loud snoring, trouble staying awake, and witnessed apnea. From the medical history, we extracted hypertension information. Together, these 4 hallmarks of OSA comprise the 4-item OSA screening questionnaire called STOP that was validated against polysomnography (Chung *et al.*, 2008). STOP was developed to identify individuals likely to have OSA, so that special precautions could be taken during/after general anesthesia. Affirmative responses to ≥ 2 of these questions indicated high likelihood for OSA. We adopted this scoring convention, and, consistent with the scoring of STOP, we defined ≥ 2 affirmative responses to these signs/symptoms as indicative of high likelihood of OSA. In addition, people with a self-reported history of sleep apnea were classified as having high likelihood for OSA, regardless of their responses to the four approximated STOP questions.

Autonomic Parameters

Sympathetic nerve activity and arterial pressure are commonly elevated among people with OSA (Leuenberger *et al.*, 2005). To explore the potential role of autonomic regulation, we measured arterial blood pressure and heart rate during 20 min of rest, using a blood pressure cuff. Average resting heart rate variability was measured with a 3-lead electrocardiogram to provide indirect measures of baroreflex sensitivity, described elsewhere (Maixner *et al.*, 2011).

Covariates

Demographic characteristics were gender, age, race and ethnicity (White, African American, Asian, Hispanic). Standardized equipment measured height and weight to compute body mass index (BMI = weight/height^2). Since cigarette smoking is associated with TMD (Sanders *et al.,* 2012) and OSA, we classified smoking history as never smoked, former smoker, or current smoker. Subjective sleep quality was assessed with one item in the PSQI.

Statistical Analysis

Statistical analyses were conducted with SAS 9.2 (SAS Institute Inc., Cary, NC,

Table 1.

Associations of Baseline Characteristics of Participants with Signs/Symptoms of Obstructive Sleep Apnea (OSA) and Hazard Ratios for First-onset Temporomandibular Disorder (TMD), OPPERA Prospective Cohort Study (n = 2,604), 2006-2011

Characteristic	N	Column Percent	% at High Risk for OSA[a]	Rate of First-onset TMD (% *per annum*)	Site-adjusted Hazard ratio (95% CL) for TMD[b]
Likelihood of OSA[a]					
Low	2,445	93.9	n/a	3.02	Referent
High	159	6.1	n/a	6.96	2.29 (1.54, 3.42)
Gender					
Male	1,057	40.6	7.7	2.72	Referent
Female	1,547	59.4	5.0	3.59	1.32 (1.02, 1.72)
Age group (yrs)					
18–24	1,370	52.6	3.1	2.47	Referent
25–34	702	27.0	5.8	3.73	1.55 (1.14, 2.09)
35–44	532	20.4	14.1	4.34	1.81 (1.29, 2.54)
Race/ethnicity					
White	1,397	53.7	4.5	2.98	Referent
African American	700	26.9	11.4	4.79	1.58 (1.16, 2.15)
Hispanic	249	9.6	1.6	1.05	0.35 (0.17, 0.71)
Asian	172	6.6	3.5	2.89	0.96 (0.59, 1.57)
Other/multiple/not stated	86	3.3	7.0	1.90	0.65 (0.27, 1.60)
Mean arterial pressure (mm Hg)[c]					
< 75	435	16.7	2.8	2.40	Referent
75- < 80	597	22.9	5.7	2.82	1.18 (0.73, 1.58)
80- < 85	672	25.8	4.6	3.31	1.39 (0.93, 1.98)
>85	900	34.6	9.1	3.87	1.62 (1.07, 2.21)
Heart rate (beats *per* min)					
< 55	609	23.4	4.9	2.58	Referent
55–61.9	675	25.9	4.6	2.77	1.07 (0.75, 1.83)
62–68.9	628	24.1	6.5	3.55	1.36 (0.91, 2.13)
>69.0	692	26.6	8.2	3.99	1.54 (1.09, 2.42)
Body mass index (kg/m²)					
Underweight/normal (< 25)	1,409	54.1	3.1	2.97	Referent
Overweight (25– < 30)	712	27.3	7.0	2.60	0.87 (0.64, 1.20)
Obese (≥ 30)	483	18.6	13.7	4.96	1.68 (1.24, 2.27)
Smoking history					
Never	1,973	75.8	4.4	2.51	Referent
Former	224	8.6	9.4	5.76	2.33 (1.62, 3.34)
Current	407	15.6	12.5	5.45	2.15 (1.54, 2.99)
PSQI[d] subjective sleep quality					
Very good	759	29.2	3.0	2.68	Referent
Fairly good	1,444	55.5	5.6	2.89	1.07 (0.79, 1.46)
Fairly bad and very bad	401	15.4	13.7	5.74	2.11 (1.49, 3.00)

