INVESTIGATION OF AN ASSOCIATION BETWEEN OBSTRUCTIVE SLEEP APNEA AND TWO CHRONIC ORAL HEALTH CONDITIONS

Elizabeth Collins Kornegay

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Approved By:

Gregory Essick

Jennifer Brame

Antonio Moretti

Heidi Roth

Anne Sanders

ABSTRACT

Elizabeth Collins Kornegay: Investigation of an Association between Obstructive Sleep Apnea and Two Chronic Oral Health Conditions
(Under the direction of Greg Essick)

Obstructive sleep apnea (OSA) is gaining attention across the nation with a high prevalence in the United States. Limited research is available on the association between OSA and chronic oral health conditions, such as chronic periodontitis (CP) and temporomandibular disorder (TMD). The first chapter investigated an association between CP and OSA in a case-control study of 48 subjects. In the adjusted model, our results yielded that subjects with symptomatic mild OSA (OR=0.13, 95% CL: 0.01, 1.53) or moderate/severe OSA (OR=0.13, 95% CL: 0.01,1.29) were less likely to have moderate/severe CP than subjects without OSA. The second chapter explored if OSA risk predicted first-onset TMD independently of sleep and awake bruxism in a prospective cohort study of 2,660 subjects. We found that subjects with two or more signs/symptoms of OSA had 72% greater incidence of first-onset TMD than those with fewer signs/symptoms, independently of reported sleep and awake bruxism.

To my Granddaddy. In memory of your unfailing love, never-ending support, and unending faith. Thank you for instilling the importance of education in your family. You are greatly missed and deeply loved.

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LIST OF ABBREVIATIONS

95% CL	95% Confidence Limits
AHI	Apnea Hypopnea Index
ARES	Apnea Risk Evaluation System
BMI	Body mass index
BOP	Bleeding on probing
CAL	Clinical Attachment Level
CP	Chronic periodontitis
CRP	C-reactive protein
HR	Hazard ratios
hs-CRP	High-sensitivity-CRP
IL-1β	Interleukin 1β
IL-6	Interleukin-6
IL-33	Interleukin-33
MMP-8	Matrix metalloproteinase-8
NHANES	National Health and Nutrition Examination Survey
OPPERA	Orofacial Pain: Prospective Evaluation and Risk Assessment
OR	Odds Ratio
OSA	Obstructive sleep apnea
OSM	Oncostatin M
PD	Probing depths
PSQI	Pittsburgh Sleep Quality Index
RDC/TMD	Research Diagnostic Criteria for TMD
SDB	Sleep-disordered breathing

SpO_2	Blood oxygen saturation
TMD	Temporomandibular disorder
WHO	World Health Organization

INTRODUCTION

Prior to 2009, little evidence showed that obstructive sleep apnea (OSA) was associated with oral health conditions, specifically with chronic periodontitis (CP) and temporomandibular disorder (TMD). OSA involves a reduction or complete cessation in airflow despite a continuous effort to breath.[1] Based on the findings of Peppard et al. (2013), 26% of adults between 30-70 years have OSA.[2] Characteristics of SDB are excessive daytime sleepiness,[3] pauses in breathing as witnessed by bed partner,[4] and disturbed sleep quality.[5] Increased severity of OSA is associated with hypertension,[5] diabetes[5] and other systemic conditions.

Chronic periodontitis (CP) is a nonreversible, chronic disease affecting the supporting structures of the teeth involving the bacterial subversion of host immunoinflammatory mechanisms.[6] Based on data collected from the 2009 and 2010 National Health and Nutrition Examination Survey (NHANES), the estimated prevalence of moderate/severe CP is 38.5% of adults 30 years and older in the United States.[7]

Temporomandibular disorder (TMD) is a musculoskeletal disorder described by persistent pain in the temporomandibular joint, periauricular region, and masticatory muscles.[8] Pain in the temporomandibular region occur in approximately 10% in adults 18 years and older worldwide.[8]

The thesis presents and discusses two investigations that are related to the topic of OSA and chronic oral health diseases. The first chapter will discuss OSA in relation to CP via a case-control study on 48 subjects. The second chapter will discuss TMD as a risk factor for OSA in a prospective cohort study on 2,660 subjects. In addition, each chapter explores plausible underlying mechanisms for CP/OSA and TMD/OSA.

CHAPTER ONE: INVESTIGATION OF AN ASSOCIATION BETWEEN CHRONIC PERIODONTITIS AND SLEEP-DISORDERED BREATHING

INTRODUCTION

Chronic periodontitis (CP) and sleep-disordered breathing (SDB) are both associated with systemic inflammation and local inflammation in the mouth and upper airway.[9,10,11] CP and SDB share several risk factors such as male gender,[12,13] increased age,[7,14] and obesity.[15,16] Additionally, increased severity of CP and SDB are found associated with hypertension[5,17] and diabetes.[5,17] To date, there are six studies of which we know that have investigated the association between CP and SDB.[18,19,20,21,22,23]

Chronic periodontitis (CP) is a chronic infection of the periodontium initiated by bacteria in dental plaque biofilm resulting in clinical attachment loss and bone loss.[17] It is nonreversible and affects the periodontal ligament, alveolar bone, cementum, and gingival tissues.[6] Based on data collected from the 2009 and 2010 National Health and Nutrition Examination Survey (NHANES), the estimated prevalence of moderate/severe CP is 38.5% of adults 30 years and older in the United States.[7]

Sleep-disordered breathing (SDB) ranges from snoring to obstructive sleep apnea (OSA), a sleep disorder characterized by repetitive collapse of the upper airway.[24] Based on the findings of Peppard et al, 26% of adults between 30-70 years have OSA.[2] Classification of OSA severity is based on the apnea-hypopnea index (AHI), which reports the number of apneas and hypopneas that occur each hour of sleep. A normal AHI is < 5 events per hour, mild AHI is ≥5-<15 events per hour, moderate AHI is ≥15-≤30 events per hour, and severe AHI is >30 events per hour.[24] Characteristics of SDB often include excessive daytime sleepiness,[3] pauses in breathing as witnessed by bed partner,[3] and disturbed sleep quality.[5]

The first study to explore an association was cross-sectional in design and originated in Australia. The investigators recruited patients who had a previous diagnosis of OSA from

polysomnography. A dental examiner who was blinded to OSA variables collected periodontal clinical measurements on the 66 subjects.[19] The study found that 77-79% of confirmed OSA cases exhibited CP versus an expected 21% in the general population. The investigators concluded that the prevalence of CP in individuals who had OSA was four times higher than the national average.[19]

Following this first pilot study, a cross-sectional study of 687 subjects from the Korean Genome and Epidemiology study was conducted. Subjects had a previous periodontal examination and polysomnogram.[23] The study found that 17.5% of subjects had CP, 46.6% of subjects had OSA, and 60% of subjects diagnosed with CP had OSA. OSA was positively associated with CP (odds ratio (OR):1.84, 95% confidence limits (CL): 1.18,2.87), probing pocket depths (OR:2.22, 95% CI: 1.30,3.77), and clinical attachment levels (CAL) (OR:1.86, 95% CI: 1.07,3.21) compared to controls without CP (referent). Additional analysis revealed that OSA was positively associated with CP in subjects 55 years or older (OR: 2.51, 95% CI: 1.37-4.62), but not in subjects less than 55 years old.[23]

