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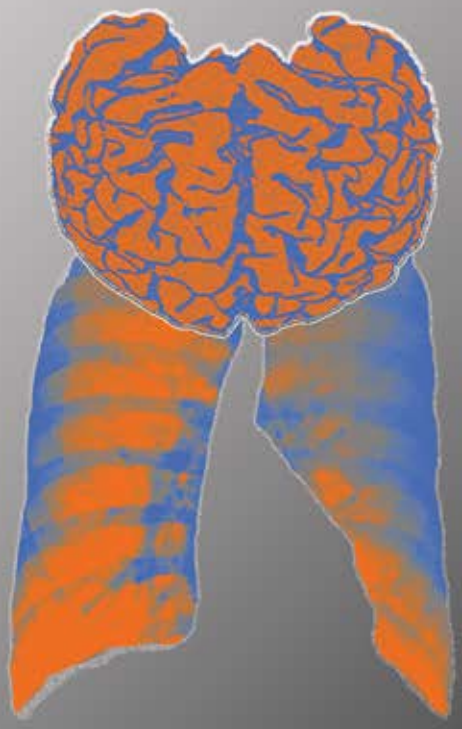

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On bruxing and breathing

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Faculteit der Tandheelkunde

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Chapter 1

General introduction

Sleep medicine is a medical specialty that focuses on the diagnosis and treatment of sleep disturbance and disorders.[1] Although sleep-related conditions fall under sleep medicine, the causes, consequences, and treatment of some sleep conditions are associated with dentistry. Consequently, dental sleep medicine has emerged as a highly multidisciplinary area in dentistry, which is defined as "a discipline concerned with the study of the oral and maxillofacial causes and consequences of sleep-related problems."[2] With the development of dental sleep medicine, dentists may be able to identify risk factors, to conduct preliminary screening, to prevent the occurrence of consequences of dental sleep conditions, or to treat those sleep-related disorders by using oral devices (such as mandibular advancement appliance for OSA). Vice versa, sleep doctors may be able to recognize the negative consequences of sleep-related conditions in the orofacial area and provide better patient care in interdisciplinary settings.[2]

As summarized by Lobbezoo et al, dental sleep conditions currently involve orofacial pain (e.g., headaches), oral moistening disorders (e.g., dry mouth), gastroesophageal reflux disease, mandibular movement disorders or behavior (e.g., sleep bruxism, SB), and sleep-related breathing disorders (e.g., obstructive sleep apnea, OSA).[2,3] Both OSA and SB are common sleep-related conditions in the general population that have frequently been associated with each other.[4–7]

OSA is a sleep-related breathing disorder characterized by repetitive respiratory events of partial (hypopnea) or complete (apnea) upper airway collapse during sleep.[7] The obstructive respiratory events often result in oxygen desaturation (hypoxemia and hypoxia) and sleep arousal.[7,8] SB is a masticatory muscle activity occurring during sleep that is characterized as rhythmic (phasic) or non-rhythmic (tonic), and that manifests as clenching or grinding of the teeth and/or bracing or thrusting of the mandible.[9,10] Previous studies suggested that SB is highly prevalent in adults with OSA and that there might be a close association between respiratory events and masticatory muscle activity in adults with OSA, suggesting that SB might be secondary to OSA.[11,12] Thus, insight into this association is important from an assessment and management point of view. However, the association between OSA and SB as well as the underlying mechanism for their possible association are inconclusive yet. Therefore, this thesis aims to investigate the associations between both conditions in adults

with OSA from four perspectives: (1) the accuracy of the scoring of SB; (2) the prevalence and risk factors of SB; (3) the associations between OSA and SB events; (4) and the effects of OSA therapies on SB. Both conditions, including their prevalence, risk factors, consequences, etiology, assessment, and therapy modalities, as well as the current knowledge on their associations will be described below. This chapter ends with the general aims of this thesis, followed by an overview of each chapter.

Obstructive Sleep Apnea

Prevalence, risk factors, and consequences of OSA

Individuals with OSA often complain of tiredness, fatigue, excessive daytime sleepiness, morning headache, and memory or concentration problems.[7,13,14] Their bedpartners commonly report habitual snoring sounds, breathing interruption, or both during the patient's sleep.[7] OSA has been proven to be an independent risk factor for cardiovascular diseases (e.g., hypertension, myocardial infarction, and stroke), neurological diseases (e.g., neurodegeneration, brain damage), metabolism diseases (e.g., diabetes), and sleep-related movement disorders (e.g., periodic leg movement in sleep and SB).[14–23]

The overall prevalence of OSA in adults ranges from 9% to 38%.[24] It is higher in males and in obese individuals, and increases with age.[25] Further, OSA prevalence varies among different ethnic groups.[14,26] Studies showed that Chinese and Hispanics have higher odds of OSA than African Americans and Caucasians.[14,27] Other OSA risk factors include, amongst others, smoking, alcohol consumption, nasal congestion, and menopause.[28]

Etiology of OSA

Current evidence indicates that there are at least four key endotypic traits that contribute to OSA pathophysiology, including anatomical factors, impaired pharyngeal dilator muscle function, waking up too easily to restore upper airway patency (low respiratory arousal threshold), and unstable breathing control (high loop gain).[7,13,29] OSA is largely due to anatomical factors that promote upper airway collapses, such as a narrow pharyngeal airway and an increased upper airway length. In addition, approximately 70% of individuals with OSA have one or more non-anatomical traits that contribute to their OSA.[30,31] Although all

individuals with OSA are considered as having the same generic diagnosis, the role of the four key endotypic traits between individuals varies considerably, and patients commonly show different signs and symptoms as well.[30] For example, individuals with cardiovascular diseases have a high risk of OSA, but they may have no symptoms of OSA at the time of diagnosis. The wide clinical spectrum suggests there is a complex interaction between underlying mechanisms and clinical phenotypes.

Assessment of OSA

The diagnosis of OSA relies on the combination of symptoms, clinical signs, and objective assessment of obstructive respiratory events. Signs and symptoms of OSA include, amongst others, habitual snoring and breathing interruptions as witnessed by the bedpartner, family members, or the patient him/herself, excessive daytime sleepiness, and non-restorative sleep or fatigue.[7] The gold standard for assessing respiration during sleep is full-night polysomnography (PSG), which records brain activity (electroencephalogram, EEG), eye movement (electrooculogram, EOG), breathing airflow and pressure, respiratory effort, oxygen saturation, heart rate (electrocardiogram, ECG), sleep position, and muscle activities (electromyography, EMG, including (sub-)mentalis, bilateral masseter and/or temporalis, and anterior tibialis muscles).

One commonly used indicator of OSA severity is the number of respiratory events (apneas and/or hypopneas) per hour of sleep during PSG recording, viz., apnea-hypopnea index (AHI).[7] An adult showing an AHI of at least 5 events/hour is diagnosed with OSA.[7] Based on the AHI, OSA severity for adults is classified as mild ($5 \leq AHI < 15$ events/hour), moderate ($15 \leq AHI \leq 30$ events/hour), or severe (AHI > 30 events/hour).[32,33] It is important to note that there is now a broad agreement that this simple metric poorly reflects and predicts the symptoms and consequences of OSA as well as responses to OSA treatment.[30,34] Thus, alternative metrics of OSA severity are warranted.

Management of OSA

Considering that OSA is a heterogeneous condition from the perspectives of its diverse pathophysiology (endotypes) and various clinical manifestations (phenotypes), treatment options should also differ at the individual level.[34] Common non-surgical treatment options

for OSA include lifestyle interventions, such as weight loss; continuous Positive Airway Pressure (CPAP); Mandibular Advancement Appliance (MAA); and positional therapy in case of positional OSA. Surgical therapy includes upper airway surgery (e.g., various forms of palatal surgery, tongue base interventions, multilevel surgery, hypoglossal nerve stimulation, and maxillomandibular advancement).[33,35,36] In this thesis, we focused on CPAP and MAA in the treatment of OSA.

CPAP is considered the first-line treatment of choice for adults with moderate and severe OSA.[33] CPAP delivers continuous pressure to the airway during both inspiration and expiration, which prevents the upper airway from collapsing during sleep.[37] Although CPAP is a highly efficacious treatment, the effectiveness of CPAP is often limited by poor patient acceptance and tolerance.[38] Patients with CPAP often complain about nasal congestion, oral dryness, eye irritation, a sense of suffocation, and so on.[39–41] MAA is nowadays considered an effective alternative for patients who cannot accept CPAP.[40] The rationale behind the efficacy of MAAs is that the advancement of the mandible and tongue improves upper airway patency during sleep, thereby preventing collapse during sleep.[42] Individuals who sleep with MAA may experience side effects, in particular temporomandibular pain, hypersalivation or dry mouth, and permanent changes in dental occlusion.

Sleep Bruxism

Prevalence, risk factors and consequences of SB

The prevalence of SB in the general population, based on self-report, decreases with aging, from 14%-20% in children, to 12% in adults, and to 3% in the elderly.[43–45] Based on two systematic reviews, there is no significant difference in SB prevalence between adult males and females.[45,46] However, a recent large-scale survey reported a significant gender difference in the SB prevalence in the Dutch population, with females reporting SB more often than males.[47] In addition, another large-scale epidemiological study showed that SB is more prevalent in participants with normal weight (12%) than in overweight individuals (9%) and in obese individuals (2.4%).[48] SB prevalence increases in patients with certain sleep-related disorders, such as gastroesophageal reflux disease (73%), REM behavior disorder (25%), epilepsy (23%), nightmare (38%), and OSA (26% to 54%).[49]

SB is no longer regarded as a disorder that is a harmful dysfunction *per se* but is rather seen as a behavior that may be harmless or associated with some negative (as a risk factor) or positive (as a protective factor) health outcomes.[9] Being a risk factor, SB may increase the risk of tooth wear, tooth sensitivity, tooth, restoration, or dental implant fracture or failure, temporomandibular joint dysfunction, orofacial pain, and masticatory muscle hypertrophy.[50–54]. Regarded as a protective factor, SB may be able to reduce chemical tooth wear by promoting saliva secretion in patients with gastroesophageal reflux disease,[55] and prevent upper airway collapse and/or restore airway patency in individuals with OSA.[56,57]

Etiology of SB

The underlying mechanism of SB's occurrence is still unclear. Currently, the etiology of SB is considered multifactorial, including sleep arousal-, neurochemical-, psychosocial-, genetic-, and/or respiratory-related factors.[50,52,58–60] Further, SB could be classified as primary, i.e., without identifiable causes, or secondary to other conditions, such as insomnia, gastroesophageal disorders, periodic limb movement disorder, and OSA.[11,50,60–63] For example, some studies showed that the majority of SB events occur after respiratory events, suggesting that SB might be secondary to OSA.[11,12,64]

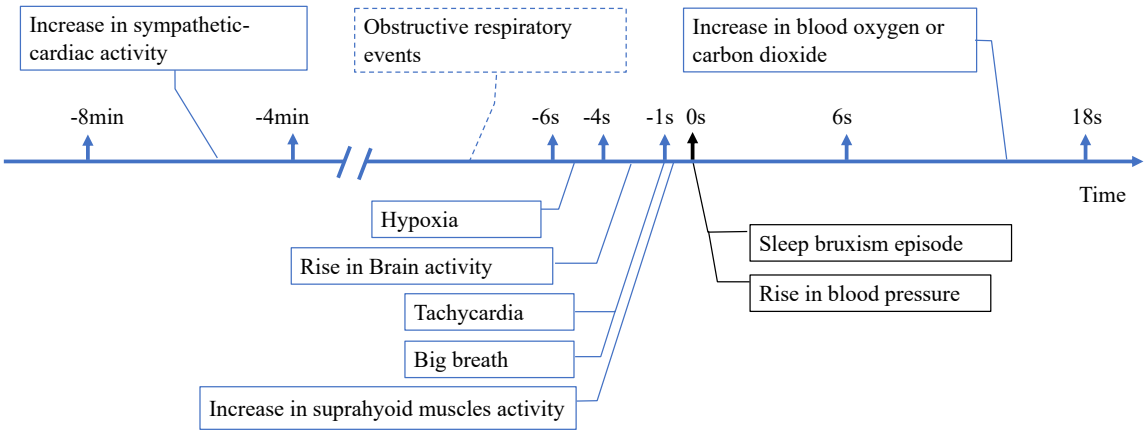

Figure 1 Sleep bruxism genesis sequence[65]

A recent study proposed an SB genesis sequence that is in relation to sleep arousal, including an increase in sympathetic-cardiac activity (-8 to -4 minutes), mild hypoxia (-6 to -4 seconds), rise in brain activity (sleep arousal, -4 seconds), tachycardia (-1 second), big breath (-1 second), elevation in muscle tone of opener suprahyoid muscles (-0.8 second), rise in blood pressure

(0 second), and possibly increase in blood oxygen or carbon dioxide (+6 to +18 seconds).[65] (Figure 1.1)