(a) High likelihood of OSA defined as ≥ 2 affirmative responses to 4 questions that approximate the STOP screening questionnaire for OSA, or a self-reported history of sleep apnea.
(b) From Cox regression model controlling for OPPERA study site.
(c) Millimeters of mercury.
(d) Pittsburgh Sleep Quality Index item #6: During the past month, how would you rate your sleep quality overall?

Table 2.

Multivariable Model Showing Hazard Ratios (95% confidence limits) for Incident First-onset TMD, OPPERA Prospective Cohort (n =2,604), 2006-2011

	Model 1 HR (95%CL)	Model 2 HR (95%CL)	Model 3 HR (95%CL)
High likelihood of obstructive sleep apnea [a]	1.90 (1.26, 2.87)	1.85 (1.22, 2.79)	1.73 (1.14, 2.62)
Gender, female [ref = male]	1.30 (1.00, 1.69)	1.29 (0.99, 1.69)	1.31 (1.00, 1.72)
Age in yrs/10	1.21 (1.01, 1.44)	1.17 (0.98, 1.41)	1.05 (0.86, 1.27)
Race/ethnicity African American [ref = White]	1.38 (1.01, 1.90)	1.29 (0.93, 1.79)	1.32 (0.94, 1.85)
Race/ethnicity Hispanic [ref = White]	0.37 (0.18, 0.76)	0.37 (0.18, 0.76)	0.39 (0.19, 0.80)
Race/ethnicity Asian [ref = White]	0.99 (0.61, 1.62)	0.98 (0.60, 1.60)	0.96 (0.59, 1.57)
Race/ethnicity Other [ref = White]	0.62 (0.25, 1.52)	0.61 (0.25, 1.50)	0.66 (0.27, 1.62)
Average resting heart rate (bpm/10)		1.07 (0.94, 1.21)	1.04 (0.92, 1.18)
Average resting mean arterial blood pressure (mm Hg/10)		1.11 (0.95, 1.29)	1.08 (0.92, 1.25)
BMI overweight [ref = underweight/normal]			0.78 (0.56, 1.08)
BMI obese [ref = underweight/normal]			1.21 (0.87, 1.70)
Smoking history: Former [ref = Never]			2.20 (1.51, 3.21)
Smoking history: Current [ref=Never]			1.81 (1.27, 2.57)

(a) High likelihood of OSA is a summary variable derived from ≥ 2 affirmative responses to four questions that approximate items in the STOP screening questionnaire for OSA or self-reported history of sleep apnea.

USA). Of the 3,258 people enrolled in the OPPERA cohort, this analysis omitted participants with missing follow-up data (n = 521), missing OSA classification (n = 1), or missing covariates (n = 132), yielding a sample size of 2,604. A Cox proportional hazard models estimated hazard ratios (HR) and 95% confidence limits (CL) to approximate the incidence rate ratio of first-onset TMD. Unlike odds ratios used for case-control studies where there is no time element, hazard ratios are appropriate for prospective cohort studies, since they take into account the length of time during which TMD-free participants are "at risk" of developing TMD. The exposure of interest was binary: low or high likelihood for OSA.

Recognizing that OSA signs/symptoms and TMD might have common contributing factors, we created 3 successive multivariable Cox models to determine the degree to which the OSA-TMD relationship was independent of those contributing factors: model 1 adjusted for study site and demographic characteristics; model 2 added autonomic parameters; and model 3 added BMI and smoking history. In the prospective cohort, mean site-adjusted and fully adjusted values of baseline resting autonomic parameters were examined against the summary OSA likelihood classification. Least-squares means were contrasted to determine the statistical significance of differences in mean autonomic measures between/among OSA symptom groups.