At the same time of the Korean study, a case-control study on 7,673 subjects with OSA (cases) and 21,963 without OSA (controls) from the Longitudinal Health Insurance Database 2000 in Taiwan was published.[20] Determination of cases was based on previous polysomnography. Subjects who previously had at least three primary chronic periodontitis (CP) diagnoses from dental appointments and who received either scaling and root planing or a surgical procedure (periodontal flap surgery or gingivectomy) were considered to have chronic periodontitis (CP).[20] The study found a significant difference in the prevalence of CP between cases and controls (33.8% vs. 22.6%, $p<0.001$). Odds of CP were 1.75 (95% CI: 1.68,1.88) times greater for cases than for controls (referent), after adjustment for confounding variables.[20]

Shortly thereafter, Ahmad et al. (2013) reported periodontal parameters and OSA risk status for 154 subjects from the dental hygiene preventive care clinic at the University of North Carolina School of Dentistry.[18] Cases included 50 subjects with moderate or severe CP, while controls included 104 subjects

with gingivitis or slight CP. OSA risk status was determined on subjects from the "STOP" screening questionnaire:[18] self-reported 1) snoring, 2) excessive daytime sleepiness, 3) witnessed apnea during sleep, and 4) hypertension history. Subjects responding affirmatively to two or more of the questions were considered to be at high risk for OSA. It was found that individuals with moderate or severe CP (cases) were 4.1 times (95% CI: 1.48, 11.45) more likely to be at high risk for OSA than individuals with slight CP or gingivitis after adjustment for potential confounding variables.[18]

Sanders et al. (2015) conducted a cross-sectional study of data from 12,469 subjects from the Hispanic Community Health Study/Study of Latinos.[22] Full-mouth periodontal examinations were collected on each subject followed by a single in-home overnight sleep test using the Apnea Risk Evaluation System (ARES Unicorder) to evaluate SDB. The study found that compared to the non-apneic referent, the likelihood of severe CP were 40% higher in individuals with subclinical SDB (OR: 1.4, 95% CL: 1.0, 1.9), 60% higher in individuals with mild SDB (OR:1.6, 95% CL: 1.1, 2.2), and 50% higher in individuals with moderate/severe SDB (OR: 1.5, 95% CL: 1.0,2.3). The findings were more pronounced at milder levels for SDB ($p=0.015$) and stronger in younger adults ($p<0.001$).[22]

In contrast to the above five studies, Loke et al. (2014) found that OSA was not significantly associated with moderate/severe CP or the periodontal parameters examined, except for the plaque index.[21] One hundred veterans at the VA Hospital in San Antonio, Texas participated in this cross sectional study. Data from a comprehensive periodontal evaluation and overnight polysomnography were evaluated. The study found an insignificant association between AHI severity and CP ($p=0.246$) in this predominantly male study with a mean age of 52.6. AHI categories were significantly associated with percent of plaque sites ($p=0.037$), but not significantly associated with percent of sites with bleeding on probing ($p=0.126$) or CAL ($p=0.842$).[21]

Although pilot studies have investigated possible causes of the association, the mechanism is unknown. Mouth-breathing causing xerostomia (dry mouth), oxidative stress, and systemic

inflammation are suggested mechanisms. (Table 1.1) Individuals with SDB commonly breathe through their mouth leading to reports of xerostomia upon waking.[25] A dry mouth may decrease bacterial clearance effectiveness of oral tissues creating more migration of periodontal microbiota.[22] Subjective dry mouth (xerostomia) measures include assessment questions on single-item (i.e. "How often does your mouth feel dry?") or multi-item questionnaires via rating scales. Objective measures of the condition are through salivary gland hypofunction by measuring stimulated or unstimulated salivary flow.[26] While there is little evidence on xerostomia being a direct influence of CP, one study has found an effect of xerostomia on bleeding upon probing and dental plaque in young adults.[27] Oxidative stress is an imbalance between free radical production and antioxidant defenses.[28] It has been found that an increase in oxidative stress biomarkers is found in individuals with OSA[29] and influences the progression rate of CP.[30]

The third suggested mechanism is systemic inflammation. Systemic inflammation has been observed in both CP and OSA as detected by pro-inflammatory biomarkers in saliva. It is suggested that biomarkers in the saliva are elevated in CP and are additionally altered by the coexistence of OSA. Biomarkers that show an association with CP include Interleukin-6 (IL-6), Interleukin-33 (IL-33), Interleukin-1 β (IL-1β), Matrix metalloproteinase-8 (MMP-8), Oncostatin M (OSM), and C-Reactive Protein (CRP). A few of these biomarkers have also been found associated with OSA.

IL-6 is a multifunctional cytokine with pro-inflammatory and anti-inflammatory properties[31] that regulates bone resorption and stimulates clot formation.[32] Increased levels of IL-6 are associated with many inflammatory processes such as in CP[31] and OSA.[33] Studies have found subjects with gingivitis and CP have increased levels of IL-6 in gingival crevicular fluid compared to subjects without periodontal inflammation.[34] Nizam et al. (2015b) found salivary IL-6 levels were significantly higher in OSA cases than controls.[35]

IL-33 is a cytokine[36] associated with acute and chronic inflammation.[37] It has both a protective function against infection and a destructive function in several inflammatory diseases.[36] IL-33 has been found to be a biomarker of CP[36] and have higher levels in patients with OSA independently of periodontal status.[38] When IL-33 is released in periodontal structures, it destructs cells by necrosis and induces the production of macrophages, eosinophils, and basophils.[36]

IL-1β is a highly inflammatory cytokine protein that enhances T-cell activation and recognition of antigen.[37] It is associated with acute and chronic inflammation.[37] Elevated levels of IL-1 β are associated with CP[39] and OSA.[40] Increased levels of IL-1β are found in saliva and gingival crevicular fluid of patients with CP.[39]

MMP-8, also known as neutrophil collagenase, is important in tissue destruction for inflammatory diseases and is a marker of CP progression.[41] MMP-8 is found at increased levels in gingival crevicular fluid and whole saliva samples in adults with CP.[41]

OSM is a cytokine belonging to the IL-6 family. It is associated with biological processes and cellular responses that include growth, inflammation, and differentiation.[42] OSM is associated with chronic inflammatory conditions such as lung inflammatory diseases.[42] Thorat et al. (2010) found that OSM levels in gingival crevicular fluid and serum increased with progression of CP and decreased after scaling and root planing, suggesting OSM that is an inflammatory biomarker for CP.[43] To date, no studies have looked at OSM in relation to OSA.

CRP is an acute phase protein[44] and is a sensitive systemic marker of inflammation and tissue damage.[45] When inflammation throughout the body occurs, the level of CRP rises.[45] CRP is associated with CP[46] and SDB,[47] and might be a biomarker underlying the association.