Assessment of SB

SB can be diagnosed by non-instrumental or instrumental methods.[9] Non-instrumental approaches include self-report of regular or frequent tooth grinding sounds (e.g., questionnaires, interviews), and clinical inspection of signs or symptoms of SB (such as tooth wear, jaw-muscle pain or fatigue, temporal headache, and jaw locking).[7,9] The gold standard for SB assessment is a full-night PSG with audio-video recordings. The characteristic EMG pattern of SB is rhythmic masticatory muscle activity (RMMA). According to the American Academy of Sleep Medicine (AASM) scoring manual,[66] bruxism may include jaw-muscle activities that are at least twice the amplitude of the background EMG, and a period of at least 3 seconds of stable background EMG must occur before a new episode of SB can be scored. Based on this, three phenotypes of SB/RMMA episodes are defined: phasic, tonic, and mixed. Phasic RMMA is at least three elevations of the chin or masseter EMG activity of 0.25–2 seconds in duration (defined as a phasic burst) in a sequence within a single episode. A tonic RMMA episode is an elevation of chin or masseter EMG activity of more than 2 seconds in duration (tonic RMMA burst). If both phasic and tonic RMMA bursts are present in a single episode, the episode is scored as a mixed RMMA episode. Audio and video recordings can assist PSG to distinguish RMMA from other jaw-closing muscle activities, such as other non-specific orofacial activity (e.g., swallowing, yawning, coughing, and sleep talking) and other oromotor activity that is part of the body movement (e.g., head or neck movement, and position changing during sleep). [50,67,68] RMMA can be observed both in individuals with SB as well as in more than 60% of healthy individuals.[69] The RMMA index or SB index obtained from EMG, defined as the number of RMMAs per hour of sleep, defines the severity of SB. When an RMMA index is at least 2 episodes per hour, the individual is regarded as having SB and when the RMMA index is at least four episodes per hour, the individual is considered as having severe SB.[7]

Although PSG yields objective information for SB assessment, some problems concerning the scoring criteria still need more attention. Based on the AASM manual for scoring sleep and associated events, bruxism can be scored on either the masseter EMG or chin EMG.[66]

However, so far, studies on the difference in the accuracy of RMMA scoring between masseter EMG and chin EMG are lacking. Moreover, previous studies suggest that SB is preferably scored based on a bilateral masseter and temporalis EMG, while many PSG or EMG devices are equipped with only one or two jaw-muscle EMG channels.[68,70–74] It is noteworthy that a recent in-hospital PSG study showed that the more EMG channels are employed for scoring SB, the fewer RMMA episodes are scored, suggesting that some RMMA episodes may only be visible on the masseter muscle EMG trace(s), but not on the temporalis muscle EMG traces and that some are only detectable on a unilateral EMG channel but not on bilateral EMG channels.[74] Thus, the differences in the SB scoring accuracy between jaw-muscles' EMGs and between unilateral or bilateral jaw-muscles' EMGs demand further studies. For this, a methodological study was performed in **Chapter 2** to determine the essential number and type of jaw muscles (e.g., masseter, temporalis, or submentalis) for valid SB scoring.

Management of SB

Evidence-based recommendations on the management of SB at the individual level are unavailable yet. The management of SB currently focuses on the treatment of the negative consequences of SB and follows a conservative "Multiple-P" approach, namely, pep talk (counseling strategies, including biofeedback and cognitive-behavioral approach), plates (oral appliance), physiotherapy, psychotherapy, and pills (medication, such as clonazepam).[75] It is noteworthy that when SB is comorbid with other diseases or disorders, the treatment procedure may vary depending on the associations between SB and the comorbid conditions.[49]

Associations between OSA and SB

Previous studies have reported that OSA is an independent risk factor for SB.[76,77] In adults with OSA, the prevalence of SB is much higher than that in the general population, supporting a possible association between the two conditions. However, as yet, studies on the association between SB and OSA are inconsistent.[12,78–80] Therefore, a systematic review in **Chapter 3** was performed which aimed: (1) to determine the prevalence of SB in adults with other sleep-related disorders, including OSA; (2) to determine the associations between SB

and other sleep-related disorders; and (3) to search for the possible underlying mechanisms of their associations.

Due to the limited sample sizes included and different diagnostic methods employed in previous studies, the occurrence rate of SB in adults with OSA varies widely among studies (from 26% to 100%).[19,77,81–84] Therefore, a large-scale PSG study in **Chapter 4** was performed to determine the prevalence and risk factors of SB in adults with OSA.

Previous studies suggested that the occurrence of SB in OSA might be related to respiratory events.[65,85] There are four possibilities concerning the temporal relationship between RMMA and respiratory events:[12] (1) RMMA precedes respiratory events with SB having an OSA-inducing role; (2) respiratory events precede RMMA with SB having an OSA-protective role; (3) the two events occur at the same time with SB and OSA share an unknown mechanism; (4) and RMMA is time-unrelated to respiratory events indicating that SB and OSA are two sleep conditions with different mechanisms. Several studies investigated the temporal relationship between respiratory events and RMMA.[11,83,86] One study reported that most RMMA occurred after respiratory events,[11] while some other studies showed that the majority of RMMA were time-unrelated to respiratory events.[83,86] Since these studies enrolled limited samples and came to contrary findings, the temporal relationship between respiratory events and RMMA still needed further studies. Therefore, a pilot study in **Chapter 5** was conducted to investigate the sequences of respiratory events and masticatory muscle activities in adults with OSA.

In addition to the unclear relationship between RMMA and respiratory events, a growing number of studies suggest that SB is secondary to sleep arousals.[81,83,86–92] However, another study reported that there was only a weak association between arousal and RMMA in participants with OSA.[93] Besides, some studies stated that arousals only create a permissive window for SB occurrence, but do not function as a trigger.[89,94] Altogether, the role of respiratory events and arousals in the association between SB and OSA demanded further studies to confirm. Therefore, based on the large sample, the study in **Chapter 4** also investigated the relationships between RMMAs, arousals, and respiratory events in adults with OSA.

Evidence showed that treatment for OSA may also relieve concomitant SB in some cases.[95,96] However, so far, clinical studies on the effect of OSA therapies on SB are still limited. Two case reports showed that RMMA episodes disappeared during CPAP treatment, while after removing CPAP, RMMA recurred.[95,96] However, another case report presented that a patient with OSA complained about orofacial pain and sleep-related clenching during nasal CPAP treatment.[97] Also, several studies reported that MAA could significantly reduce the RMMA index in participants with SB.[98–100] In short, although some evidence showed that OSA therapies may be beneficial for SB as well, no study has been performed in adults with OSA to confirm these effects. Such a study would not only contribute to the insight into the association between SB and OSA, but also yield useful information for clinicians when treating OSA individuals with comorbid SB. Therefore, the study in **Chapter 6** of this thesis aimed to determine and compare the effects of CPAP and MAA on SB in adults with OSA.

Overview of chapters

The general aim of this thesis was to gain insight into the associations between OSA and SB from an assessment and management point of view. A short description per chapter is provided below:

Chapter 1 is a general introduction to this thesis.

Chapter 2 presents a study about the SB scoring accuracy based on EMG activity of different jaw muscles in individuals with OSA.

Chapter 3 presents a systematic review on the prevalence of SB in patients with other sleep-related disorders (including OSA), as well as on the associations and possible explanations for the association between SB and other sleep-related disorders.

Chapter 4 presents a polysomnographic study on the prevalence and risk factors of SB in a large sample of adults with OSA. In addition, the associations between RMMA, sleep arousals, and respiratory events were also determined in this chapter.

Chapter 5 presents a pilot study on the time relationship between masticatory muscle activity and respiratory events in adults with OSA.

Chapter 6 presents a cohort study on the effects of CPAP and MAA on SB.

Chapter 7 provides a general discussion and describes the clinical implications of the main findings of this thesis, as well as recommendations for future research.

Chapter 8 presents the summary of this thesis.

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Chapter 2

Accuracy of sleep bruxism scoring based on electromyography traces of different jaw muscles in individuals with obstructive sleep apnea

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Abstract

Study objectives: Sleep bruxism is characterized by rhythmic masticatory muscle activity (RMMA). This study aimed to determine the number and type of jaw muscles needed for a valid RMMA scoring in individuals with obstructive sleep apnea (OSA).

Methods: 10 individuals with OSA (4 males; age = 50.1 ± 8.1 years) were included in this study. RMMA was scored using one or more of the following jaw muscles' electromyography (EMG) traces of polysomnography recordings: bilateral masseter and temporalis (4MT; the reference standard), unilateral masseter (1M), bilateral masseter (2M), unilateral temporalis (1T), bilateral temporalis (2T), unilateral chin EMG (1C), and bilateral chin EMG (2C).

Results: 1M, 2M, 1T, and 2T showed excellent agreement with 4MT (intraclass correlation coefficient [ICC] = 0.751, 0.976, 0.815, and 0.950, respectively), while 1C and 2C presented fair agreement (ICC= 0.662 and 0.657). Besides, 2M and 2T displayed good sensitivity (87.8% and 72.0%) and positive predictive value (PPV; 83.1% and 76.0%). In contrast, 1M and 1T had good sensitivity (88.4% and 87.8%) but fair PPV (60.1% and 53.2%). 1C and 2C showed poor sensitivity (41.1% and 40.3%) and fair PPV (62.9% and 60.6%).

Conclusions: Polysomnography with bilateral masseter or temporalis muscle EMG traces is regarded valid in RMMA scoring in individuals with OSA. In contrast, unilateral masseter or temporalis muscle EMG showed only fair accuracy, and chin EMG had poor accuracy. Consequently, these montages cannot be recommended for RMMA scoring in the presence of OSA.

Keywords: polysomnography; electromyography; masseter; temporalis; chin; sleep bruxism; obstructive sleep apnea; scoring accuracy

Introduction

Sleep bruxism (SB) is a masticatory muscle activity during sleep, including teeth grinding and clenching.[1] Individuals with SB may experience conditions like severe tooth wear, orofacial pain, temporomandibular disorders, and/or fractures or failures of dental restorations or implants, while their bed partners may be disturbed by the teeth grinding sounds during the night.[2–5] Interestingly, recent studies suggested that SB may also play a positive, protective role in individuals with certain medical conditions,[1] e.g., obstructive sleep apnea (OSA, by preventing the collapse or restoring the patency of the upper airway)[6–8] and gastroesophageal disorder (by increasing saliva secretion to reduce chemical tooth wear).[9] A systematic review on the epidemiology of SB showed that the prevalence of frequent SB in the general population is close to 13%.[10] However, in the OSA population, the SB prevalence rises to around 50%,[11–13] suggesting that SB is a common comorbidity of OSA that needs the clinician's full attention, although the exact nature of the association between SB and OSA is still inconclusive.[6,11,14,15] In addition, recent studies reported that OSA therapies, such as continuous positive airway pressure and mandibular advancement appliance, can reduce the frequency of SB, while in some cases, they could induce or aggravate SB.[16–19] This suggests demand for routine screening and monitoring of SB in individuals with OSA.

Currently, the gold standard of SB diagnosis is full-night polysomnography (PSG) with audio-video recordings (type I PSG) that allows the scoring of sleep, respiration, and muscle activity. SB is characterized by rhythmic masticatory muscle activity (RMMA).[20] It is noteworthy that RMMA is also commonly observed in normal subjects and in individuals with OSA.[11,21] According to previously published scoring criteria, RMMA is scored on the bilateral masseter and temporalis electromyography (EMG) traces when at least three out of these four channels show positive EMG patterns.[20,22,23] However, Type I PSG is expensive and time-consuming. Given this, portable devices, such as Type II PSG, type III polygraphy or type IV EMG, have been introduced into research and for clinical application for the detection of SB.[24,25] It is noteworthy that these portable devices, which are equipped with a limited number of electrodes or a single channel (e.g., Type IV), do not usually allow the recording of both the bilateral masseter and temporalis muscles. A recent in-hospital type I PSG study[23] reported that the RMMA index (events/hour) scored on bilateral masseter muscle EMG traces was

higher than that scored on four EMG traces (i.e., bilateral masseter and temporalis muscle), suggesting that some RMMA episodes may only be visible on the masseter muscle EMG traces, but not on the temporalis muscle EMG traces. To some extent, this discrepancy is supported by several other EMG studies that demonstrated that during different oral tasks, the masseter and temporalis muscles presented EMG heterogeneity, including the signal's frequency and peak amplitudes.[26–31] In addition, chin EMG is routinely collected in sleep studies to reflect motor activity and muscle tone, supplying useful information in sleep staging (i.e., the identification of REM sleep), arousal scoring, and detecting some sleep-related movement disorders, e.g., REM behavior disorders.[32,33] According to the American Academy of Sleep Medicine (AASM) scoring manual, the characteristic changes in the masseter muscle EMG are often more prominent than changes in the chin EMG.[33] All this evidence suggests that the number and type of jaw muscles used for RMMA scoring may significantly impact upon the diagnosis of SB.

No specific and systematic study has reported the possible discrepancy in RMMA scoring accuracy between different jaw muscle EMG traces (masseter, temporalis, and chin) with otherwise identical PSG montages. Also, the difference in the accuracy between unilateral and bilateral jaw muscle EMG is unclear yet. Therefore, this study aimed to determine the number and type of jaw muscles needed for valid RMMA scoring by investigating the accuracy of different scoring montages in individuals with OSA. We hypothesized that PSG with bilateral masseter or bilateral temporalis muscle EMG traces will show good accuracy in RMMA scoring in individuals with OSA. In contrast, chin EMG, the unilateral masseter muscle EMG, or the unilateral temporalis muscle EMG will show a low accuracy in RMMA scoring in individuals with OSA.

Materials and Methods

Participants

This is a secondary analysis of a randomized clinical trial that investigated the effects of a mandibular advancement appliance on sleep-related jaw muscle activity in participants with OSA (registered at www.clinicaltrials.gov; NCT02011425).[34] The participants' recruitment criteria have been reported in detail by Aarab et al.[34] Participants aged between 35 and 65

years with moderate to severe OSA without other comorbid respiratory or sleep disorders (except SB), severe orofacial pain, severe temporomandibular disorders, untreated periodontal problems, and medication usage that could influence the respiration or sleep were included in this study.[34] The PSG recordings of this study were collected at the Faculté de Médicine Dentaire, Université de Montréal, Montréal, Québec, Canada. The scientific and ethical aspects were approved by the Medical Ethics Committee of the Université de Montréal (13-105-CERES-D).