Excluded from the 1,818 people in the OPPERA case control study were people missing an OSA classification (n = 1) or missing covariates (n = 101), for a sample size of 1,716. Odds ratios (ORs) and 95% confidence limits (CL) were estimated by binary logistic regression. As with the cohort analysis, multivariate logistic regression adjusted for potential confounding in the same three-staged manner.

Regression models subsequently tested the effect of further adjustment for subjective sleep quality to investigate whether an association between OSA likelihood and TMD was independent of sleep quality.

Results

Within the prospective cohort, 248 people developed first-onset TMD in 7,068 person-years of follow-up, yielding an average annual incidence rate of 3.5% in this analysis. Among the 6.1% of people with high likelihood for OSA, the rate of first-onset TMD was two-fold greater relative to that of people with low likelihood for OSA (site-adjusted HR = 2.29 [95% CL: 1.54, 3.42]) (Table 1).

Other putative predictors were female gender, older age, African-American race, obesity, cigarette smoking, and poor self-rated sleep quality. Incidence of first-onset TMD increased across successive categories of mean arterial pressure and mean heart rate in a monotonic fashion.

Adjustment for confounding (Table 2) attenuated the strength of association between high likelihood of OSA and first-onset TMD. The association remained statistically significant, with 73% higher incidence of TMD among people with high likelihood for OSA (HR = 1.73; 95% CL, 1.14, 2.62).

Table 3.

Odds Ratios (OR) for Chronic Temporomandibular Disorder (TMD), OPPERA Case Control Study (n = 1,716), 2006-2008

	N	%	OR (95%CL)
Likelihood of OSA [a]			
Low	1,614	94.1	Referent
High	102	5.9	2.98 (1.77, 5.00)
Gender			
Male	687	40.0	Referent
Female	1,029	60.0	3.80 (2.53, 5.71)
Age group (yrs)			
18-24	876	51.1	Referent
25-34	480	28.0	1.70 (1.17, 2.48)
35-44	360	21.0	2.24 (1.46, 3.43)
Race/ethnicity			
White	909	53.0	Referent
African American	474	27.6	2.15 (1.29, 3.57)
Hispanic	157	9.2	3.99 (2.28, 7.00)
Asian	123	7.2	2.35 (1.41, 3.93)
Other/multiple/not stated	53	3.1	0.21 (0.13, 0.35)
Mean arterial pressure (mm Hg)			
< 75	619	36.1	Referent
75- < 80	274	16.0	1.33 (0.78, 2.27)
80- < 85	392	22.8	1.08 (0.63, 1.86)
>85	431	25.1	1.54 (0.94, 2.52)
Mean heart rate (bpm)			
< 55	397	23.1	Referent
55-61.9	433	25.2	1.25 (0.77, 2.02)
62-68.9	408	23.8	1.36 (0.84, 2.20)
>69.0	478	27.9	1.88 (1.20, 2.95)
Body mass index (kg/m^2)			
Underweight/normal (< 25)	888	51.8	Referent
Overweight (25- < 30)	490	28.6	0.82 (0.57, 1.19)
Obese (> = 30)	338	19.7	0.90 (0.59, 1.36)
Smoking history			
Never	1,244	72.5	Referent
Former	160	9.3	2.28 (1.47, 3.53)
Current	312	18.2	0.76 (0.46, 1.24)
PSQI subjective sleep quality [b]			
Very good	487	28.4	Referent
Fairly good	925	53.9	2.03 (1.30, 3.17)
Fairly bad and very bad	304	17.7	4.46 (2.75, 7.24)

(a) High likelihood of OSA is a summary variable derived from ≥ 2 affirmative responses to 4 questions that approximate items in the STOP screening questionnaire for OSA or self-reported history of sleep apnea.

(b) Pittsburgh Sleep Quality Index item #6: During the past month, how would you rate your sleep quality overall?

Table 4.