Of relevance to the present study described below, Ahmad et al. (2013) found subjects with moderate or severe CP (cases) were 4.1 times more likely to be at high risk for OSA than those with slight or no CP (controls);[18] however, it was unknown whether the subjects had OSA as sleep apnea

testing was not conducted. Moreover, salivary samples were not collected for biomarker assays. The present study is similar in design and subjects as Ahmad et al. (2013). The aim of the present study was to determine if the prevalence of SDB is greater in patients with moderate to severe CP (cases) than in patients with slight CP or gingivitis (controls) based on objective measures of SDB. The secondary aim was to investigate underlying inflammatory mechanisms of CP and SDB by analyzing biomarkers in saliva that might contribute to an association.

METHODS

Study Population and Recruitment

Subjects were patients who attended dental clinics at the University of North Carolina at Chapel Hill between March and December 2015 and consented to participate. Inclusion criteria included having at least 10 teeth, being 40 to 75 years of age, been assigned a periodontitis case classification, and speak English. The institutional review board at the University of North Carolina at Chapel Hill approved this study.

Study Design

One hundred fifty subjects were scheduled to participate in this case-control study: 75 subjects with moderate/severe chronic periodontitis (cases) and 75 with gingivitis/slight chronic periodontitis (controls).

Sample Size Determination

For a fixed sample size of 150, we calculated power to detect a clinically important difference of 100% in mean AHI between cases and controls. We assumed equal numbers of cases and controls, an alpha of 0.05 and applied the pooled standard deviation of 9.5 reported by Seo et al.[23] Estimating AHI means of 3.5, 4.0 4.5 or 5.0 for controls and corresponding AHI means of 7.0, 8.0, 9.0 and 10.0, for cases power was 61%, 73%, 82% and 89% respectively.

Demographic and Medical Information

Demographic, medical, behavioral, and sleep information was collected via a questionnaire administered to each subjects. Demographic information was obtained by use of questions regarding age, sex, and race. Medical information was obtained by use of questions regarding diabetes status (none, Type 1, and Type 2), high blood pressure (yes/no), and a previous diagnosis with OSA. Behavioral information was obtained by use of questions regarding smoking status (current smoker, ex-smoker, not a smoker), alcohol consumption per week, bruxism frequency (awake and sleep), and dry mouth (yes/no and frequency).

Screening questions were used to evaluate risk of OSA: the STOP questionnaire,[48] the STOP-Bang questionnaire,[48] and the Epworth Sleepiness Scale.[49] The questions on the STOP include: do you snore loudly, do you often feel tired during the day, has anyone observed you stop breathing during sleep, and do you have hypertension.[48] High risk for OSA based on the STOP questionnaire is indicated by two or more affirmative responses. The added questions on the STOP-BANG include: BMI, age, neck circumference, and sex.[48] High risk for OSA based on the STOP-Bang questionnaire is indicated by three or more affirmative responses. The Epworth Sleepiness Scale evaluates an individual's chance of dozing off (scale of 0-3) in eight scenarios (1. Sitting and reading; 2. Watching TV; 3. Sitting, inactive in a public place; 4. As a passenger in a car for an hour without a break; 5. Lying down to rest in the afternoon when circumstances permit; 6. Sitting and talking to someone; 7. Sitting quietly after a lunch without alcohol; 8. In a car, while stopped for a few minutes in traffic). A score of >10 is considered excessive daytime sleepiness.[49]

In addition to the questionnaire, height, weight, and neck circumference measurements were collected on each patient. Height and weight were calculated to obtain the patient's body mass index (BMI). BMI classifications were based on the definition by the World Health Organization (WHO) where

a BMI less than 25 classified as underweight/healthy, a BMI of 25.0-29.9 classified as overweight, and a BMI of 30.0 or greater classified as obese.

All information was recorded by the examiner using TeleForm, an optical scanning system that efficiently transfers information to an electronic format for statistical analysis.

Periodontal Examination

Full mouth periodontal charting, including attachment level (CAL), bleeding on probing (BOP), probing depths (PD), gingival recession, mobility, and furcation involvement were obtained on all fully erupted teeth. CAL, BOP, PD, and recession were obtained at six sites per tooth (distofacial, facial, mesiofacial, mesiolingual, lingual, and distolingual) with a UNC-15 Probe. Furcation involvement was measured with a Naber's probe. Chronic periodontitis case status was classified based on the American Academy of Periodontology classifications (Table 1.2).[50] The periodontal measurements were taken within a year prior to the completion of the home sleep apnea test. Cases missing some of the periodontal data were interpreted by a periodontist who judged case on treatment history and radiographs.

Home Sleep Apnea Testing

Each subject underwent a two-night home sleep apnea test administered by NovaSom, Inc.®, an accredited home sleep testing company. The home sleep-testing device uses three sensors located on the finger, chest, and nose/mouth, which collect channels of data pertinent to sleep respiration. The finger sensor collected blood oxygen saturation (SpO_2) and pulse. The chest sensor collected respiratory effort. The nose/mouth sensor collected measures of snoring noise. The home sleep apnea test provided estimates of AHI, oxygen saturation parameters (number of drops and duration), and snoring (maximum, average, percentage and time over 50 decibels). Apneas were defined as a decrease in peak signal excursion of around 90% from the pre-event baseline with duration of ≥10 seconds. Hypopneas

were defined as a 50% or more reduction in airflow for at least 10 seconds, accompanied by a decrease in blood oxygen saturation of 4%.

Saliva Samples

Saliva samples were obtained to investigate mechanisms underlying CP and SDB. A 3-milliliter unstimulated saliva sample was taken, centrifuged, aliquoted, and stored in an -80 degree Celsius freezer. Analysis of levels of IL-6, IL-33, IL-1β, MMP-8, Oncostatin, and CRP was planned.

Statistical Analysis

Univariate analysis examined the relationship between periodontitis case status and three ordinal categories of AHI severity, setting the referent set asymptomatic OSA (AHI<15). Participants were said to be asymptomatic if they reported <2 STOP screening symptoms. Symptomatic slight OSA was defined as AHI 5–15 and with ≥2 STOP symptoms. Moderate/severe OSA was defined as AHI of >15. Pearson's chi-square tested the hypothesis of no relationship between periodontitis case status and SDB.

In binary logistic regression, the dependent variable was periodontitis case status and the main exposure was categories of AHI severity. Models estimated the odds of having moderate/severe periodontitis relative to no/slight periodontitis across the three categories of AHI severity. Tables 1.4 and 1.5 report odds ratios (OR) and their corresponding 95% confidence limits (CL).

Covariates

Covariates were sex (male, female), age (44–59, 60–69, ≥70 years), body mass index (underweight/healthy, overweight, obese), xerostomia frequency (never/monthly/weekly, most days/always), and sleep bruxism frequency (less than once a week, at least once a week). Studies have shown that the prevalence of CP and severity of OSA are greater in males than females,[12,51] increased age,[14,51] and a higher BMI.[15,16] Additionally, dry mouth upon waking up from sleep[52] and self-reported sleep tooth grinding[53] are considered a significant symptom of OSA. Toikwa et al. (2008) reported that

grinding patterns during sleep tooth grinding is a plausible causative factor of increased CAL.[54] While there is little published evidence suggesting that dry mouth has a direct influence on CP, one study did find that xerostomia was related to bleeding upon probing and dental plaque formation in young adults.[55] Therefore, these five covariates are included in the analyses as they could have an effect on the hypothesized relationship between CP and SDB.