Polysomnography

PSG recordings were obtained using type II Embla Titanium hardware and analyzed by RemLogic software (Embla, Ontario, Canada). The application of PSG electrodes was performed by a trained sleep technician following the AASM scoring manual[35]. The following channels were recorded: electroencephalogram (F3M2, F4M1, C3M2, C4M1, O1M2, O2M1), electrooculogram (right and left), electrocardiogram, EMG (bilateral chin, masseter, temporalis, and anterior tibialis muscles), airflow, abdominal and thoracic respiratory effort, oxygen saturation, and body position.

In order to avoid the possible influence of mandibular advancement appliance on muscle activity, only the baseline PSG recordings without mandibular advancement appliance in situ were used in the present study. Moreover, PSG recordings with missing data on any of the masseter, temporalis, or chin EMG traces were excluded.

Scoring criteria

Standard sleep stages (N1, N2, N3, REM, and wake) were scored manually by a single experienced and registered polysomnographic technologist from an independent company (Sleep Strategies, Ottawa, Canada), following the criteria of the AASM.[35]

In this study, RMMA was scored manually by the first authors (D.L.) according to previously published criteria.[20] The intra-rater agreement was excellent (0.925) for RMMA scoring. Each EMG burst had a mean amplitude at least two times higher than the baseline EMG amplitude. A period of at least 3s of baseline EMG activity must occur between different RMMA episodes. RMMA episodes were classified as phasic (three or more phasic EMG bursts lasting 0.25–2 s),

tonic (one or more tonic EMG bursts ≥ 2 s), and mixed (at least one phasic and one tonic bursts present within a single episode). Only RMMA episodes that occurred during sleep were scored in this study.

RMMA episodes were scored in seven rounds, using PSG scoring montages with different jaw muscle EMG trace(s): 1) unilateral masseter muscle EMG (1M); 2) bilateral masseter muscle EMG (2M); 3) unilateral temporalis muscle EMG (1T); 4) bilateral temporalis muscle EMG (2T); 5) unilateral chin EMG (1C); 6) bilateral chin EMG (2C); and 7) bilateral masseter and temporalis muscle EMG (4MT). For scoring montages with a unilateral muscle EMG trace (i.e., 1M, 1T, and 1C), the left or right-side EMG trace was selected randomly for each patient. If an RMMA pattern was present on the selected side of the EMG trace, it would be scored as a positive episode. For scoring based on bilateral muscle EMG traces (i.e., 2M, 2T, and 2C), the RMMA pattern should be simultaneously and consistently visible on both muscle EMG traces. For scoring based on bilateral masseter and temporalis muscle EMG traces (i.e., 4MT), the RMMA pattern should appear on at least three of the four EMG traces.[20] During each scoring round, only the essential EMG trace(s) was (were) visible. The electroencephalogram, electrooculogram, electrocardiogram, and body position traces were always visible during RMMA scoring.

Statistical analysis

The number of RMMA episodes was transformed into indices, defined as the number of RMMA episodes per hour of sleep. Individuals with RMMA index ≥ 2 episodes/hour were diagnosed with SB. 4MT was regarded as the reference standard to analyze the accuracy of the tested scoring montages, i.e., 1M, 2M, 1T, 2T, 1C, and 2C.

The discrepancy in RMMA scoring between scoring montages was evaluated by comparing the RMMA indices obtained from different scoring montages. The normality of the RMMA index was tested by the Shapiro-Wilks test. The differences in the RMMA indices between scoring montages were analyzed by the Friedman test. Post-hoc pairwise comparisons were analyzed by the Dunn test, and the significance values were adjusted for multiple comparisons by the Bonferroni correction.

The accuracy of the tested scoring montages includes their agreement on the RMMA index with the reference standard and their validity in RMMA scoring. Bland-Altman plots and intraclass correlation coefficient (ICC) were applied to evaluate the agreement on the RMMA index between the tested scoring montages and 4MT. ICC analysis was performed using a single measurement, two-way random, and absolute agreement model. ICC values larger than 0.75 indicate excellent agreement; values below 0.40 imply poor agreement; ICC values between 0.40 and 0.75 suggest fair to good agreement.[36] The validity was assessed using sensitivity and positive predictive value (PPV). Since there was no true negative RMMA episode, the specificity and negative predictive value are not applicable in this study. RMMA episodes scored on the tested scoring montages were regarded as true positive RMMA episodes if they were consistent with those scored on 4MT. Sensitivity was defined as the percentage of true positive RMMA episodes on the tested scoring montage out of the total RMMA episodes scored on 4MT. PPV was defined as the percentage of true positive RMMA episodes scored on the tested scoring montage out of the total RMMA episodes scored on the tested scoring montage.

The level for statistical significance was set at 0.05. Data analysis was performed using SPSS (IBM SPSS Statistics, version 26, Chicago, IL, USA).

Results

Participants

Eighteen individuals with OSA were included in the original study.[34] After removing PSG recordings with missing data (possibly due to loose electrodes) on any one of the masseter, temporalis, or chin EMG traces, 10 PSG recordings were eligible for this secondary analysis study. Thus, 10 participants (50.1 ± 8.1 years old), including 4 males and 6 females, were included. Their median RMMA index was 2.8 episodes/hour (interquartile = 1.7). Among the 10 participants, 7 were diagnosed with SB (RMMA ≥ 2 episodes/hour); the other three cases did show RMMA episodes but did not meet the criteria for SB diagnosis.

RMMA scoring discrepancy between scoring montages

RMMA indices obtained from all tested scoring montages (viz., 1M, 2M, 1T, 2T, 1C, and 2C) were similar to that from 4MT (all $P > 0.05$). Also, there was no significant difference in the RMMA index between 2M and 2T ($P > 0.05$), as well as between 1M and 1T ($P > 0.05$). However, 1C showed a significantly lower RMMA index than 1M ($P = 0.023$) and 1T ($P = 0.009$). In addition, the RMMA index scored on unilateral jaw muscle EMG trace did not show a significant difference with that scored on bilateral jaw muscle EMG traces (1M vs 2M, 1T vs 2T, and 1C vs 2C; all $P > 0.05$). Detailed results of the pairwise comparisons are shown in Table 2.1.

Table 2.1 Pairwise comparisons of rhythmic masticatory muscle activity (RMMA) indices [a]

Scoring montages	RMMA index[b]	*P* values						
		4MT	1M	2M	1T	2T	1C	2C
4MT	1.6|2.8|3.3							
1M	1.6|3.9|5.8	0.363						
2M	1.8|3.2|3.6	1.000	1.000					
1T	1.9|3.2|4.9	0.174	1.000	0.624				
2T	1.5|2.5|3.9	1.000	1.000	1.000	0.711			
1C	0.6|1.3|2.9	1.000	0.023	1.000	0.009	1.000		
2C	0.5|1.3|2.8	1.000	0.009	1.000	0.003	1.000	1.000	

[a] Friedman test and Dunn test; P values have been adjusted for multiple comparisons by the Bonferroni correction; significant differences (P <0.05) are underlined; [b] Non-normally distributed data are shown in quartiles (25%|median|75%); 4MT: reference standard, polysomnography (PSG) with bilateral masseter and temporalis muscle electromyography (EMG) traces; 1M: PSG with unilateral masseter muscle EMG trace; 2M: PSG with bilateral masseter muscle EMG traces; 1T: PSG with unilateral temporalis muscle EMG trace; 2T: PSG with bilateral temporalis muscle EMG traces; 1C: PSG with unilateral chin EMG trace; 2C: PSG with bilateral chin EMG traces.

RMMA scoring accuracy

The Bland-Altman plots of the RMMA index for each scoring montage are shown in Figure 2.1. The bilateral masseter or temporalis muscle EMG showed better agreement with 4MT than the unilateral masseter or temporalis muscle EMG (2M vs 1M, 2T vs 1T). Besides, 2M showed a slightly better agreement with 4MT (the limits of agreement were narrower) than 2T in the RMMA index. On the other hand, the chin EMG showed a substantial disagreement with 4MT in the RMMA index, regardless of whether the scoring was based on 1C or 2C.

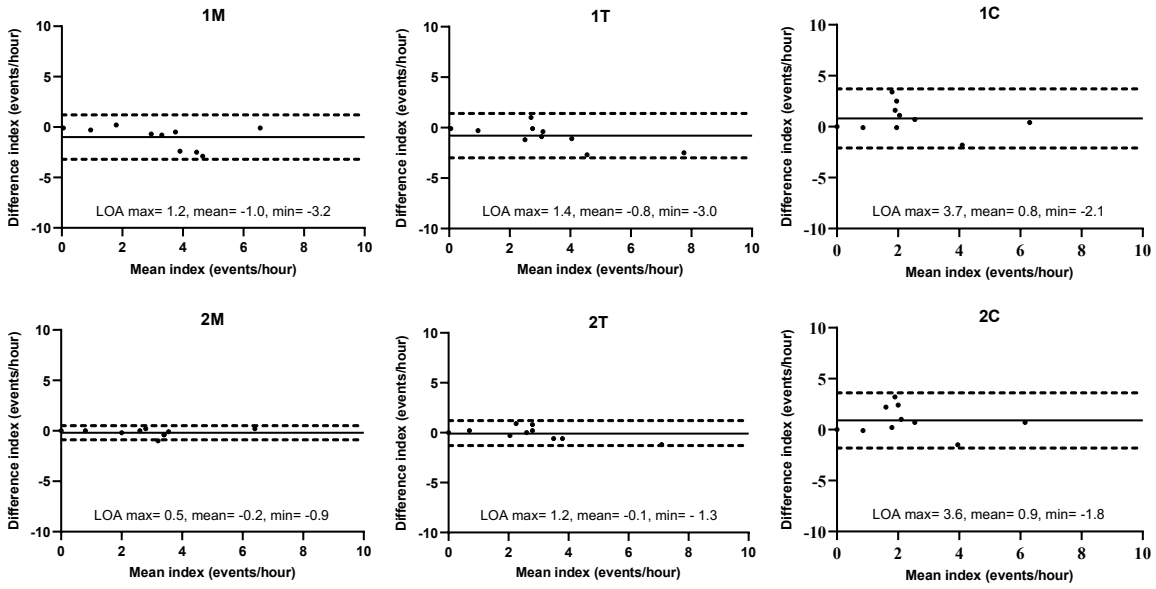

Figure 2.1 Bland-Altman plots of rhythmic masticatory muscle activity (RMMA) indices for tested scoring montages. Note: Comparisons of tested scoring montages were made against polysomnography (PSG) with bilateral masseter and temporalis muscle electromyography (EMG) traces. LOA: limits of agreement; solid line: the mean difference; dashed line: 95% LOA (max: the upper 95% LOA; min: the lower 95% LOA); 1M: PSG with unilateral masseter muscle EMG trace; 2M: PSG with bilateral masseter muscle EMG traces; 1T: PSG with unilateral temporalis muscle EMG trace; 2T: PSG with bilateral temporalis muscle EMG traces; 1C: PSG with unilateral chin EMG trace; 2C: PSG with bilateral chin EMG traces.

The ICCs in the RMMA index for 1M, 2M, 1T, and 2T were 0.751, 0.976, 0.815, and 0.950, respectively (all $P < 0.01$), indicating excellent agreement with 4MT. In contrast, 1C and 2C showed only fair to good agreement with 4MT, with ICC of 0.662 and 0.657, respectively (both $P < 0.01$).

Figure 2.2 shows the sensitivity and PPV of each scoring montage in identifying RMMA. The masseter muscle EMG (1M and 2M) showed the best sensitivity in identifying RMMA (88.4% and 87.8%, respectively). The temporalis muscle EMG (1T and 2T) showed lower sensitivity values (73.9% and 72.0%), while the chin EMG (1C and 2C) showed the poorest sensitivity (41.1% and 40.3%). On the premise of the same muscle, unilateral jaw muscle EMG and bilateral jaw muscle EMG displayed similar sensitivity in identifying RMMA. In addition, 2M

showed the best PPV in identifying RMMA (83.1%), followed by 2T (76.0%), while 1M, 1T, 1C, and 2C displayed only fair PPV (60.1%, 53.2%, 62.9%, and 60.6%, respectively).

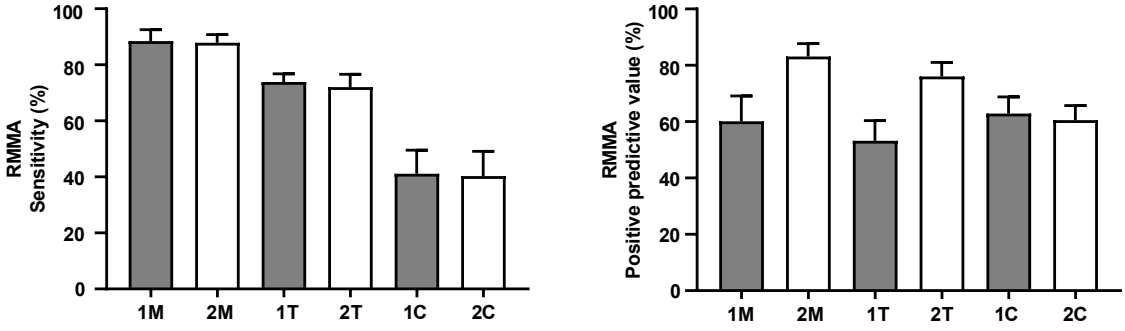

Figure 2.2 Sensitivity and positive predictive values of different polysomnographic scoring montages. Note: The reference standard for calculating sensitivity and positive predictive value of tested scoring montages was polysomnography (PSG) with bilateral masseter and temporalis muscle electromyography (EMG) traces. RMMA: rhythmic masticatory muscle activity; 1M: polysomnography (PSG) with unilateral masseter muscle electromyography (EMG) trace; 2M: PSG with bilateral masseter muscle EMG traces; 1T: PSG with unilateral temporalis muscle EMG trace; 2T: PSG with bilateral temporalis muscle EMG traces; 1C: PSG with unilateral chin EMG trace; 2C: PSG with bilateral chin EMG traces.