Multivariable Model Showing Odds Ratios (95% confidence limits) for Chronic TMD, OPPERA Case Control Study (n = 1,716), 2006-2008

	Model 1 OR (95%CL)	Model 2 OR (95%CL)	Model 3 OR (95%CL)
High likelihood of obstructive sleep apnea [a]	3.48 (1.95, 6.19)	3.34 (1.87, 5.96)	3.63 (2.03, 6.52)
Gender, female [ref = male]	4.07 (2.67, 6.19)	4.08 (2.66, 6.26)	3.96 (2.58, 6.08)
Age in yrs/10 [b]	1.57 (1.26, 1.95)	1.48 (1.18, 1.86)	1.49 (1.17, 1.88)
Race/ethnicity African American [ref = White]	0.16 (0.10, 0.28)	0.14 (0.08, 0.25)	0.16 (0.09, 0.28)
Race/ethnicity Hispanic [ref = White]	0.29 (0.12, 0.68)	0.30 (0.13, 0.70)	0.30 (0.13, 0.72)
Race/ethnicity Asian [ref = White]	0.58 (0.30, 1.11)	0.57 (0.30, 1.09)	0.59 (0.31, 1.13)
Race/ethnicity Other [ref = White]	0.34 (0.11, 1.01)	0.33 (0.11, 0.99)	0.35 (0.12, 1.06)
Average resting heart rate (bpm/10) [c]		1.14 (0.97, 1.35)	1.16 (0.98, 1.37)
Average resting mean arterial blood pressure (mm Hg/10) [d]		1.20 (0.97, 1.48)	1.22 (0.98, 1.51)
BMI overweight [ref = underweight/normal]			0.88 (0.59, 1.31)
BMI obese [ref = underweight/normal]			0.84 (0.52, 1.36)
Smoking history: Current [ref = Never]			1.60 (0.99, 2.59)
Smoking history: Former [ref = Never]			0.68 (0.40, 1.16)

(a) High likelihood of OSA is a summary variable derived from ≥ 2 affirmative responses to 4 questions that approximate items in the STOP screening questionnaire for OSA or a self-reported history of sleep apnea.
(b) Age in yrs scaled to decades.
(c) Mean heart rate scaled to units of 10 beats.
(d) Mean arterial pressure scaled to units of 10 mm Hg.

In the case-control study of chronic TMD (Table 3), 5.9% of participants (n = 102) had high likelihood for OSA. Compared with controls, chronic TMD cases had three-fold greater odds of high likelihood for OSA (site-adjusted OR = 2.98; 95% CL, 1.77, 5.00). Adjustment for potential confounders (Table 4) strengthened the association (OR = 3.63; 95% CL, 2.03, 6.52).

Subsequent adjustment for subjective sleep quality further attenuated associations between OSA symptoms and TMD in both the cohort (HR = 1.52; 95% CL, 1.00, 2.31) and the case-control study (OR = 2.62; 95% CL, 1.43, 4.79) (not tabulated).

In the prospective cohort, high likelihood for OSA was significantly associated with elevated baseline mean arterial pressure and mean heart rate, and with lower baseline standard deviation of normal-to-normal intervals (Appendix Table 1). Only mean heart rate remained

significantly associated with OSA risk after adjustment for all covariates.

Discussion

Key Findings

In the population-based cohort of adults free of TMD at baseline, OSA signs/symptoms were associated with increased incidence of first-onset TMD. Men and women with 2 or more signs/symptoms of OSA had 73% greater incidence of first-onset TMD, in relative terms, than those with fewer signs/symptoms, independently of age, gender, race/ethnicity, obesity, smoking history, and autonomic parameters. In the case-control study, chronic TMD was more than 3 times as frequent among adults with low relative to high likelihood of OSA, independently of these same factors. In both studies, the effects of high likelihood of OSA were independent of sleep quality.

Comparison with Previous Findings

Earlier studies of OSA and TMD, conducted in unrepresentative clinic samples without a comparison group, were nonetheless informative because of the inclusion of in-laboratory polysomnographic recordings. Among 87 adults diagnosed by polysomnography as having mild or moderate OSA, 32 (36.8%) had TMD determined by RDC/TMD criteria (Cunali *et al.*, 2009). In another study, 11 adults (28%) of 53 with RDC/TMD-based myofascial pain were diagnosed by polysomnography as having OSA (Smith *et al.*, 2009). OPPERA's population-based studies extend these case series reports by quantifying the strength of association and demonstrating that OSA symptoms are associated with both first-onset TMD and chronic TMD. This study's findings of an association between OSA symptoms and TMD contribute to a growing body of evidence documenting a relationship

75S

between sleep-disordered breathing and other idiopathic pain conditions, including fibromyalgia (Moldofsky *et al.,* 1975), irritable bowel syndrome (Rotem *et al.,* 2003), and headache (Rains and Poceta, 2012).