RESULTS

To date, 48 subjects have been enrolled (26 cases and 22 controls). Eleven subjects with insufficient sleep data were excluded from analysis. One subject had insufficient home sleep data and ten did not open or place the sensors of the home sleep apnea test. Thus, data for 22 cases and 15 controls were available for analyses.

Out of the 37 subjects analyzed, 22 (59.5%) were periodontal cases. Twenty-two (59.5%) out of the 37 subjects had OSA based on the home sleep test. Twenty-seven percent (n=10) had both CP and OSA; whereas, 8.1% (n=3) had neither disorder (Table 1.3).

Table 4 describes demographic, behavioral, and sleep characteristics of the sample, and whether those characteristics are associated with case status. The majority of the sample was female and overweight (BMI ≥ 25). Age groups were equally divided among categories of age. Approximately two thirds of subjects reported dry mouth and sleep tooth grinding less than once a week.

There was no significant association between CP case status and OSA status (p=0.104; see table 1.4). Contrary to expectation, subjects having symptomatic mild OSA (OR=0.25, CL: 0.04, 2.63) or moderate/severe OSA (OR= 0.19, 95% CL: 0.04, 0.98) were less likely to have moderate/severe CP than subjects without OSA. In addition, the univariate analyses revealed no significant associations between CP case status and sex (p=0.259), age (p=0.719), body mass index (p=0.767), xerostomic frequency (p=0.417), and sleep tooth grinding frequency (p=0.681).

Multivariate binary logistic regression revealed that adjustment for confounding variables confirmed the lack of an association between CP and OSA (Table 1.5). In the adjusted model, subjects with symptomatic mild OSA (OR=0.13, CL: 0.01, 1.53) or moderate/severe OSA (OR=0.13, 95% CL: 0.01,1.29) were less likely to have moderate/severe CP than subjects with asymptomatic mild or no OSA (referent). None of the covariates predicted CP case status as was observed in the univariate analyses.

Saliva samples have not been analyzed to date.

DISCUSSION

Relationship between CP and OSA

The main objective of this study was to investigate the association between CP and OSA. Unlike in the five studies reviewed in the introduction, we found no association between CP and OSA. The results were opposite to the hypothesized relationship: SDB tended to be more prevalent in control subjects than in CP cases. Exploratory analyses using different OSA classification based on AHI were conducted but led to similar results (see Appendix). Additionally, roughly 60% of the subjects had at least symptomatic mild OSA compared to the estimated 26% of the population, which is over twice the expected prevalence. We attribute these unexpected findings to recruitment bias. Subjects who believed they had OSA may have been more likely to enroll in this study.

Salivary Biomarkers in CP and OSA

The biomarkers have not been analyzed to date; however, studies have investigated salivary biomarkers as a potential mechanism underlying an association between OSA and CP.[22,35,38,56]

An inflammatory mechanism associated with CP and OSA was studied in 52 subjects with complaints of sleep apnea related symptoms and referred for a polysomnogram to the Department of Chest Disease at Ege University in Turkey. The authors found increased numbers of periodontal microorganisms in subjects with increasing severity of OSA. Additionally, subjects with the most severe

OSA showed the most alteration in the biomarkers analyzed, suggesting that OSA impacts CP and colonization of salivary biomarkers.[35]

Sanders et al (2015) conducted a cross-sectional study of data from 12,469 subjects from the Hispanic Community Health Study/Study of Latinos.[22] Blood samples were collected on each subject to measure high-sensitivity-CRP (hs-CRP) in serum. The authors found that hs-CRP did not explain the relationship between SDB and CP.[22]

To date, the knowledge about salivary biomarkers in patients with both CP and OSA is limited to four papers. Research is needed to determine the effects of salivary biomarkers on the association between OSA and CP. Extending the previous studies, the present study adds other biomarkers that are associated with both CP and OSA.

Confounding Variables

The multivariate analysis took into consideration a number of factors that have been associated with CP, and some that are associated with SDB also. The present study did not demonstrate a significant association between any of the factors and CP. This may be due to more of the subjects being females (70.3%) than males (29.7%) and reporting less than once a week of dry mouth (67.6%) and sleep tooth grinding (62.2%). Additionally, controls were more likely to be overweight and be older (at least 60 years) than CP cases, which may have affected the lack of an association between BMI and age with CP.

Limitations

Limitations to this study include a small sample size, recruitment (self-selection) bias, a non-representative sample, and non-calibrated examiners for the periodontal examination. Based on our predicted sample size needed to show significant effects, our current sample is too small. A smaller sample will give a result that may not be sufficiently powered to detect a difference between the groups and the study may turn out to be falsely negative leading to a type II error. This sample has likely suffered to some degree of self-selection bias, which arises when individuals select themselves into a

group, causing a biased sample. In the present study, people with OSA enrolled which may suggest selection bias. A non-representative sample occurs when a sample does not accurately reflect the members of the entire population. The present study collected data from a few clinics in one dental school and had more women and non-smokers; therefore, not reflecting the entire population. There was no additional calibration for examiners collecting periodontal information and the periodontal charting was obtained up to 12 months prior to the home sleep apnea test.

CONCLUSION

This case-control study found no association between chronic periodontitis and sleep-disordered breathing based on standard of care periodontal measurements and home sleep test estimates of AHI. We suspect that this finding may be of limited validity given the small sample size and biases present in the subjects enrolled and are expecting to collect more data.

Table 1.1. Suggested mechanisms underlying the association between chronic periodontitis and sleep-disordered breathing.

Suggested Mechanism	Studies investigating	Evidence
Increased systemic inflammation	Nizam (2013) Nizam (2015a) Nizam (2015b)	Increased numbers of periodontal microorganisms in subjects with increased severity of OSA
		Severe OSA subjects showed most alteration in salivary biomarkers detected, suggesting that OSA does impact CP[b] and colonization of salivary biomarkers
	Sanders (2015)	Investigated high sensitivity C-reactive protein as a possible inflammatory mediator of relationship and found it did not explain the relationship between SDB and CP
Mouth breathing leading to dry mouth	Seo (2012)	Little published evidence suggesting direct influence on CP
		People at higher risk for OSA may be identified with complains of mouth breathing, dry mouth, and CP
	Mizutani (2015)	Subjective measures of xerostomia related to bleeding upon probing and dental plaque formation in young adults
Oxidative stress	Passali (2015)	Increase in oxidative stress biomarkers found in OSA individuals
	Tamaki (2009)	Systemic increase in oxidative stress may influence the progression rate of CP

[a] OSA = Obstructive Sleep Apnea

[b] CP = Chronic Periodontitis

Table 1.2. Chronic periodontal classifications based on the American Academy of Periodontology (AAP) classifications

Healthy Periodontium	Gingivitis	Slight Chronic Periodontitis	Moderate Chronic Periodontitis	Severe Chronic Periodontitis
No CAL	No CAL [a] OR Periodontium with CAL that is not progressing	1-2 mm CAL	3-4 mm CAL	≥5 mm CAL

(a) CAL = Clinical Attachment Level

(b) Classifications can be:

Localized = ≤30% of sites involved

Generalized = >30% of sites involved

Table 1.3. Univariate analysis between chronic periodontitis case status and AHI[c] Classification (N=37)