Discussion

This study found that RMMA scoring based on either bilateral masseter or temporalis muscle EMG traces is valid and comparable with the reference standard of PSG with bilateral masseter and temporalis muscle EMG traces in individuals with OSA. However, the unilateral masseter or temporalis muscle EMG, in addition to unilateral or bilateral chin EMG used in RMMA scoring, showed only poor to fair accuracy.

Accuracy of different jaw muscle EMG

Both the masseter muscles and the temporalis muscles are masticatory muscles, and as reported by a previous study, they are equally activated in the majority of oral tasks.[26] This is supported by our results that both the masseter and temporalis muscle EMG showed excellent agreement on the RMMA index with the reference standard, and that no significant

difference in the RMMA index was found between the unilateral (or bilateral) masseter and temporalis muscle EMG in participants with OSA (Table 2.1).

However, the masseter muscle EMG showed higher sensitivity and PPV in RMMA scoring than the temporalis muscle EMG when comparing scoring montages with the same number of EMG trace(s) (Figure 2.2), suggesting that the former has better accuracy than the latter in individuals with OSA. These discrepancies indicate that the masseter and temporalis muscle(s) sometimes showed different EMG patterns in our OSA cohort. This is in line with another study, which reported that RMMA scoring based on the bilateral masseter muscles showed more RMMA episodes than that based on both the bilateral masseter and the bilateral temporalis muscles.[23]

The discrepant EMG patterns between the masseter and temporalis muscles can be explained by a heterogeneous activation theory.[26–31] Anatomically, the masseter is a quadrilateral muscle with superficial and deep portions, while the temporalis muscle is a fan-shaped muscle with different fibers in different directions. The regional differences in fiber direction are the premise for various oral tasks.[29] Conversely, the masseter and temporalis muscles are activated heterogeneously during different jaw movements.[26–31,37] Specifically, the masseter muscle is more active than the temporalis muscle during tasks like mouth opening or closing excursions, and keeping the jaw protruded or laterotruded, while the temporalis is more active during tasks like jaw retrusion.[26,30,38] As a result, the heterogeneous activation of the masseter and temporalis muscles may cause discrepancies in the amplitude as well as in the time domain (e.g., start time, end time, and duration) of EMG bursts between jaw muscles. Consequently, according to the predetermined RMMA scoring criteria, the RMMA episodes scored on the masseter muscle EMG trace(s) may not be consistent with those scored on the temporalis muscle EMG trace(s), and vice versa.

As the chin EMG does not record a masticatory muscle, we hypothesized that chin EMG has poor accuracy in scoring RMMA in individuals with OSA. Based on our results, we accepted this hypothesis. As shown in Table 2.1, 1C showed a significantly lower RMMA index than 1M (P = 0.023) as well as 1T (P = 0.009), which suggests that scoring based on only chin EMG trace(s) may yield missing an SB diagnosis in individuals with OSA. Furthermore, chin EMG (both 1C and 2C) showed poor sensitivity (around 40%) and fair PPV (around 60%), suggesting

that chin EMG has poor ability to identify true positive RMMA episodes, and that most RMMA episodes scored on chin EMG trace(s) are actually false positive ones.

The poor accuracy of chin EMG in RMMA scoring in participants with OSA can be supported by another EMG study by Farella et al.,[26] in which it was found that during teeth clenching, jaw elevators (i.e., the masseter and temporalis muscles) showed very high activity, while the suprahyoid muscles recorded by the chin EMG showed only moderate activity.[26] In contrast, the suprahyoid muscles were more active than the jaw elevators during other orofacial activities (e.g., deep breathing, reading aloud, yawning, coughing, and drinking), indicating that they are mainly responsible for other mandibular movements.[26] Taking all this evidence into consideration, chin EMG seems invalid for RMMA scoring; therefore, it is not recommended to be used as the EMG source for RMMA scoring in individuals with OSA.[33]

Unilateral versus bilateral jaw muscle EMG

As mentioned above, chin EMG was regarded as having poor accuracy in RMMA scoring. Therefore, we omitted chin EMG from the comparison of RMMA scoring accuracy between unilateral and bilateral jaw muscle EMG. The present study found that bilateral masseter or temporalis muscle EMG (i.e., 2M and 2T) displayed good sensitivity and PPV in RMMA scoring. In contrast, unilateral jaw muscle EMG (i.e., 1M and 1T) displayed good sensitivity but only fair PPV (60% and 53%), indicating that around half of the RMMA episodes scored on unilateral jaw muscle EMG trace were false positive. Based on this, 2M and 2T are considered as having good accuracies in RMMA scoring, while 1M and 1T only have fair accuracy. Consequently, RMMA scoring based on unilateral EMG trace could potentially overestimate the RMMA index. To some extent, this agrees with another study in which it was reported that, based on only EMG, the fewer EMG channels were applied in the scoring, the more RMMA episodes were scored.[23]

The discrepancies in the accuracy between scoring montages with unilateral and bilateral muscle EMG traces suggest that RMMA episodes were present occasionally only on unilateral jaw muscle EMG trace instead of on bilateral jaw muscle EMG traces. This might be attributed mainly to the unbalanced EMG activity of the jaw muscles between two sides during jaw movement,[39,40] resulting in only one side surpassing the predetermined amplitude threshold

of an EMG burst (two times higher than the baseline EMG amplitude). In addition, facial asymmetry (e.g., in individuals with one habitual chewing side) may also contribute to the bilateral discrepancy in RMMA scoring.[41–43]

Limitations

First of all, this study was conducted in a small sample of participants. Therefore, we did not perform an analysis for RMMA subtypes (i.e., phasic, tonic and mixed). As RMMA subtypes (i.e., phasic, tonic, and mixed) could be regarded as different jaw movements, as demonstrated by their different scoring rules, the scoring accuracy of RMMA subtypes based on different jaw-muscle EMG traces could be different. It is worth future studies to investigate the scoring accuracy of RMMA subtypes based on different jaw muscles. Despite this, the sample had a fair number of RMMA episodes to be analyzed, which ensures the reliability of our results. Besides, it is of importance to note that this study was performed in individuals with OSA. Although, as far as we know, no study points out any differences in the EMG pattern of SB between individuals with OSA and those without OSA, the generalization of our results to the general population needs caution. It is therefore recommended to perform similar studies to determine the accuracy of SB scoring based on different jaw muscles in individuals with SB and in the general population. Secondly, we did not collect any information of participants' maxillofacial morphology. Several studies[44,45] reported that individuals with different maxillofacial morphology (e.g., mandibular prognathism versus retrognathism, high- versus low-angle vertical facial morphology) present significant differences in the masticatory muscle function and activity. The accuracy of SB/RMMA scoring may be further improved in future studies by taking this important factor into consideration. Thirdly, the absence of audio and video represents a critical shortcoming of this study. As reported by Carra et al.[20], the absence of audio-video may lead to an overestimation of the RMMA index. However, as we mentioned before, both Carra et al.[20] and Miettinen et al.[23] concluded that PSG systems without audio-video recordings still displayed relatively good accuracy in RMMA scoring, supporting their use for both research and clinical purposes.

Conclusions

Within the limitations of this study, we concluded that polysomnography with bilateral masseter or temporalis electromyography traces yields good accuracy, and can thus be regarded as valid in the scoring of sleep bruxism in individuals with obstructive sleep apnea. In contrast, analysis using unilateral masseter or temporalis muscle electromyography results in only fair accuracy, and chin electromyography even yields poor accuracy. Consequently, these montages cannot be recommended for sleep bruxism scoring in the presence of obstructive sleep apnea.

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Chapter 3

Associations between sleep bruxism and other sleep-related disorders in adults: a systematic review

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Abstract

Study objectives: Systematic reviews on sleep bruxism (SB) as a comorbid condition of other sleep-related disorders are lacking. Such reviews would contribute to the insight of sleep clinicians into the occurrence of SB in patients with other sleep-related disorders, and into the underlying mechanisms of such comorbid associations. This systematic review aimed: 1. to determine the prevalence of SB in adults with other sleep-related disorders; and 2. to determine the associations between SB and other sleep-related disorders, and to explain the underlying mechanisms of these associations.

Methods: A systematic search on SB and sleep-related disorders was performed in PubMed, Embase, Cochrane Library, and Web of Science to identify eligible studies published until May 15, 2020. Quality assessment was performed using the Risk of Bias Assessment tool for Non-randomized Studies.

Results: Of the 1539 unique retrieved studies, 37 articles were included in this systematic review. The prevalence of SB in adult patients with obstructive sleep apnea, restless leg syndrome, periodic limb movement during sleep, sleep-related gastroesophageal reflux disease, REM behavior disorder (RBD), and sleep-related epilepsy was higher than that in the general population. The specific mechanisms behind these positive associations could not be identified.

Conclusions: SB is more prevalent in patients with the previously mentioned disorders than in the general population. Sleep arousal may be a common factor with which all the identified disorders are associated, except RBD and Parkinson's disease. The associations between SB and these identified sleep-related disorders call for more SB screening in patients with the abovementioned sleep-related disorders.

Keywords: sleep bruxism; sleep disorders; prevalence; mechanism; sleep arousal; systematic review

Introduction

Sleep bruxism (SB) is a repetitive jaw-muscle activity characterized by clenching or grinding of the teeth and/or by bracing or thrusting of the mandible [1]. The criteria for the assessment of definite SB are so far based on polysomnographic (PSG) recordings, which allow the identification of rhythmic masticatory muscle activity (RMMA) on electromyographic (EMG) traces [1,2]. Based on a systematic review on the epidemiology of SB, the prevalence of self-reported SB in adults is 12.8±3.1% [3].

The etiology of SB is multifactorial [4,5], including biological factors, psychosocial factors, and lifestyle factors. According to observations among family members [6] and gene analysis studies [7,8], the occurrence of SB may partially be explained by both environmental and genetic factors [9,10]. Moreover, an imbalance in centrally acting neurotransmitters (e.g., dopamine, serotonin) may play a role in the genesis of RMMA and SB [11,12]. Many psychosocial factors, such as anxiety, depression, stress, and maladaptive coping strategies, have been suggested to increase risk for SB [13,14]. Lifestyle factors like smoking, alcohol and caffeine intake have also been suggested to increase the risk of SB [15,16].

The potential negative consequences of SB described in literature are, amongst others, headache upon awakening, temporomandibular pain complaints [17,18], severe mechanical tooth wear, and tooth/dental *restoration*/implant fractures/failures [19,20]. Interestingly, nowadays, also some positive consequences of SB are suggested, for example, the condition having a protective role in maintaining airway patency in patients with obstructive sleep apnea (OSA) [21,22], promoting saliva secretion by mechanical salivary (parotid) gland stimulation for esophageal acid clearance [23,24], and even preventing cognitive decline when aging [25]. Although SB management should be based on the negative clinical consequence of SB [26], evidence-based recommendations at the individual level are not available at this moment [27]. So, it is still recommended that SB management is provided with caution within the framework of a conservative “multiple-P” approach (i.e., pep talk (counseling), plates (occlusal appliances), physiotherapy, psychotherapy, and pills (pharmacotherapy)) [26].

The genesis of most RMMA episodes seems to be preceded by a cascade of events in relation to sleep arousals, such as an increase in the autonomic sympathetic-cardiac activity, in the

frequency of electroencephalographic (EEG) activity, in heart rate, in EMG activity of jaw-opening muscles, in breathing amplitude, and in blood pressure [28,29]. Several studies [28,30–32] further suggested that sleep arousals could be regarded as a permissive window for the initiation of RMMA episodes. The occurrence of arousals may therefore explain the correlations found in previous studies between SB and other sleep-related disorders that are associated with arousals (e.g., OSA, periodic limb movements during sleep (PLMS), and epilepsy) [33–37]. However, systematic reviews on SB as a comorbid condition of other sleep-related disorders are lacking so far. Such reviews would contribute to the insight of sleep clinicians into the occurrence of SB in patients suffering from other sleep-related disorders, as well as into the underlying mechanisms of such comorbid associations. Therefore, the aims of this systematic review were: 1. to determine the prevalence of SB in adult patients with other sleep-related disorders; and 2. to determine the associations between SB and other sleep-related disorders, and to explain the underlying mechanisms of these associations. This systematic review will finalize with recommendations for sleep clinicians on how to proceed with the further prevention, assessment, and management of the possible negative consequences of SB as a comorbid condition in their patients with sleep disorders.

Materials and Methods

The entire review process was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement [38]. This systematic review is registered at PROSPERO (registration number: CRD42020186555).