One mechanism by which SDB may contribute to pain over time is through the effect of central sensitization and pain amplification in decreasing function in pain inhibitory systems (Smith *et al.,* 2007), for example, *via* baroreceptor pathways. Experimental inspiratory resistance reduces baroreceptor reflex sensitivity in humans, and impaired baroreceptor reflex sensitivity is implicated in TMD (Maixner *et al.,* 1997). It is also possible that the increased stimulation of the sympathetic nervous system observed in OSA underlies an increased prevalence of TMD: Individuals who are genetically predisposed to an increased sensitivity to catecholamines are at increased risk of developing first-onset TMD (Diatchenko *et al.,* 2005). Third, although a causal association remains controversial (Manfredini *et al.,* 2012), bruxism—which is more common in people with OSA than in those without OSA (Ohayon *et al.,* 2001)—may be implicated in TMD development.

Strengths and Limitations

Strengths of the study include the prospective cohort design, which established the presence of OSA signs/symptoms prior to first-onset TMD, the rigorous OPPERA protocols, and the rich OPPERA dataset. Both the cohort and case-control studies were large and population-based, with statistical power to detect small effects. Multiple study sites and community recruitment optimized the diversity and representativeness of the study population to improve the generalizability of findings. Although causality cannot be inferred from observational data alone, the prospective cohort findings imply that OSA contributes to the onset of painful TMD symptoms. Our adjustment for subjective sleep quality in analytic models constitutes "over-adjustment", because poor sleep quality is a consequence both of pain and of the fragmented sleep

evoked by sleep-disordered breathing. Over-adjustment tends to bias results toward the null. Instead, our purpose in adjusting for subjective sleep quality was to demonstrate that our main exposure–OSA symptomatology–was independently associated with TMD rather than merely a proxy of sleep quality. Even with this excessively conservative approach, OSA symptoms remained a significant factor.

The gold-standard for OSA diagnosis is laboratory polysomnography. The STOP has sensitivity of 0.66 and specificity of 0.60 to classify OSA in adults without history of sleep disorders (Chung *et al.,* 2008) and inevitably misclassifies OSA risk. However, since there is no reason for misclassification to differ between TMD cases and non-cases, resulting bias will shift estimates of association conservatively toward the null.

The strength of association between OSA signs/symptoms and TMD may be underestimated in this young OPPERA population. It is likely that the relationship between OSA and TMD is stronger among older adults, especially those with co-morbid conditions, including obesity.

Missing data arising from loss to follow-up poses a major threat to validity in prospective cohort studies. We did not impute values for participants lost to follow-up or data missing through non-report. This decision was justified because our multiple imputation techniques and sensitivity analyses showed that doing so did not appreciably change the incidence rate (Bair *et al.*, manuscript under review).

Acknowledgments

References

Bair E, Brownstein N, Ohrbach RO, Greenspan JD, Dubner R, Fillingim RB, *et al.* (under review). Study design, methods, sample characteristics and loss-to-follow-up: the OPPERA prospective cohort study. *J Pain.*

Chung F, Yegneswaran B, Liao P, Chung SA, Vairavanathan S, Islam S, *et al.* (2008). STOP questionnaire: a tool to screen patients for obstructive sleep apnea. *Anesthesiology* 108:812-821.

Cunali PA, Almeida FR, Santos CD, Valdrighi NY, Nascimento LS, Dal'Fabbro C, *et al.* (2009). Prevalence of temporomandibular disorders in obstructive sleep apnea patients referred for oral appliance therapy. *J Orofac Pain* 23:339-344.

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

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

Gotsopoulos H, Chen C, Qian J, Cistulli PA (2002). Oral appliance therapy improves symptoms in obstructive sleep apnea: a randomized, controlled trial. *Am J Respir Crit Care Med* 166:743-748.

Hasan A, Uzma N, Swamy TL, Shoba A, Kumar BS (2012). Correlation of clinical profiles with obstructive sleep apnea and metabolic syndrome. *Sleep Breath* 16:111-116.

Johannes CB, Le TK, Zhou X, Johnston JA, Dworkin RH (2010). The prevalence of chronic pain in United States adults: results of an Internet-based survey. *J Pain* 11:1230-1239.