		Chronic Periodontitis Case Status		
		Slight CP[a]/gingivitis	Moderate/severe CP	
OSA[b] Status	No/subclinical mild OSA	3 (8.1%)	12 (32.4%)	40.5%
	Symptomatic mild/moderate/severe OSA	12 (32.4%)	10 (27.1%)	59.5%
		40.5%	59.5%	100%

(a) CP = Chronic Periodontitis

(b) OSA = Obstructive Sleep Apnea

(c) AHI = Apnea Hypopnea Index

Table 1.4. Univariate analysis between key characteristics and chronic periodontitis case status with odds ratio (OR) (95% confidence limits [CL]) for moderate/severe chronic periodontitis (CP) (n=37)

	N (%)	Case [a] row %, n=22	Control [b] row %, n=15	P-value	OR (95% CL)	P-value
Total	37 (100.0)	59.5	40.5	…	…	…
OSA status						
No OSA or subclinical mild OSA	15 (40.5)	80.0	20.0	0.104	Referent	
Symptomatic mild	8 (21.6)	50.0	50.0		0.25 (0.04, 1.63)	0.148
Moderate or severe	14 (37.8)	42.9	57.1		0.19 (0.04, 0.98)	0.047
Sex						
Male	11 (29.7)	45.5	54.6	0.259	0.44 (0.10, 1.85)	0.264
Female	26 (70.3)	65.4	34.6		Referent	
Age group (years)						
44–59	12 (32.4)	50.0	50.0	0.719	Referent	
60–69	14 (37.8)	64.3	35.7		1.80 (0.37, 8.68)	0.464
≥70	11 (29.7)	63.6	36.4		1.75 (0.33, 9.30)	0.511
Body mass index [c]						
Underweight/healthy (<25.0)	10 (27.0)	50.0	50.0	0.767	Referent	
Overweight (25.0–29.9)	14 (37.8)	64.3	35.7		1.80 (0.34, 9.40)	0.486
Obese (≥30.0)	13 (35.1)	61.5	38.5		1.60 (0.30, 8.49)	0.581
Xerostomia frequency [d]						
Never/monthly/weekly	25 (67.6)	64.0	36.0	0.417	Referent	
Most days/always	12 (32.4)	50.0	50.0		0.56 (0.14, 2.27)	0.419
Nocturnal bruxism frequency [e]						
Less than once a week	23 (62.2)	60.87	39.1	0.681	Referent	
At least once a week	13 (35.1)	53.85	46.2		0.75 (0.19, 2.97)	0.682
Missing	1 (2.7)					

[a] Moderate or severe chronic periodontitis; (b) Healthy, gingivitis, or slight chronic periodontitis

[c] World Health Organization categories

[d] How frequently do you experience mouth dryness immediately after waking?

[e] How often do you clench or grind your teeth when asleep, based on any information you may have?

Table 1.5. Multivariate association between characteristics and moderate/severe chronic periodontitis (N=37)

	Odds ratio (95% confidence limit)	P-value
OSA status		
No OSA or subclinical mild OSA	Referent	
Symptomatic mild	0.13 (0.01, 1.53)	0.105
Moderate or severe	0.13 (0.01, 1.29)	0.082
Sex		
Male	0.42 (0.06, 2.84)	0.377
Female	Referent	
Age group (years)		
44–59	Referent	
60–69	1.67 (0.20, 13.76)	0.633
≥70	1.68 (0.17, 16.54)	0.659
Body mass index [a]		
Underweight/healthy (<25.0)	Referent	
Overweight (25.0–29.9)	3.14 (0.35, 28.47)	0.309
Obese (≥30.0)	6.52 (0.46, 91.87)	0.165
Xerostomia frequency [b]		
Never/monthly/weekly	Referent	
Most days/always	0.51 (0.08, 3.34)	0.485
Nocturnal bruxism frequency [c]		
Less than once a week	Referent	
At least once a week	0.99 (0.16, 6.10)	0.995

[a] World Health Organization categories

[b] How frequently do you experience mouth dryness immediately after waking?

[c] How often do you clench or grind your teeth when asleep, based on any information you may have?

CHAPTER TWO: OBSTRUCTIVE SLEEP APNEA SYMPTOMS PREDICT FIRST-ONSET TEMPOROMANDIBULAR DISORDER INDEPENDTLY OF REPORTED TOOTH GRINDING: OPPERA COHORT

INTRODUCTION

One plausible risk factor for temporomandibular disorder (TMD) to gain attention in recent years is sleep disordered breathing (SDB). A large population-based epidemiological family of TMD studies known as OPPERA (Orofacial Pain: Prospective Evaluation and Risk Assessment) measured signs and symptoms of SDB at baseline in a TMD-free cohort that was followed for a median 2.8 years to investigate the development of incident TMD, determined by calibrated examiners using Research Diagnostic Criteria (RDC).[57] Subjects with at least two of four cardinal OSA signs/symptoms or a history of OSA were classified as being high-risk for OSA. Subjects at risk for OSA were found to have 1.7 times the incidence of TMD over the median 2.8 year follow-up period, independently of demographic, autonomic and behavioral characteristics. The association remained statistically significant with further adjustment for subjective sleep quality.

Although the mechanisms underlying this finding are unknown, self-reports of bruxism/tooth grinding have consistently been associated with SDB and TMD in separate studies. For example, a cross-sectional telephone survey of 13,057 individuals in Europe aged ≥ 15 years found reported OSA to be the highest risk factor (odds ratio = 1.8) for tooth grinding among all sleep symptoms and disorders queried by the investigators.[58] Another cross sectional questionnaire study of 1930 residents in Japan found that individuals who reported snoring were 2.6 times as likely to report that they ground their teeth during sleep as those who did not report snoring.[59] Similarly, an association between patient report of tooth grinding and temporomandibular pain was observed in most studies reviewed over a 10-year period

ending in 2008.[60] A more recent investigation found that 64.5% of subjects with TMD based on RDC criteria, compared to 19.6% of control subjects, reported grinding their teeth at night.[61] Another study that found an association between polysomnographically confirmed sleep bruxism and TMD also found that subjects with TMD were more likely to report daytime clenching (85.7%) compared to control subjects (33.3%).[62]

The aim of this research was to investigate self-report of tooth grinding in the OPPERA data and its impact on the association between signs/symptoms of OSA and first onset TMD. We tested the hypothesis that the association is dependent on reported tooth grinding while sleep. A secondary aim was to investigate the extent to which the association is additionally dependent on reports of tooth grinding while awake.

METHODS

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

Study Design and Recruitment

From 2006 to 2008, potential participants were recruited by community-wide advertising at four U.S. study sites at Baltimore, Maryland; Buffalo, New York; Chapel Hill, North Carolina; and Gainesville, Florida.[63] Eligibility criteria included 18–44 years of age, good health, no history of facial injury or surgery, no significant TMD pain symptoms, and no previous diagnosis of TMD. An adaptation of a restricted version of the Research Diagnostic Criteria for TMD (RDC/TMD) was used in the orofacial clinical examination to exclude people who had TMD myalgia or TMD arthralgia. Inclusion also required an absence of orofacial pain symptoms in the month before enrollment and, prior to that period, no more than 4 days of orofacial pain per month. Participants completed a battery of self-administered psychological, clinical and sociodemographic questionnaires at baseline.