Search strategy

To identify relevant publications, systematic searches were conducted in the bibliographic databases PubMed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com), Cochrane Library (https://www.cochranelibrary.com/advanced-search), and Web of Science (https://www.webofknowledge.com/) from inception up to May 15, 2020, in collaboration with a medical information specialist (R.V.). In all four databases, the names and synonyms of sleep bruxism and all sleep-related disorders (including sleep wake disorders, parkinsonian disorders, epilepsy, gastroesophageal reflux, and REM behavior disorder) have been searched using text word to identify articles that used these names in their title or abstract. Moreover,

in PubMed and Embase, where the index term (MeSH term and Emtree term, respectively) is available, the index term for sleep bruxism (appeared in PubMed as "Sleep Bruxism"[Mesh]; in Embase as 'sleep'/exp AND 'bruxism'/exp), as well as the index term containing all the sleep disorders (appeared in PubMed as "Sleep Wake Disorders"[Mesh]"; in Embase as 'sleep disorder'/exp) were further added into the search strategy to identify relevant articles. The reference lists of the identified articles were manually searched for relevant publications. Duplicate articles were excluded. All languages were accepted. The full search strategies for all databases can be found in Supplement 3.A

Article screening

The article screening included two phases: title and abstracts screening, and full-text review. Firstly, all identified titles and abstracts were independently screened by two reviewers (B.K. and D.L.). The inclusion criteria were: (1) studies on adult human subjects (age over 18 years old); (2) studies dealing with sleep-related disorders, diagnosed based on self-report (questionnaire or interview), clinical inspection, or PSG/polygraph; (3) studies dealing with SB, diagnosed by self-report (e.g., reporting of teeth grinding sound by questionnaire or interview), clinical inspection (e.g., tooth wear, masseter hypertrophy, and masticatory muscle fatigue or pain), and/or instrumental assessment (e.g., scoring of SB episodes based on PSG, polygraphy, or EMG) [2]; and (4) studies having the following designs: observational studies, controlled clinical trials, or randomized controlled clinical trials. The exclusion criteria were: (1) studies on animals; (2) studies on children; and (3) certain publication types: editorials, letters, legal cases, interviews, and conference abstracts.

Secondly, for all potentially eligible studies identified after the first phase, the two reviewers (B.K. and D.L.) read the full texts independently to check if they fulfilled the eligibility criteria. Studies without accessible full text were excluded.

For both title and abstract screening and full-text review, differences in judgment were resolved through a consensus procedure between the two reviewers. If the differences remained, the issue was resolved by discussion with a third reviewer (G.A.).

Data concerning study design, methods, and results of the final selected studies were extracted by the above-identified two reviewers (B.K. and D.L.).

Quality assessment

Two reviewers (B.K. and D.L.) independently evaluated the methodological quality of the full-text papers, using an adapted version of "Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS)" (See Supplement 3.B for the adapted version, and the study by Kim et al. [39] for the original version). The checklist assesses the potential risk of bias in the following aspects: (1) selection of participants, (2) confounding variables, (3) measurement of exposure, (4) blinding of outcome assessments, (5) incomplete outcome data, and (6) selective outcome reporting.

Different diagnostic methods have different advantages and disadvantages. Self-report could reflect the condition of SB over a prolonged period of time and reach a very large population. The clinical inspection could elevate the objectiveness of SB measurement by documenting related clinical signs and symptoms of SB, such as tooth wear, masticatory muscle hypertrophy, while it is still difficult to acquire objective sleep information and to determine the possible mechanisms for SB. PSG could offer objective and detailed parameters of sleep and jaw-muscle contraction during the night. However, PSG only records jaw-muscle activity over a limited period of time and is less accessible for a large sample because its availability is limited and due to the high costs associated with this approach. During the adaptation of the RoBANS, the different characteristics of the diagnostic methods were taken into consideration. Specifically, when evaluating articles regarding our aim concerning prevalence, it was further required that sample size, based on empirical knowledge, should not be smaller than 100 for self-report studies, and 30 for PSG studies, in order to be categorized as low risk of bias for the 'selection of participants' section. When evaluating articles regarding our aim concerning mechanism, as long as the sample size was justified in the article, a low risk of bias was given for the 'selection of participants' section. In addition, studies using either self-report or PSG would be scored as low risk of bias for the 'measurement of exposure' section when evaluating articles regarding our aim concerning prevalence. In contrast, when evaluating articles regarding our aim concerning mechanism, only studies that employed PSG to diagnose SB would be regarded as low risk for the 'measurement of exposure' section.

Results

Literature search results

The literature search process and results are presented in Figure 3.1. The employed search strategy identified 2635 articles in total, and the manual search identified one more. After duplicates were eliminated, 1593 articles remained for the title and abstract screening. According to the inclusion and exclusion criteria mentioned above, 1556 articles were excluded, and 37 articles thus qualified for the full-text reading phase. After full-text reading, all 37 articles qualified for this systematic review.

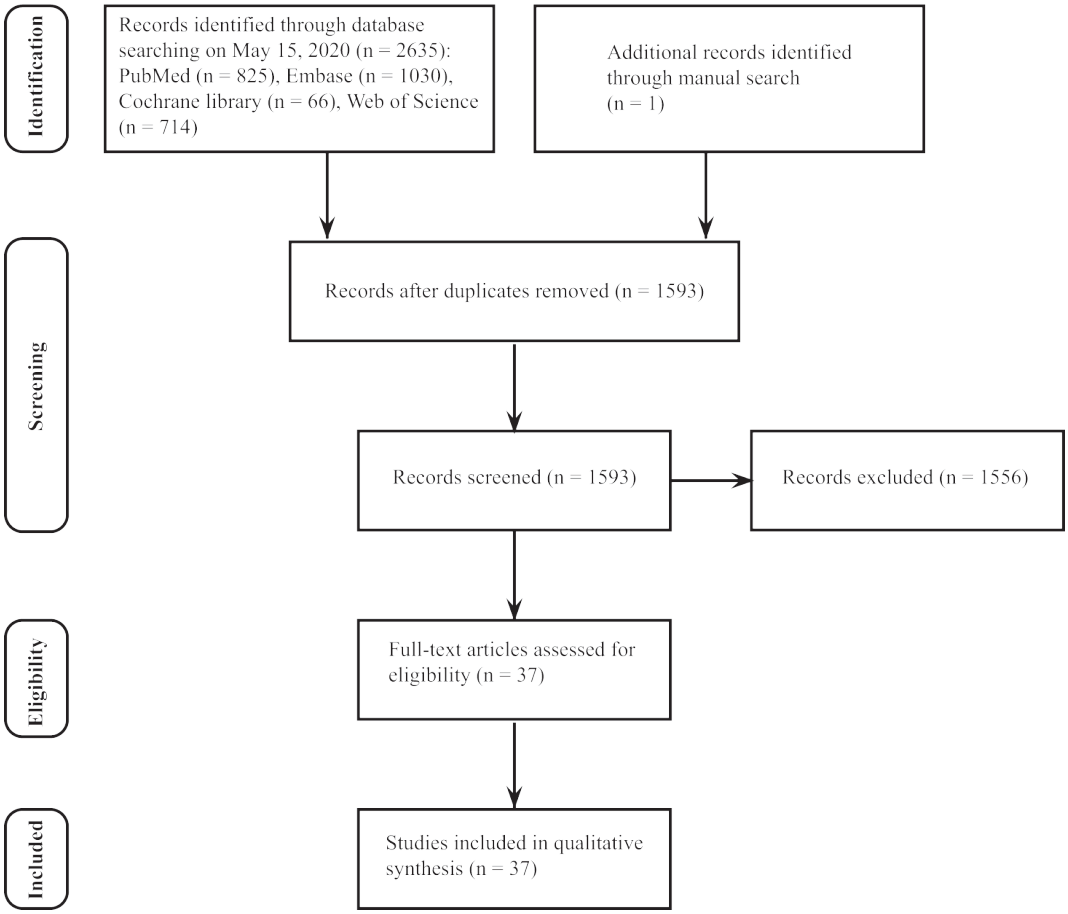

Figure 3.1 Flow diagram of search strategy

Among the 37 articles, 14 articles were related to SB and OSA, 7 articles to SB and restless legs syndrome (RLS)/ PLMS, and 6 articles to SB and sleep-related gastroesophageal reflux disease (GERD). Another 5 articles were related to SB and insomnia, 3 articles to SB and Parkinson's Disease (PD), 1 article to SB and REM behavior disorders (RBD), and 3 articles to SB and sleep-related epilepsy. Further, there was one article studying SB with sleep talking

and sleepwalking. Finally, there was one article that investigated the associations between SB and nightmares. Some of the articles included were involved in multiple associations, and subsequently counted more than once.

Sleep bruxism and obstructive sleep apnea

Fourteen articles [36,40–52] investigated the associations between SB and OSA. The characteristics of these articles are shown in Table 3.1.

Among these articles, six articles [41,42,46–48,50] reported the prevalence of SB in adult patients with OSA. One study [48] used a questionnaire to assess SB, while the other five studies [41,42,46,47,50] used PSG. Due to the limited number of participants and lack of representativeness of patients with OSA, four articles [41,46–48] were regarded as having high risks of bias in the "selection of participants" section. Besides, five articles [41,42,46,47,50] have high risks of bias in the "blinding of outcome assessment" section. Detailed quality assessment results of the articles that reported the prevalence of SB in adult patients with OSA are shown in Table 3.2. Based on the quality assessment, four articles [41,42,48,50] are regarded to have relatively higher quality than the other two articles [46,47], with only two sections of high risks of bias. The mean ages of the participants with OSA in the above four studies [41,42,48,50] ranged from 44.6 to 54.3 years. In addition, among these four studies, only Hesselbacher et al. [48] recruited the same number of females and males, while the other three studies [41,42,50] enrolled more males than females. Based on these four articles, the prevalence of self-reported SB in adult patients with OSA is 26.0% [48], while PSG-confirmed SB prevalence in adults with OSA ranges from 33.3% to 53.7% [41,42,50].

There were thirteen [36,40–46,48–52] out of the fourteen articles that studied the association between SB and OSA. Based on RoBANS, all these articles have high risks of bias in the "blinding of outcome assessment" section, because they fail to describe whether the investigators were blinded to the patients' information during the scoring of the PSG recordings. All but two articles [42,43] have high risks of bias in the "selection of participants" section because of a limited number of participants. Due to a lack of appropriate matching

Table 3.1 Characteristics of studies on sleep bruxism (SB) and obstructive sleep apnea (OSA)

Ref.(authors, year)	Sample	Match	Age (years)	Gender (M, %)	Country /Race	OSA/SDB diagnosis	SB diagnostic methods	SB scoring / diagnosis criteria	SB (%)	Associations/mechanisms
Phillips et al, 1986 [40]	SDB 14; control 10	NR	SDB 52.0±15.9; Control 50.2±16.4	SDB 85.7; Control 90.0	USA/ NR	PSG: AHI ≥10	PSG (masseter)	NR	N/A	The clench index and the AHI are positively correlated.
Okeson et al, 1991 [45]	SDB 12; control 12	age, gender	SDB 57.0±11.5; Control 57.0±11.7	SDB 100; Control 100	USA/ NR	PSG: AHI≥10	PSG (masseter)	NR	N/A	Bruxing events are closely associated with sleep arousals.
Sjöholm et al, 2000 [46]	OSA 21	N/A	40.0±9.2	90.5	Canada/ NR	diagnosed by sleep Physician	SR; CA; PSG (submentalis)	Fulfill 2 out of 3: (1) SR (positive); (2) CA (positive); (3) RJM > 2.5/h	47.6	SB is rarely directly associated with apneic or hypopneic events but is rather related to the disturbed sleep of patients with OSA.
Maluly et al, 2013 [47]	general population 1019	N/A	NR	NR	Brazil/ NR	NR	QNR+PSG (masseter)	1) QNR (positive) 2) PSG (AASM [53]; RMMA≥2)	9.0	The presence of SB was not associated with the presence of OSA.
Hosoya et al, 2014 [50]	OSA 67; control 16	NR	OSA 54.3±13.2; Control 23.9±5.5	OSA 73.1 Control 50.0	Japan/ NR	PSG: AHI ≥5	PSG+AV (masseter)	Lavigne, et al. [54]; RMMA index > 4;	47.8	SB is a sequential event secondary to an arousal event that result from an obstructive apneic event;
Saito et al, 2014 [49]	OSA and SB 10	N/A	46.7±11.5	100.0	Japan/ NR	PSG: AHI>5	PSG+AV (masseter)	ICSD-2 [55]; Lavigne, et al. [54]; RMMA index > 4	N/A	SB events occurring close to sleep apneic hypopneic events are a secondary form of sleep bruxism.
Hesselbacher et al, 2014 [48]	OSA 300	N/A	M 46.8±10.8; F 51.7±9.5	50.0	USA /Caucasian, African American, Hispanic	PSG: AHI>5	QNR	QNR (positive)	26	The mean AHI and SpO_2 nadir were similar between OSA patients with and without sleep bruxism.
Saito et al,2016 [36]	possible SB with suspicious OSA 59	N/A	44.8±10.8	79.0	Japan /Japanese	PSG: AHI ≥5	PSG+AV (masseter)	ICSD-3 [56]; Rompré, et al. [57]; RMMA index > 2; and/or RMMA bursts >25/h	N/A	RMMA was moderately correlated with arousal, but not apneic or hypopneic events. SB genesis and OSA activity are probably influenced by different mechanisms.
Winck et al,2017 [51]	OSA 9	N/A	46.3±11.3	55.6	Portugal/ NR	polygraph: AHI ≥15; or AHI≥5 +symptoms	QNR+EMG (masseters)	AASM criteria [53]; RMMA index ≥2	N/A	No significant correlation was found between AHI and bruxism.
Tsujisaka et al, 2018 [52]	SB 16; SB+OSA 6	gender, BMI	SB 23.6±1.9; SB+OSA 25.5±1.2	SB 56.3; SB/OSA 83.3	Japan/ NR	PSG: AHI≥5	QNR+PSG+AV (masseter and temporalis)	Rompré, et al. [57] RMMA index≥4;	N/A	RMMA after respiratory events was followed to arousals while those before respiratory events were mostly associated with central apnea;
Tan et al, 2019 [41]	OSA 147	N/A	44.6±12.8	68.0	Singapore /NR	PSG: AHI≥5	PSG+AV (masseter)	AASM criteria [58]; Lavigne, et al. [54]; RMMA index > 4;	33.3	Patients with SB had more respiratory events and arousals than non-bruxers. A phenotypic subtype of OSA patients may present with SB as a physiologic response to a respiratory-related event.
Martynowicz et al, 2019 [42]	suspicious OSA 110	N/A	51.0±14.2	60.0	Poland/ NR	PSG: AHI≥5	PSG+AV (masseter)	Lavigne, et al. [54]; RMMA index ≥2	53.7	The relationship between OSA and SB depends on the degree of severity of OSA.
Smardz et al, 2020 [44]	probable SB; bruxer: 58, control: 19	NR`	total: 34.8±10.8 /subgroup NR	total 27.3 (subgroup NR)	Poland /Caucasian	NR	PSG+AV (masseter)	ICSD-3 [56]: NR; RMMA index ≥2	N/A	The occurrence of tonic RMMA may be the key to understanding the causality between SB and sleep-disordered breathing.
De Holanda et al, 2020 [43]	bruxer: 58 Nonbruxer:58	Sex, age	bruxers 42.2±14.5; control 42.6±14.8	bruxers 43.1; control 43.1.	Brazil/ NR	NR	PSG+AV (masseter)	20% MVC; Carra et al. [59]; RMMA index >2	N/A	Arousals index, respiratory disturbance index, and AHI were lower in bruxers than in non-bruxers.