Khalid I, Roehrs TA, Hudgel DW, Roth T (2011). Continuous positive airway pressure in severe obstructive sleep apnea reduces pain sensitivity. *Sleep* 34:1687-1691.

Lal C, Strange C, Bachman D (2012). Neurocognitive impairment in obstructive sleep apnea. *Chest* 141:1601-1610.

Leuenberger UA, Brubaker D, Quraishi S, Hogeman CS, Imadojemu VA, Gray KS (2005). Effects of intermittent hypoxia on sympathetic activity and blood pressure in humans. *Auton Neurosci* 121:87-93.

Maixner W, Fillingim R, Kincaid S, Sigurdsson A, Harris MB (1997). Relationship between pain sensitivity and resting arterial blood pressure in patients with painful temporomandibular disorders. *Psychosom Med* 59:503-511.

Maixner W, Greenspan JD, Dubner R, Bair E, Mulkey F, Miller V, *et al.* (2011). Potential autonomic risk factors for chronic TMD: descriptive data and empirically identified domains from the OPPERA case-control study. *J Pain* 12(11 Suppl):T75-91.

Manfredini D, Winocur E, Guarda-Nardini L, Lobbezoo F (2012). Self-reported bruxism and temporomandibular disorders: findings from two specialised centres. *J Oral Rehabil* 39:319-325.

Moldofsky H (2008). The significance of the sleeping-waking brain for the understanding of widespread musculoskeletal pain and fatigue in fibromyalgia syndrome and allied syndromes. *Joint Bone Spine* 75:397-402.

Moldofsky H, Scarisbrick P, England R, Smythe H (1975). Musculosketal symptoms and non-REM sleep disturbance in patients with "fibrositis syndrome" and healthy subjects. *Psychosom Med* 37:341-351.

Ohayon MM, Li KK, Guilleminault C (2001). Risk factors for sleep bruxism in the general population. *Chest* 119:53-61.

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* 10:35-42.

Onen SH, Onen F, Albrand G, Decullier E, Chapuis F, Dubray C (2010). Pain tolerance and obstructive sleep apnea in the elderly. *J Am Med Dir Assoc* 11:612-616.

Peppard PE, Young T, Palta M, Skatrud J (2000). Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* 342:1378-1384.

Rains JC, Poceta JS (2012). Sleep-related headaches. *Neurol Clin* 30:1285-1298.

Redline S, Yenokyan G, Gottlieb DJ, Shahar E, O'Connor GT, Resnick HE, *et al.* (2010). Obstructive sleep apnea-hypopnea and incident stroke: the sleep heart health study. *Am J Respir Crit Care Med* 182:269-277.

Roehrs TA, Harris E, Randall S, Roth T (2012). Pain sensitivity and recovery from mild chronic sleep loss. *Sleep* 35::1667-1672.

Rotem AY, Sperber AD, Krugliak P, Freidman B, Tal A, Tarasiuk A (2003). Polysomnographic and actigraphic evidence of sleep fragmentation in patients with irritable bowel syndrome. *Sleep* 26:747-752.

Sanders AE, Maixner W, Nackley AG, Diatchenko L, By K, Miller VE, *et al.* (2012). Excess risk of temporomandibular disorder associated with cigarette smoking in young adults. *J Pain* 13:21-31.

Skinner GO, Damasceno F, Gomes A, de Almeida OM (2011). Increased pain perception and attenuated opioid antinociception in paradoxical sleep-deprived rats are associated with reduced tyrosine hydroxylase staining in the periaqueductal gray matter and are reversed by L-dopa. *Pharmacol Biochem Behav* 99:94-99.

Slade GD, Bair E, By K, Mulkey F, Baraian C, Rothwell R, *et al.* (2011). Study methods, recruitment, sociodemographic findings, and demographic representativeness in the OPPERA study. *J Pain* 12(11 Suppl):T12-T26.

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

Smith MT, Wickwire EM, Grace EG, Edwards RR, Buenaver LF, Peterson S, *et al.* (2009). Sleep disorders and their association with laboratory pain sensitivity in temporomandibular joint disorder. *Sleep* 32:779-790.

Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S (1993). The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 328:1230-1235.