Signs and Symptoms of OSA

From the Pittsburgh Sleep Quality Index (PSQI) we extracted responses to three questions that ask about loud snoring, trouble staying awake, and witnessed apnea. From the medical history we extracted hypertension information. Together these four hallmarks of OSA comprise the 4-item OSA screening questionnaire called STOP that was validated against polysomnography.[48] 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, irrespective of their responses to the four approximated STOP questions.

Sleep and Awake Tooth Grinding

From the Oral Behaviors Checklist we extracted responses to two questions that measured reported tooth grinding.[64] Sleep tooth grinding was assessed by asking how often did the respondent "clench or grind teeth when asleep, based on any information you may have" for which options were: none of the time; <1 night/month; 1-3 nights/month; 1-3 nights/week; 4-7 nights/week. The corresponding awake tooth grinding question asked how often did the respondent "grind teeth together during waking hours", for which response categories were: none of the time; a little/some of the time; most/all of the time. The Checklist has been validated and assesses conscious awareness of parafunctional jaw behaviors that occurred over the last month. Its summary score is a strong predictor of first-onset TMD.[65]

Covariates

Demographic characteristics were sex, age, race/ethnicity (White, African American, Hispanic, other/unknown), and height and weight, which were used to compute body mass index (BMI = weight in kilograms/height in meters^2).

Follow-up

Once enrolled, subjects completed a Quarterly Health Update every three months. This screening questionnaire monitored development of TMD pain symptoms. Those who responded affirmatively to a question about having experienced "headaches or pain in your face, jaw, temples, in front of the ear, or in the ear," were asked about the duration of their pain. Participants who met the threshold of orofacial pain ≥5 days for at least 1 of the preceding 3 months, including ≥1 day in the preceding week were recalled for clinical examination to establish a definitive classification of first-onset TMD.

TMD Classification

At baseline and during follow-up of symptomatic participants, the case classification for TMD was determined in clinical examination using Research Diagnostic Criteria for TMD (RDC/TMD).[66] (adapted for OPPERA.) TMD cases met two 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).

Statistical Analysis

Statistical analyses were conducted with Stata SE Release 13 (College Station, TX: StataCorp LP). Of the 2,737 subjects who completed one or more Quarterly Health Update screening questionnaire, this analysis omitted those with missing: OSA classification (n=4); sleep- or awake tooth grinding (n=31) or covariates (n=42), yielding a sample size of 2,660. The rate of first-onset TMD was calculated as the number of subjects who developed TMD divided by the period of follow-up.

In descriptive analysis, Pearson's chi-square test or Fisher's Exact test were used to test the statistical significance of differences among categorical variables. To investigate potential for effect

modification, crude associations of baseline reports of tooth grinding and first-onset TMD were described in separate strata of low and high likelihood for OSA.

Multivariable Cox proportional hazard models were fitted via maximum likelihood with the Breslow method for handling tied failures to estimate hazard ratios (HR) and 95% confidence limits (CL). These models permit the computation of first-onset TMD probabilities for variable lengths of follow-up. For any variable in the model, its HR is interpreted as the proportional change in hazard of developing first-onset TMD for a one-unit increase in the corresponding variable, while controlling for all other variables. Recognizing that each of sleep tooth grinding and awake tooth grinding could contribute to the association between likelihood for OSA and TMD and that sleep and awake grinding might be correlated, we created four successive multivariable Cox models to determine the degree to which the OSA-TMD relationship is independent of those contributing factors: model 1 included likelihood for OSA adjusted for study site and demographic characteristics; model 2 added four response categories of sleep tooth grinding to model 1; model 3 added three categories of awake tooth grinding to model 1; and model 4 added the response categories of both sleep and awake tooth grinding to model 1. In addition to assessing main effects of predictor variables, effect modification was formally tested with the product terms of OSA and sleep- and awake tooth grinding.

RESULTS

In this analysis 9.5% (n=252) of the 2,660 subjects developed first onset TMD in 7,215 person-years of follow-up, yielding an annual rate of first-onset TMD 3.5%. At baseline, 5.8% (n=154) of the participants had high likelihood of OSA based on their sign/symptoms or medical history, 27.3% (n=726) reported tooth grinding during sleep, and 14.5% (n=386) reported tooth grinding while awake.

Characteristics of Participants at Risk for OSA

Subjects with high likelihood of OSA were more frequently male, older, African American, overweight or obese, and conscious of tooth grinding while awake (Table 2.1) – characteristics that have

been reported for patients diagnosed with OSA by polysomnography.[67] The subjects were 3.9 times as likely to report awake tooth grinding most or all of the time than none of the time ($p<0.001$). The 44% greater tendency for participants with high likelihood of OSA to report frequent tooth grinding during sleep did not reach statistical significance ($p=0.394$).

Univariate Analyses of First-onset TMD

Among the participants with high- versus low likelihood of OSA , rate of first-onset TMD was elevated two-fold (site-adjusted HR = 2.32 [95% CL: 1.54, 3.48]) (Table 2.1). Other putative predictors of first-onset TMD were female sex, older age, African-American race, and obesity. Incidence of first-onset TMD increased across successive response categories of both sleep tooth grinding and awake tooth grinding. (Table 2.1). Subjects who reported sleep tooth grinding ≥1 night/week were 1.8 times as likely to develop first-onset TMD as subjects who reported sleep tooth grinding none of the time (site-adjusted HR = 1.84 [95% CL: 1.28, 2.65]). Subjects who reported awake tooth grinding most/all of the time were 3.1 times as likely to develop first-onset TMD as subjects who reported awake tooth grinding none of the time (site-adjusted HR = 3.09 [95% CL: 1.36, 7.03]).

To investigate potential effect modification of high versus low likelihood of OSA, the percentage of participants who reported tooth grinding a little or more of the time ('more than none') versus none of the time was calculated for those who did versus did not develop first-onset TMD (Table 2.2). Only for those with low likelihood for OSA did tooth grinding predict first-onset TMD. Sleep grinders with low likelihood for OSA were 52% more likely to develop first-onset TMD than non-grinders. Awake tooth grinders with low likelihood for OSA were 70% more likely to develop first-onset TMD than non-grinders. For participants with high likelihood for OSA, the presence of tooth grinding during sleep or wakefulness did not increase the likelihood of first-onset TMD.

Multivariable Models

Adjustment for confounding in multivariate Cox models (Table 2.3) variably attenuated the strength of the association between high likelihood for OSA and first-onset TMD. Upon controlling for the study site and demographic characteristics (Model 1), the association weakened but remained statistically significant with 84% higher incidence of TMD among people with high likelihood for OSA (HR=1.84, 95% CL: 1.21, 2.80). Further attenuation was minimal upon adjustment for confounding with sleep tooth grinding or/and awake tooth grinding (Models 2-4). Even accounting for both sleep and awake tooth grinding (Model 4), a 72% higher incidence of TMD among people with high versus low likelihood for OSA was observed (HR=1.72, 95% CL: 1.12, 2.63).