AASM: American Academy of Sleep Medicine; AHI: apnea-hypopnea index; AV: audio and video; BMI: body mass index; CA: clinical assessment; EMG: electromyography; ICSD: International Classification of Sleep Disorders; M: male; F= female; MVC: maximum voluntary contraction; N/A: not applicable; NR: not reported; PSG: polysomnography; QNR: questionnaire; RJM: rhythmic jaw movement; RMMA: rhythmic masticatory muscle activity; SDB: sleep-disordered breathing; SR: self-report.

Table 3.2 Quality assessment of the studies reporting the prevalence of sleep bruxism (SB) in patients with other sleep-related disorders using the Risk of Bias Assessment tool for Non-Randomized Studies (RoBANS)

Disorders	References (authors, year)	Risk of bias					
		Selection of participants	Confounding variables	Exposure measurement	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting
OSA	Sjöholm et al., 2000 [46]	high	high	low	high	low	low
OSA, RLS, Insomnia	Maluly et al., 2013 [47]	high	low	low	high	low	high
OSA	Hesselbacher et al., 2014 [48]s	high	high	low	low	low	low
OSA	Hosoya et al., 2014 [50]	low	high	low	high	low	low
OSA	Tan et al., 2019 [41]	high	low	low	high	low	low
OSA	Martynowicz et al., 2019 [42]	low	low	low	high	low	high
RLS/PLMS	Lavigne et al., 1994 [60]	high	low	low	low	low	low
Sleep-related GERD	Mengatto et al., 2013 [61]	high	low	low	low	low	low
Insomnia	de Campos et al., 2006 [62]	high	high	high	low	low	high
Insomnia	Blanken et al., 2019 [63]	low	high	high	low	low	low
RBD or PD	Abe et al., 2013 [64]	high	high	low	low	low	low
PD	Ylikoski et al., 2014 [65]	low	low	high	low	low	low
Sleep-related epilepsy	Khatami et al., 2006 [66]	high	high	high	low	low	low
Sleep-related epilepsy	Bisulli et al., 2010 [67]	low	high	low	low	low	low
Sleep-related epilepsy	Khachatryan et al., 2020 [37]	low	low	low	low	low	low
Nightmare	Serra-Negra et al., 2019 [68]	high	high	high	low	low	low

GERD: gastroesophageal reflux disease; OSA: obstructive sleep apnea; PD: Parkinson's disease; PLMS: periodic limb movement during sleep; RBD: rapid eye movement sleep behavior disorder; RLS: restless legs syndrome.

between the control group and the patients group, seven articles [36,40,44,48–50,52] were deemed to have high risks of bias in the "confounding variables" section. Detailed quality assessment results of articles that reported the association between SB and OSA are shown in Table 3.3. Overall, five PSG studies [41–43,45,46] only have two sections of high risks of bias, and were thus regarded as having high quality. Okeson et al. [45] reported that bruxing events are closely associated with sleep arousals. Sjöholm et al. [46] showed that sleep bruxism is rarely directly associated with respiratory events but is related to disturbed sleep in OSA. Martynowicz et al. [42] displayed that there is a positive correlation between SB events and sleep arousal in the entire group, while the association between SB and AHI was observed only in participants with mild and moderate OSA. Tan et al. [41] indicated that OSA patients with SB demonstrated a significantly higher respiratory arousal index (*P*: 0.001), AHI (*P*: 0.003) and oxygen desaturation index (*P*: 0.005) than OSA patients without SB. In addition, De Holanda et al. [43] reported that the AHI and arousal index were lower in bruxers than in non-bruxers.

Sleep bruxism and restless legs syndrome/ periodic limb movement during sleep

Seven articles [34,48,60,69–72] investigated SB and RLS/PLMS. The extracted data are shown in Table 3.4.

Only Lavigne et al. [60] reported that, based on questionnaires, the prevalence of SB was 17.3% in adults who reported RLS, and 14.5% in those who reported unpleasant leg sensation during sleep. There were roughly equal male and female participants in the study. The age distribution of the participants had also been controlled for this study to have a similar number of participants in every age range. This article only has a high risk of bias in the "selection of participants" section, and was thus regarded as having high quality. Detailed quality assessment results of this article are shown in Table 3.2.

The other six articles [34,48,69–72] studied the association between SB and RLS/PLMS. Five of these articles [34,48,69,71,72] have high risks of bias in the "selection of participants" section because of small sample sizes and the samples' lack of representativeness. Two articles [34,70] were regarded as relatively high quality articles, with only one high risk of bias section. Detailed quality assessment results of articles that reported the association between SB and RLS/PLMS are shown in Table 3.3. Saletu et al. [70] performed a case-control study with PSG and

demonstrated that the PLM index was higher in SB patients than in controls ($P < 0.05$). Moreover, in another PSG study, van der Zaag et al. [34] found that the combined SB/PLMS events are more likely to be linked with arousal than without arousal in SB patients ($P < 0.001$).

Sleep bruxism and sleep-related gastroesophageal reflux disease

Six articles [48,61,73–76] were identified that studied SB and sleep-related GERD (extracted data in Table 3.4).

Mengatto et al. [61] reported the occurrence of probable SB (validated by self-report and clinical inspection) in adult patients with sleep-related GERD to be 73.7%. The majority of the selected participants of this study were females (71.7%). The mean age of these participants was 44 years old. According to the assessment tool, this article was regarded as having high quality, with only the "selection of participants" section being scored as high risk of bias. Detailed quality assessment results of this article are shown in Table 3.2.

All six articles [48,61,73–76] reported the association between SB and sleep-related GERD. Five articles [48,73–76] have high risks of bias for the "selection of participants" section because of low validity of the selection mechanism and limited number of participants. Three articles [61,75,76] have a relatively higher quality than the other three articles [48,73,74], with only one section scored as high risk of bias. Detailed quality assessment results of articles that reported the association between SB and sleep-related GERD are shown in Table 3.3. In the three articles of high quality [61,75,76], SB was diagnosed based on self-report and clinical inspection, but not on PSG. Mengatto et al. [61] demonstrated that sleep-related GERD was associated with SB (*P*: 0.017; OR: 6.58). In addition, age [61], gender [75], and the duration of GERD episodes [76] influence the association between SB and sleep-related GERD.

Sleep bruxism and insomnia

There are five articles [47,62,63,70,77] that studied SB and insomnia (extracted data in Table 3.5).

Three [47,62,63] out of the five articles reported the prevalence of SB in adult patients with insomnia. All of these three articles have high risks of bias in the "selection of participants" section. De Campos et al. [62] only included postmenopausal females, and the other two articles [47,63] only reported insomnia-related findings for a part of their included participants. Among

Table 3.3 Quality assessment of the studies investigating the association between sleep bruxism (SB) and other sleep-related disorders using the Risk of Bias Assessment tool for Non-Randomized Studies (RoBANS)

Disorders	References (authors, year)	Risk of bias					
		Selection of participants	Confounding variables	Exposure measurement	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting
OSA	Phillips et al., 1986 [40]	high	high	low	high	low	low
OSA	Okeson et al., 1991 [45]	high	low	low	high	low	low
OSA	Sjöholm et al., 2000 [46]	high	low	low	high	low	low
OSA	Hesselbacher et al., 2014 [48]	high	high	high	high	low	high
OSA	Hosoya et al., 2014 [50]	high	high	low	high	low	low
OSA	Saito et al., 2014 [49]	high	high	low	high	low	low
OSA	Winck et al., 2017 [51]	high	low	high	high	low	low
OSA	Saito et al., 2016 [36]	high	high	low	high	low	low
OSA	Tsujisaka et al., 2018 [52]	high	high	low	high	low	low
OSA	Tan et al., 2019 [41]	high	low	low	high	low	low
OSA	Martynowicz et al., 2019 [42]	low	low	low	high	low	high
OSA	Smardz et al., 2020 [44]	high	high	low	high	low	high
OSA	De Holanda et al., 2020 [43]	low	low	low	high	low	low
RLS/PLMS	Ahlberg et al., 2005 [69]	high	high	high	low	low	low
Insomnia, RLS/PLMS	Saletu et al., 2010 [70]	low	low	low	high	low	low
RLS/PLMS	van der Zaag et al, 2014 [34]	high	low	low	low	low	low
RLS/PLMS	Han et al., 2019 [71]	high	low	low	high	low	low
RLS/PLMS	Miki et al., 2020 [72]	high	high	low	low	low	low
Sleep-related GERD	Miyawaki et al., 2003 [73]	high	low	low	high	low	low
Sleep-related GERD	Miyawaki et al., 2004 [74]	high	high	low	low	low	low
Sleep-related GERD	Mengatto et al., 2013 [61]	low	low	high	low	low	low
Sleep-related GERD	Li et al., 2018 [75]	high	low	low	low	low	low
Sleep-related GERD	Li et al., 2018 [76]	high	low	low	low	low	low
Insomnia	Ahlberg et al., 2008 [77]	high	high	high	low	low	low
Sleep-related RBD/PD	Abe et al. 2013 [64]	high	high	low	low	low	low
Sleep-related PD	Verhoeff et al., 2018 [78]	high	high	high	low	low	high
Sleep talking, Sleepwalking, Nightmare	Hublin et al., 2001 [79]	high	low	high	low	low	low

GERD: gastroesophageal reflux disease; OSA: obstructive sleep apnea; PD: Parkinson's disease; PLMS: periodic limb movement during sleep; RBD: rapid eye movement sleep behavior disorder; RLS: restless legs syndrome.

Table 3.4 Characteristics of studies on restless legs syndrome/periodic leg movement during sleep (RLS/PLMS) and sleep-related gastroesophageal reflux disease (GERD)

Ref (authors, year)	Sample	Match	Age (years)	Gender (M, %)	Country /Race	Diagnostic criteria for sleep-related disorders	SB diagnostic method	SB diagnosis criteria	SB (%)	Associations/mechanisms
Lavigne et al., 1994 [60]	general population 2019	N/A	18-29: 29%, 30-44: 31%, 45-59: 20%, >60: 20%	49.0	Canada/ Canadian	RLS: QNR	QNR	SR (positive)	RLS: 10.9	NR
Ahlberg et al., 2005 [69]	regular shift 257; irregular shift 617	N/A	regular shift: M 45.0±10.6, F 42.6±10.7; irregular shift: M 47.4±9.7, F 45.5±10.1	regular shift: 46.7; irregular shift: 56.6	Finland/NR	RLS: SR based on NIH workshop report	QNR	SR (positive)	NR	Self-reported bruxism was positively associated with RLS (OR: 2.0; *P*=0.036)
Saletu et al., 2010 [70]	SB 21; control 21	age, gender	SB 45.1±12.6; control 45.0±12.7	SB: 47.6; control: 47.6	Austria/NR	PLMS: ASDA Atlas Task Force	PSG	Lavigne, et al.[54]	NR	PLMs were significantly elevated in bruxers as compared with control.
van der Zaag et al., 2014 [34]	SB 17; control 11	age, gender	SB: 32.1±6.5; control:34.5±12.8	SB 29.4; control 36.4	Netherlands/ NR	PLMS: ICSD, revised [80] criteria	PSG	Automatic analyzing tool; 10% MVC	NR	The combined SB/PLMS index is larger than isolated SB index or isolated PLM index; the combined SB/PLMS with arousal events are larger than combined SB/PLMS without arousal.
Han et al., 2019 [71]	SB 8; control 9	NR	SB: 21.4±1.9; control:21.8±1.8	SB: 37.5; control: 22.2	China/NR	Leg movement: ICSD-3 [56] criteria	SR; CA; PSG+AV	SR (positive); CA (positive) PSG: ICSD-3 [56]	NR	In SB patients, most RMMAs and LMs are associated with each other. In controls, most RMMAs are associated with LMs, while most LMs are isolated.
Miki et al., 2020 [72]	Subjects 14	N/A	31.5±5.7	71.4	Japan/NR	Leg movement: video + EMG (tibialis)	PSG+AV	Automatic analyzing tool; 10% MVC	NR	Lower leg movement was observed more frequently in concomitance with arousal and SB than in arousal without SB ($P < 0.01$).
Miyawaki et al., 2003 [73]	SB 10; control 10	age, gender height, weight	SB: 27.0±7.0; Control: 26.4 ±4.7	SB: 50; control: 60	Japan/NR	GERD: Esophageal PH-metric	AV+ polygraph	10% MVC; Lavigne, et al.[54]	NR	Around 60% of the RMMAs occurred during GER episodes; frequency of RMMA is lower after PPI intake compared with after placebo intake.
Miyawaki et al., 2004 [74]	volunteers 12	N/A	24.0±2.1	33.3	Japan/NR	GERD: Kahrilas et al. [81]	AV+ polygraph	10% MVC, confirmed by AV	NR	The frequency of RMMA was significantly higher during periods of decreased esophageal pH than during other times.
Mengatto et al., 2013 [61]	GERD 19; Non-GERD 26	NR	44.6±14.0	GERD:36.9 Non-GERD: 23.1	Brazil/NR	GERD: Montreal criteria [82]	SR+CA	SR (positive); CA (positive)	GERD: 73.7	GERD was associated with SB (P= 0.001).
Hesselbacher et al., 2014 [48]	300 OSA	N/A	M 46.8±10.8; F 51.7±9.5	50	USA/ Caucasian, African American, Hispanic	GERD/RLS: QNR	QNR	QNR (positive)	NR	Bruxism was associated with nocturnal GERD (P= 0.008) and with RLS (P= 0.01).
Li et al., 2018 [75]	SB 887; control 887	age, gender	SB: 27 (22-37); control: 28 (22-37)	SB: 39.7 control: 39.7	China/NR	GERD: Montreal criteria [82]	QNR+CA	ICSD-3 [56]	NR	GERD was significantly associated with bruxism (OR: 7.95, P< 0.001).
Li et al., 2018 [76]	SB 398; control 398	age, gender	SB: 28 (22-38); control: 28 (23-39)	SB: 40.5 control: 40.5	China/NR	GERD: Montreal criteria [82]	QNR+CA	ICSD-3 [56]	NR	GERD was associated with bruxism; Patients with a longer duration of GERD symptoms have a higher OR for bruxism than those with a shorter duration.

AASM: American Academy of Sleep Medicine; ASDA: American Sleep Disorders Association; AV: audio and video; CA: clinical assessment; F: female; GERD: gastroesophageal reflux disease; ICSD-3: International Classification of Sleep Disorders; M: male; MVC: maximum voluntary contraction; N/A: not applicable; NR: not reported; OR= odd ratio; PH= potential of hydrogen; PLMS: periodic limb movement during sleep; PPI= proton pump inhibitor; PSG: polysomnography; Q1: first quartile; Q3: third quartile; QNR: questionnaire; RLS: restless legs syndrome; SB: sleep bruxism; SR: self-report.

Table 3.5 Characteristics of studies on insomnia, REM behavior disorder (RBD), Parkinson's Disease (PD), epilepsy, and other sleep-related disorders

Ref.(authors, year)	Sample	Match	Age (years)	Gender (M, %)	Country /Race	Diagnostic criteria for sleep-related disorders	SB diagnostic methods	SB scoring/ diagnosis criteria	SB%	Associations/mechanism
Hachul de Campos et al., 2006 [62]	38 females with insomnia complaints	N/A	55.0±4.0	0	Brazil/NR	Insomnia: SR & PSG	QNR	NR	insomnia 2.6	NR
Ahlberg et al., 2008 [77]	regular shift: 257; irregular shift: 617	N/A	irregular shift: M 45.0±10.6, F 42.6±10.7; regular shift: M 47.4±9.7, F 45.5±10.1	irregular shift: 56.6; regular shift: 46.7	Finland/NR	Insomnia: QNR based on ICSD[80]	QNR	NR	NR	Frequent SB was associated with DIS (P= 0.019) and DS (P= 0.021)
Saletu et al., 2010 [70]	SB 21; Controls 21	age, gender	SB: 45.1±12.6; control: 45.0±12.7	SB: 47.6; control: 47.6	Austria/NR	Insomnia: ICD-10[83]	PSG	Lavigne et al. [54]	NR	SB group showed no significant difference in sleep initiation but significantly deteriorated sleep maintenance.
Maluly et al., 2013 [47]	1019 (partially reported)	N/A	20-29(22.72%); 30-39(24.48%); 40-49(23.04%); 50-59(15.84%); 60-80(13.92%)	45.8 (partially reported)	Brazil/NR	Insomnia: QNR	PSG	AASM criteria [53]	Insomnia 16.5	An association between SB and insomnia was detected (χ^2: 5.69, $P < 0.01$).
Blanken et al., 2019 [63]	126	NR	NR	NR	Netherlands/NR	Insomnia: QNR	QNR	NR	Insomnia 6.6	NR
Abe et al., 2013 [64]	iRBD 13; RBD-PD 13; control 9	age	iRBD: 65.3±3.1; RBD-PD: 67.1±2.6; control: 65.1±4.0	iRBD: 76.9; RBD-PD: 80; control: 55.6	Canada/NR	(1) RBD based on ICSD [55] (2) PD diagnosed by specialist	PSG+AV (EMG: chin/ masseter)	Lavigne et al. [54]	RBD 25.0	1) iRBD patients had significantly higher RMMA index during REM than controls; 2) iRBD and RBD-PD patients had higher RMMA index during sleep than controls
Ylikoski et al., 2014 [65]	PD 661	N/A	68.8±8.5	53.0	Finland/NR	PD by neurologist	QNR	NR	PD 4.7	NR
Verhoeff et al., 2018 [78]	PD or PR 368; control 340	NR	PD or PR: 67±9.3; Control: 65±9.3	PD or PR: 49; control: 37.	Netherlands/NR	PD: NR	QNR	Lobbezoo et al. [1]	NR	A significant association between possible SB and PD (P: 0.001).
Khatami et al., 2006 [66]	Epilepsy 100; non-epilepsy 90	age	epilepsy: 47(mean); non-epilepsy:44(mean)	epilepsy: 63; non-epilepsy: 46	Switzerland/NR	Epilepsy: QNR International League Against Epilepsy	QNR	NR	Epilepsy10	NR
Bisulli et al., 2010 [67]	NFLE 33; Control 31	age, gender	NFLE: 31.9±12.4; control: 31.3±11.8	NFLE: 54.5 control: 51.6	Italy/NR	Epilepsy: PSG +video:≥1 major epileptic episode or ≥2 minor stereotyped episodes	Interview	NR	NFLE 12	Bruxism occurred more frequently in the proband versus the control group (OR: 5.4; P: 0.017)
Khachatryan et al., 2020 [37]	Epilepsy 175; Controls 130	age, gender	epilepsy: 35.4±13.7; control: 33.6±11.3	epilepsy: 52.6; control: 52.3	Armenia /NR	Epilepsy: Fisher et al. [84] + neuroimaging and EEG	Interview	ICSD-3[56]	Epilepsy 23.7	SB occurred more frequently in epilepsy group than in control (χ^2: 18.7; $P < 0.05$).
Serra-Negra et al., 2019 [68]	119 adults	N/A	24.8±2.6	43.9	Brazil/NR	Nightmare: QNR[85]	QNR	Lobbezoo et al. [1]	Nightmare 38.3	Possible SB is associated with nightmares at least once a week.
Hublin et al., 2001 [79]	11220 twins (8567 responded in adult)	N/A	NR	NR	Finland/NR	Parasomnia: NR	QNR	QNR	NR	There is significant correlation between SB and sleepwalking, sleep talking, and nightmare.

AASM: American Academy of Sleep Medicine; ASDA: American Sleep Disorders Association; AV: audio and video; DIS: difficulty initiating sleep; DS: disturbed sleep; EEG: electroencephalograph; EMG: electromyography; F: female; ICD= International Statistical Classification of Diseases and Related Health Problems; ICSD: International Classification of Sleep Disorders; (i)RBD: (idiopathic) REM behavior disorder; M: male; N/A: not applicable; NFLE: nocturnal frontal lobe epilepsy; NR: not reported; PD: Parkinson's disease; PR: parkinsonism; PSG: polysomnography; QNR: questionnaire; SB: sleep bruxism; SR: self-report; AV: audio and video.

the portion of participants, on which Maluly et al. [47] based their insomnia findings, 54% of them were female, but the age distribution was not reported for these participants. Two articles [62,63] did not describe their criteria for SB diagnosis. Detailed quality assessment results of articles that reported the prevalence of SB in patients with insomnia are shown in Table 3.2. Taking the above-indicated methodological shortcomings into account, the prevalence of PSG-confirmed SB in patients with insomnia was determined to be 16.5% [47].

Two [70,77] of the five articles reported the possible mechanism and the association between SB and insomnia. The article by Saletu et al. [70] has a higher quality than the article by Ahlberg et al. [77], with only one high risk of bias. Detailed quality assessment results of articles that reported the association between SB and insomnia are shown in Table 3.3. Based on PSG outcomes, it suggested that compared with controls, sleep bruxers showed no significant difference in sleep initiation but did show significantly deteriorated sleep maintenance [70].

Sleep bruxism and REM behavior disorder, and Parkinson's disease

Three articles [64,65,78] investigated the association between SB and PD. One article [64] investigated SB and RBD (extracted data in Table 3.5).

The questionnaire-based study by Ylikoski et al. [65] included a large number of participants (n: 661) and reported an SB prevalence of 4.7% in patients with PD. Fifty-three percent of the participants in the study by Ylikoski et al. [65] were male. The mean age of the participants was 68 years old. Abe et al. [64], a PSG and medical RBD diagnosis study, reported an SB occurrence of 25% among the 25 included patients with RBD. Seventy-eight percent of the participants in the study by Abe et al. [64] were male. The mean age of those participants was 66 years old. Both of the two studies had high quality, and the detailed quality assessment results of these two articles are shown in Table 3.2.

Two articles [64,78] reported the association between SB and PD, and one article [64] investigated the association between SB and RBD. Detailed quality assessment results of articles that reported the association between SB and PD as well as the association between SB and RBD are shown in Table 3.3. Even though both articles suggested an association between SB and PD, and between SB and RBD, no underlying mechanism has been reported.

Sleep bruxism and sleep-related epilepsy

There are three articles [37,66,67] that investigated SB and sleep-related epilepsy (extracted data in Table 3.5).

All three articles reported the prevalence of SB in adult patients with sleep-related epilepsy. Detailed quality assessment results of these articles are shown in Table 3.2. The study by Khachatryan et al. [37] enrolled a relatively large number of participants (175 patients with epilepsy and 130 controls) and was regarded as the best quality article among the three identified articles [37,66,67]. 23.7% of the patients with epilepsy reported SB by an interview, compared with 5.4% of controls. The age and gender of the epilepsy and control group were matched. The mean ages of the participants of the two groups were 33 and 35 years old. Fifty-two percent of the participants of both groups were males. No underlying mechanism was reported in any of the three studies.

Sleep bruxism and other sleep-related disorders

One article [68], based on a questionnaire, reported the prevalence of possible SB in patients with nightmare. Also, another questionnaire study [79] suggested a correlation between SB and sleepwalking, as well as SB and sleep talking. The characteristics of these two articles are shown in Table 3.5. Due to the relatively high risk of bias of these two articles (details in Table 3.2 and Table 3.3), no reliable results could be extracted.

Discussion

This systematic review was conducted: 1. to determine the prevalence of SB in patients with other sleep-related disorders; and 2. to determine the associations between SB and other sleep-related disorders, and to explain the underlying mechanisms for the associations found. As such, several disorders have been identified, including OSA, RLS/PLMS, sleep-related GERD, insomnia, Parkinson's disease, RBD, and sleep-related epilepsy. Below, we will discuss these findings in relation to the clinical practice of sleep physicians as well as that of dental practitioners to promote better cooperation. Further, we provide recommendations for future studies [86,87].

Sleep bruxism and obstructive sleep apnea

Four articles [41,42,48,50] reported that the prevalence of SB in adult patients with OSA ranges from 26.0% to 53.7%, which is much higher than that in the general population (12.8%) [3]. Nonetheless, there is a significant discrepancy in the prevalence among studies. Since the diagnosis of definite SB should be confirmed by PSG [2], a prevalence of 26.0% from one questionnaire study [48] was considered biased. Although the other three PSG studies employed the American Academy of Sleep Medicine (AASM) manual for SB scoring, two of them [41,50] set the cutoff value of RMMA index at four episodes/hour for SB diagnosis while the third one [42] set the cutoff at two episodes/hour. This might partially explain the lower prevalence in the first two PSG studies than that in the last one (33.3%, 47.6% vs. 53.7%). Apart from this, previous studies have reported that the prevalence of SB differs among age groups, genders, and races [3,48,88]. Thus, the diversity of these confounders among studies may also contribute to the variation in SB prevalence in patients with OSA.

Concerning the mechanism, as OSA is characterized by repetitive apneic or hypopneic events that often result in sleep arousals, most studies identified in this review investigated the relationship between SB and apneic hypopneic events, and the relationship between SB and sleep arousals. A PSG study composed of 14 patients with OSA [40] reported that the clenching index was positively correlated with the AHI. However, later PSG studies [36,41] with larger sample sizes found no association between the RMMA index and AHI. Besides, some studies [46,49] showed that while part of SB episodes occurred after apneic hypopneic events, a large number of SB episodes were unrelated to the termination of apneic hypopneic events. The abovementioned evidence suggests a weak association between SB and apneic hypopneic events.