When each form of tooth grinding was considered alone (Model 2 and 3, Table 2.3), the hazard ratios were remarkably similar to those for the data adjusted only for site (Table 2.1). Only when both forms of tooth grinding were considered at the same time did adjustment for confounding modestly attenuate the strength of the association between tooth grinding and first-onset TMD (Model 4). Even so, participants who reported sleep tooth grinding ≥1 night/week were 1.6 times as likely to develop first-onset TMD than those who reported sleep tooth grinding none of the time (site-adjusted HR = 1.55 [95% CL: 1.03, 2.36]). Participants who reported awake tooth grinding most/all of the time were 2.3 times as likely to develop first-onset TMD than subjects who reported awake tooth grinding none of the time (site-adjusted HR = 2.28 [95% CL: 0.95, 5.48]). In contrast to the univariate analyses (Table 2.2), we observed no significant effect modification between likelihood of OSA and either sleep or awake tooth grinding.

DISCUSSION

In this population-based cohort of adults free of TMD at baseline, men and women with two or more signs/symptoms of OSA had 72% greater incidence of first-onset TMD, in relative terms, than those with fewer signs/symptoms, independently of sex, age, race/ethnicity, obesity, and reported tooth

grinding during sleep or while awake. Thus, neither the presence of sleep nor awake tooth grinding could account for the increased incidence of first-onset TMD in people at high risk for OSA. Moreover, people who reported grinding their teeth during sleep or while awake were more likely to develop TMD than people who did not grind, independently of their sex, age, race/ethnicity, obesity or their likelihood of OSA.

A growing body of literature since 2008 suggests that sleep disordered breathing (SDB), such as OSA, is a risk factor for TMD (13).[68] In one of the earliest studies, of 87 adults diagnosed with mild or moderate OSA, 32 (36.8%) had TMD as determined by RDC/TMD criteria.[69] In another study published the same year, 11 adults (28%) of 53 with RDC/TMD-based myofascial pain were diagnosed with OSA.[70] Subsequent to these earliest reports, a rigorously conducted case-control study found that women with RDC-confirmed TMD exhibited a higher frequency of respiratory effort related arousals during sleep– indicative of a mild form of sleep disordered breathing (SDB)--than control subjects.[71] OPPERA's large population-based studies extended these reports by demonstrating that OSA symptoms are not only associated with, but precede the first occurrence of TMD in initially TMD-free people.[57] Moreover, odds of chronic TMD were elevated more than three-fold in those at high risk for OSA.

SDB and Tooth Grinding During Sleep

The coexistence of self-reported sleep bruxism and SDB (see Introduction) has led many dental clinicians to conclude that SDB contributes to sleep bruxism, a sleep-related movement disorder characterized by rhythmic grinding of the teeth during sleep. Sleep bruxism is often assumed to cause TMD in susceptible individuals via micro-trauma to the temporomandibular joints or masticatory muscle from hyperactivity during sleep.[72,73,74] In this context, oral appliances that advance the mandible have been shown to reduce both SDB and sleep bruxism,[75,76,77] however their impact on the incidence or natural course of chronic TMD has not been studied.

The present study found that both a high likelihood of OSA and tooth grinding during sleep predict development of incident TMD. However, tooth grinding during sleep was only modestly and non-significantly elevated in people at increased risk of OSA. Moreover, controlling for the contribution of tooth grinding during sleep did not eliminate the impact of high OSA risk on first-onset TMD. Thus, sleep bruxism is unlikely a mechanism by which SDB contributes to the development of TMD.

SDB and Tooth Grinding While Awake

The present study is the first to report a significantly (four-fold) higher prevalence of "grinding the teeth together" while awake in people at high risk for OSA. Daytime clenching is associated with elevated masticatory muscle activity and increased levels of anxiety.[78,79] Anxiety results from chronic activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis in people with SDB[80,81] and is greater with severe, than with mild, OSA.[82] Participant self-report provides a reliable indicator of daytime clenching as measured objectively from surface EMG recordings of the jaw-closing muscles.[83]

Two recent case-control studies found daytime clenching to be a strong risk factor for RDC-confirmed TMD as compared to self-reported[84] or laboratory-confirmed bruxism during sleep.[62] Odds ratios for daytime clenching were 1.7 and 12.0, compared to 1.8 and 3.45 for bruxism during sleep, respectively. In the OPPERA data, oral parafunction was reported to be the strongest predictor of TMD incidence of all clinical measures obtained by calibrated examiners or reported by participants at baseline.[65] Unlike in the present study, a single composite score represented the frequencies of all 21 items on the Oral Behaviors Checklist preventing determination of the separate contributions of grinding the teeth during sleep and while awake. Although the present study found tooth grinding while awake to be a significant predictor of first-onset TMD in initially TMD-free adults -- extending the studies noted above – it could not explain the association between high likelihood of OSA and incident TMD. Thus,

factors other than SDB contributed to tooth grinding while awake in many participants who developed first-onset TMD.

Strengths and Limitations

Strengths of the study include the prospective cohort design, which established presence of OSA signs/symptoms prior to first-onset TMD, and the rigorous OPPERA protocols. Multiple study sites and community recruitment optimized the diversity and representativeness of the study population to improve the generalizability of findings. The prospective cohort findings imply that OSA, sleep bruxism, and daytime clenching each independently contribute to the onset of painful TMD symptoms.

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[48] and inevitably misclassify OSA risk. However as there is no reason for misclassification to differ between TMD cases and non-cases, resulting bias will shift estimates of association conservatively towards the null. Attesting to its usefulness, participants at high likelihood of OSA based on the STOP exhibited the same demographic characteristics that have been reported for patients diagnosed by polysomnography.

Information about tooth grinding during sleep was obtained by questionnaire, a method that is recognized both practical and appropriate for collecting epidemiological data from large numbers of subjects as in the present case.[84] However, the subjective nature of the data likely entails over- or underestimation of the prevalence of the stereotypic patterns of masticatory muscle activity observed during polysomnography required of definitive research diagnostic criteria for sleep bruxism.[85,86,87] However, given that all participants were TMD-pain free at the time of assessment, there was no bias to over-report tooth grinding due to an increased awareness of orofacial symptoms as a result of pain.

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Table 2.1. Univariate Associations of Subjects Characteristics with Baseline Obstructive Sleep Apnea (OSA) Symptoms and Rate and Hazard Ratio (95% confidence limits [CL]) for First-Onset Temporomandibular Disorder (TMD), OPPERA Prospective Cohort Study, 2006-2011 (n=2,660).

	N (%)	% at Baseline High Risk for OSA	P-value	Rate of First-Onset TMD (% per annum)	Site-Adjusted Hazard Ratio (95% CL) for TMD	P-value
Likelihood of OSA						
Low	2,506 (94.2)	..	..	3.28	Ref	
High	154 (5.8)	..	..	7.66	2.32 (1.54, 3.48)	<0.001
Sex						
Male	1,075 (40.4)	7.3	0.008	3.06	Ref	
Female	1,585 (59.6)	4.8		3.78	1.31 (1.01, 1.70)	0.043
Age (years)						
18-24	1,394 (52.4)	2.9	<0.001	2.94	Ref	
25-34	719 (27.0)	5.4		3.84	1.55 (1.15, 2.08)	0.004
35-44	547 (20.6)	13.5		4.44	1.79 (1.27, 2.50)	0.001
Race/Ethnicity						
White	1,419 (53.4)	4.0	<0.001	3.37		
African American	731 (27.5)	11.2		4.51	1.47 (1.08, 2.01)	0.015
Hispanic	247 (9.3)	2.0		1.40	0.39 (0.20, 0.77)	0.007
Other/Unknown	263 (9.9)	4.2		3.57	0.93 (0.61, 1.43)	0.748
Body Mass Index (kg/m^2)						
Underweight	78 (2.9)	2.6	<0.001	2.89	0.92 (0.41, 2.10)	0.849
Normal	1,351 (50.8)	2.8		3.10	Ref	
Overweight	716 (26.9)	6.0		2.84	0.90 (0.66, 1.25)	0.537
Obese	515 (19.4)	13.8		5.69	1.84 (1.37, 2.48)	<0.001
Sleep Tooth Grinding						
None of the time	1,934 (72.7)	5.5	0.394	3.06	Ref	
<1 night/month	269 (10.1)	5.2		2.99	0.96 (0.62, 1.50)	0.862
1-3 nights/month	230 (8.7)	7.0		5.50	1.74 (1.20, 2.53)	0.003
≥1 night/week	227 (8.5)	7.9		5.88	1.84 (1.28, 2.65)	0.001
Awake Tooth Grinding						
None of the time	2,274 (85.5)	5.3	0.001	3.17	Ref	
A little/some of the time	362 (13.6)	8.0		5.15	1.58 (1.16, 2.17)	0.004
Most/all of the time	24 (0.9)	20.8		10.29	3.09 (1.36, 7.03)	0.007

Table 2.2. Cross-tabulation of tooth grinding and first-onset TMD, stratified by likelihood of obstructive sleep apnea (OSA) [(a)], 2006-2011 (n=2,660).

	Low Likelihood of OSA			High Likelihood of OSA		
	No TMD	**First-onset TMD**	P value	**No TMD**	**First-onset TMD**	P-value
Total	2,281 (91.0)	225 (9.0)		127 (82.5)	27 (17.5)	
Sleep Tooth Grinding						
None of the time	1,684 (92.1)	144 (7.9)	0.002	89 (84.0)	17 (16.0)	0.468
More than none	597 (88.1)	81 (12.0)		38 (79.2)	10 (20.8)	
Awake Tooth Grinding						
None of the time	1,978 (91.8)	176 (8.2)	<0.001	99 (82.5)	21 (17.5)	0.984
More than none	303 (86.1)	49 (13.9)		28 (82.4)	6 (17.7)	

[(a)] Values are frequencies and (row percentages)

Table 2.3. Multivariable-adjusted hazard ratio and 95% confidence limits (CL) for the association between risk for obstructive sleep apnea (OSA) and first-onset TMD, with and without adjustment for reported awake tooth grinding and sleep tooth grinding, OPPERA Prospective Cohort Study, 2006-2011 (n=2,660).

	Model 1 [(a)] HR (95% CI)	P value	Model 2 [(a)] HR (95% CI)	P value	Model 3 [(a)] HR (95% CI)	P value	Model 4 [(a)] HR (95% CI)	P value
Sex								
Male	Referent		Referent		Referent		Referent	
Female	1.26 (0.97, 1.64)	0.088	1.26 (0.97, 1.65)	0.084	1.32 (1.01, 1.73)	0.041	1.31 (1.00, 1.71)	0.050
Age (years)								
18-24	Referent		Referent		Referent		Referent	
25-34	1.43 (1.05, 1.94)	0.023	1.39 (1.03, 1.89)	0.033	1.41 (1.04, 1.92)	0.027	1.39 (1.03, 1.90)	0.034
35-44	1.36 (0.95, 1.94)	0.095	1.35 (0.94, 1.94)	0.100	1.33 (0.93, 1.91)	0.118	1.34 (0.93, 1.92)	0.116
Race/Ethnicity								
White	Referent		Referent		Referent		Referent	
African American	1.20 (0.86, 1.67)	0.275	1.30 (0.93, 1.81)	0.121	1.23 (0.89, 1.71)	0.218	1.29 (0.93, 1.80)	0.130
Hispanic	0.41 (0.21, 0.81)	0.011	0.42 (0.21, 0.82)	0.011	0.42 (0.21, 0.82)	0.012	0.42 (0.21, 0.83)	0.012
Other/Unknown	0.94 (0.61, 1.43)	0.758	0.96 (0.63, 1.47)	0.843	0.95 (0.62, 1.45)	0.797	0.96 (0.63, 1.47)	0.848
Body Mass Index (kg/m^2)								
Underweight	0.98 (0.43, 2.24)	0.960	0.97 (0.42, 2.22)	0.943	0.92 (0.40, 2.11)	0.852	0.94 (0.41, 2.15)	0.878
Normal	Referent		Referent		Referent		Referent	
Overweight	0.83 (0.60, 1.16)	0.273	0.85 (0.61, 1.18)	0.325	0.83 (0.60, 1.15)	0.260	0.84 (0.60, 1.17)	0.302
Obese	1.43 (1.03, 1.98)	0.031	1.47 (1.06, 2.03)	0.020	1.49 (1.07, 2.06)	0.017	1.49 (1.08, 2.06)	0.016
Likelihood of OSA [(b)]								
Low	Referent		Referent		Referent		Referent	
High	1.84 (1.21, 2.80)	0.005	1.77 (1.16, 2.70)	0.008	1.73 (1.13, 2.64)	0.011	1.72 (1.12, 2.63)	0.012
Sleep Tooth Grinding								
None of the time	---		Referent		---		Referent	
<1 night/month	---		1.02 (0.65, 1.61)	0.915	---		0.94 (0.60, 1.49)	0.801
1-3 nights/month	---		1.80 (1.23, 2.61)	0.002	---		1.65 (1.12, 2.42)	0.011
≥1 night/week	---		1.93 (1.33, 2.79)	0.001	---		1.55 (1.03, 2.36)	0.038
Awake Tooth Grinding								
None of the time	---		---		Referent		Referent	
A little/some of the time	---		---		1.69 (1.23, 2.32)	0.001	1.44 (1.01, 2.03)	0.042
Most/all of the time	---		---		2.97 (1.29, 6.83)	0.010	2.28 (0.95, 5.48)	0.067

[(a)] All four models adjusted for study site

[(b)] High risk for OSA defined as either (a) previous diagnosis of OSA; and/or (b) ≥2 of the following OSA risk factors: loud snoring, daytime tiredness, witnessed apnea, hypertension

--- Variable not included in model

APPENDIX ONE

Univariate analysis between chronic periodontitis case status and AHI Classification (continuous and traditional categories) (N=37)

	Odds Ratio (95% Confidence Limit)	**P-value**
AHI[a] (continuous)		
Continuous	0.97 (0.93, 1.03)	0.410
AHI Categorical		
AHI <5	Referent	
AHI 5 - <15	1.73 (0.22, 13.67)	0.602
AHI 15 - <30	0.27 (0.24, 3.02)	0.286
AHI ≥30	0.89 (0.09, 9.16)	0.086

(a) AHI = Apnea Hypopnea Index

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