It is also possible that, as suggested by some PSG studies, only a subtype of RMMA (phasic or tonic) was associated with apneic hypopneic events [44,50]. Hosoya et al. [50] selected OSA patients for whom phasic type was dominant to assess such an association, and concluded that phasic RMMA positively correlated with apnea-hypopnea index. On the contrary, Smardz et al. [44] selected individuals from a dental specialty clinic (prosthodontics) with probable SB and no clear OSA diagnosis who presented a dominance of the tonic type, and concluded that tonic RMMA could be associated with the formation of respiratory events. Based on these

contrasting findings, we could speculate that the predominant subtype of RMMA may vary between the OSA population and SB population, and that different phenotypes of RMMA may have different causal relationships with respiratory events. Also, as Smardz et al. [44] enrolled participants with relatively younger age (18-63 years with a mean of 35 years) than Hosoya et al. [50] (mean age: 54 years), age might be a factor that affects the dominant pattern of jaw-muscle activity as well. In addition, another high quality PSG study suggested that the close association between SB and OSA is only present in mild to moderate OSA [42]. Taken together, these results suggest that the association between RMMA and respiratory events may be present only at a subtype or subgroup level.

Despite the above, another PSG study [89] indicated that the occurrence of masseter muscle contractions time-linked to apneic hypopneic events in patients with OSA is related to sleep arousals that result from apneic hypopneic events rather than to the apneic hypopneic events *per se*. Also, one PSG study [52] reported that after apneic hypopneic events, SB episodes occurred more frequently when sleep arousals were present than when sleep arousals were absent. In line with this, three studies [41,45,46] of higher quality included in this review denoted that SB is positively associated with sleep arousals in patients with OSA. This finding agrees with some other studies [32,90,91] that stated that SB is an oromotor activity secondary to sleep arousals. Taking all the evidence into consideration, we therefore postulate that the association between SB and OSA may depend on the presence of sleep arousals in patients with OSA.

It is noteworthy that a recent study [43] of high quality showed that PSG-confirmed bruxers had lower AHI and arousal indices than non-bruxers and that OSA decreased the risk for SB (odds ratio: 0.55, P: 0.173). The results suggested an inverse association between OSA and SB. As explained in that study, partially obstructed breathing that is not classified as OSA could explain the higher frequency of SB in patients without OSA [43]. Besides, as discussed above, the occurrence of SB might be related to arousals. In the OSA population, most arousals result from respiratory events, while in bruxers, arousal may be triggered by different stimuli. Thus, the difference in the composition of samples among studies may contribute to contrary conclusions concerning the association between OSA and SB.

In addition, OSA has been reported to be more prevalent in males than in females, and in

older patients than in the younger ones [92]. On the other hand, based on currently available evidence, SB prevalence seems to be equal between genders [47,60], and decreases with aging [60,88]. Given the fact that age and gender have different influences on SB and OSA, we can speculate that the prevalence of SB in patients with OSA, as well as the association between SB and OSA, may vary among age groups and genders. However, none of the included studies have investigated the effect of age and gender on the association between SB and OSA.

Considering the high prevalence of SB in patients with OSA (33.3% to 53.7%), sleep physicians are urged to consider SB as a common comorbidity of OSA. As SB is suggested to be related to sleep arousals, we speculate that SB episodes related to respiratory arousals would decrease significantly by effective OSA treatment. This has been proved by a previous PSG study [89]. Also, some studies [93–96] have reported that, to some extent, OSA therapies (such as oral appliances and continuous positive airway pressure) can reduce the frequency of SB episodes as well as the signs and symptoms of SB. Thus, for patients with concomitant OSA and SB, OSA should be treated first. The sleep physicians should then check if the negative consequences of SB, as summarized in the introduction, are still severe enough that the patients need collaborative management by sleep physicians and dental practitioners.

Although SB is more prevalent in OSA individuals, which may suggest a close association between the two conditions, solid evidence in the mechanism to support this association is still limited. Current evidence indicated that the close association between SB and OSA might be related to the presence of arousal. Due to the limited samples of previous studies, large-scale PSG studies in patients with OSA are still needed to confirm the role of arousals in the relationship between SB and OSA, as well as the prevalence rate of SB in adult patients with OSA. Age and gender should also be considered in future studies on SB prevalence and the underlying mechanism of the association between OSA and SB.

Sleep bruxism and restless legs syndrome/ periodic limb movement during sleep

Even though one article has reported the SB prevalence in patients with RLS [60], both SB and RLS were diagnosed based on a questionnaire. What could be concluded from this article is that the prevalence of SB in adult patients with RLS (17.3%) is relatively higher than that in the general population (12.8%) [3,60]. In addition, van der Zaag et al. [34] reported that the

combined SB/PLMS index is significantly higher than the isolated ones in SB patients, which further indicates the positive association between these disorders.

In terms of mechanism, both SB and RLS/PLMS were found to be associated with arousal events [34,70,72]. Although the three identified studies [34,70,72] employed PSG to assess SB and RLS/PLMS, they included too small sample sizes, and their methods leave room for improvement. Van der Zaag et al. [34] and Miki et al. [72] both used 10% maximum voluntary contraction (MVC) as the cutoff to score SB episodes. Saletu et al. [70] used 20% MVC as the cutoff to score SB episodes. The use of MVC to score SB episodes does not take the real-time fluctuation of the EMG signal, due to, e.g., sweating [97] and body movement [98], into consideration. However, despite these limitations, the positive correlations between SB and arousals as well as RLS/PLMS and arousals are the same for all the identified studies, which strengthens the validity of the reported findings.

According to Lavigne et al. [60], the prevalence of SB decreased, while the prevalence of RLS increased as the age of the participants increased, based on a large population survey in Canada. However, how the age differences could influence the association between SB and RLS/PLMS, is still to be investigated in future studies.

The common co-occurrence of SB and RLS/PLMS may suggest that when screening and treating patients with RLS/PLMS, sleep physicians should also take the probable SB signs and symptoms into consideration. Due to the relative scarcity of isolated SB or RLS/PLMS episodes [34], it could be speculated that successful treatment of RLS/PLMS by the sleep specialist could result in a decrease of SB as well. On the other hand, if treatment of RLS/PLMS does not decrease the severity of the symptoms of SB, and SB is causing obvious negative consequences (summarized in the introduction), the physician should seek collaboration with dental practitioners.

Future large-scale population studies, using higher validity methods, are needed to acquire a precise SB prevalence rate in patients with RLS/PLMS and further elucidate the role of sleep arousal in the association between SB and RLS/PLMS. Finally, large sample studies focusing on the effect of the RLS/PLMS treatment on SB are needed to further examine the finding that RLS/PLMS and SB episodes are more often combined than isolated in clinical settings.

Sleep bruxism and sleep-related gastroesophageal reflux disease

Only one article [61] reported the occurrence of SB in adult patients with sleep-related GERD (73.7%), which is much higher than that in the general population (12.8%) [3]. However, SB diagnosis was established based on self-report/partner-report and a clinical examination, without performing PSG. Thus, the specific prevalence rates based on PSG still need to be determined in future studies.

Based on the results of the identified articles, it is suggested that SB and sleep-related GERD are associated. The three articles of higher quality [61,75,76] all measured SB using self-reports, because PSG is not the standard of care for patients with GERD [56]. However, we still can speculate, based on Miyawaki et al. [73], that SB episodes, together with swallowing, could be a response towards acid reflux episodes. Furthermore, it has been reported that nocturnal gastroesophageal reflux episodes were often associated with arousals [23,99,100]. At the same time, SB has long been associated with arousals [28,30–32]. So, it could be summarized that SB and sleep-related GERD are associated, and that arousal seems to be the bridging factor between both conditions.

It has been speculated that masticatory muscle activity has a positive role in stimulating the salivary gland secretion, accelerating esophageal acid clearance [23]. Subsequently, a collaboration between sleep physicians and dental practitioners is recommended to manage GERD as well as the possible negative consequences of SB (summarized in the introduction).

Based on the current identified literature, SB and sleep-related GERD seem to be associated with each other, yet the specific SB prevalence in patients with sleep-related GERD needs further investigation. Moreover, no EEG monitoring was implemented in sleep-related GERD studies. Consequently, it is impossible to objectively determine whether the muscle contraction detected by EMG was during sleep or wake. Thus, we recommend future studies to use PSG to measure SB as well as arousal to study the association between SB and sleep-related GERD. We also recommend the enrollment of more participants to establish the prevalence of SB in patients with sleep-related GERD as to achieve higher statistical power. At the same time, esophageal pH monitoring is recommended to objectively measure individual sleep-related gastroesophageal reflux events.

Sleep bruxism and insomnia

A newly published PSG study by Maluly et al. [101] found that the prevalence of SB in adults with insomnia complaints is 17.7%. This is higher than the SB prevalence in the general population, which is around 12.8%, as reported by a review study [3]. However, it is necessary to point out that the gold standard for diagnosing insomnia requires not only the patients' self-reports about their insomnia complaints, but also the exclusion by sleep physicians that other sleep disorders may be causing the sleep/wake difficulty [56]. Many studies suggested that insomnia is also associated with OSA [102,103], RLS [104,105], and sleep-related GERD [106,107]. Thus, if there is no physicians' diagnosis, the reported sleep complaints may be secondary to OSA, RLS, or sleep-related GERD. Subsequently, there could very likely be an overestimation of insomnia based on questionnaires as compared to insomnia based on physician diagnosis. In the study by Maluly et al. [101], the diagnosis of insomnia was based on patients' self-reports (Diagnostic and Statistical Manual of Mental Disorders-IV criteria) and interviews. Thus, the SB prevalence rate of 17.7% in patients with insomnia reported by Maluly et al. [101] should be taken with caution. Future studies on the prevalence of SB in patients with insomnia should take the diagnosis of insomnia from physicians into account.

Regarding the mechanism, Saletu et al. [70] found that PSG-confirmed sleep bruxers showed no significant difference in sleep initiation but significantly deteriorated sleep maintenance compared with controls. Chronic insomnia, the symptoms of which include deteriorated sleep maintenance, was found to be associated with elevated physiological arousal [108]. At the same time, SB has also been found to be related to arousal [28,30–32]. Thus, we could speculate that SB is associated with insomnia via arousal. Again, the analysis in the study by Saletu et al. [70] was not based on a definite insomnia diagnosis by physicians.

To summarize, within the scope of the identified articles about SB and insomnia, we could only determine that there is a possible association between SB and the symptom of difficulty maintaining sleep. Future studies should investigate SB prevalence in insomniac patients diagnosed by physicians to avoid the subjective reporting bias caused by questionnaire usage. Moreover, when sleep physicians treat patients with major complaints related to sleep maintenance issues, it could be a good idea to ask further questions about symptoms related to SB. If the patients report obvious negative consequences related to SB (summarized in the

introduction), the sleep physician should seek collaboration with dental practitioners to further evaluate the condition of the patients.

Sleep bruxism and REM behavior disorder, and Parkinson's disease

RBD is an abnormal condition consisting of REM sleep without atonia in conjunction with a history of recurrent nocturnal dream enactment behavior [109,110]. According to a review by Dauvilliers et al. [111], RBD has been considered as a potential precursor of later development of neurodegenerative disorders, such as PD. At the same time, Sixel-Doring et al. [112] reported that among sleep-disturbed patients with PD, 46% of them were identified with RBD.

One article [64] reported the prevalence of SB in adult patients with RBD. Abe et al. [64] reported, using PSG to confirm, an SB occurrence of 25% in patients with RBD, which is significantly higher than self-reported SB prevalence in the general population (12.8% [3]). At the same time, it should be noted that the diagnostic methods of SB in these two studies were different. While the PSG could offer objective data, Abe et al. [64] only enrolled 28 patients with RBD. Manfredini et al. [3] acquired the prevalence rate by summarizing three large sample studies with a total of more than 2000 participants, albeit using questionnaires. Ylikoski et al. [65] reported, using only questionnaire, that SB occurrence in patients with PD was 4.7%, which is significantly lower than that in the general population (12.8% [3]). Even though the sample size was large, questionnaire was used to identify SB. When considering the mental and cognition status of patients with PD [113–115], their results may not be reliable. A strong point of both studies [64,65], however, is that their RBD and PD diagnoses were determined by medical specialists. The big difference in SB prevalence between in patients with either RBD or PD and in the general population suggests potential associations between SB and RBD as well as between SB and PD.

Although Abe et al. [64] mentioned that the RMMA index was higher in patients with RBD than in the healthy control group, no specific mechanism has been reported yet since associations do not provide direct support for SB causality. Thus, no specific mechanism has been found in these papers.

Since one of the main pathological findings in PD is the loss of dopaminergic neurons [116], studies that reported the association between SB and dopamine/ dopaminergic neurons

could shed some light on the association between SB and PD. Lobbezoo et al. [11] reported that the side imbalance of striatal dopaminergic receptors could be associated with SB. Lobbezoo et al. [117] also reported that short-term usage of levodopa, a dopamine precursor which is the most effective medication for the treatment of the motor symptoms of PD [118], has an attenuating effect on SB. However, a randomized crossover study by Cahlin et al. [119] found that short-term use of pramipexole, a dopamine agonist, does not affect SB. Also, a double-blind, crossover, placebo-controlled trial showed that short-term use of bromocriptine, a dopamine D2 receptor agonist, has no effect on the severity of SB [120]. However, long-term usage of levodopa could be a disruptor of the striatal dopaminergic balance, thus possibly be an SB-inducing factor. More studies are needed to further elucidate the possible roles of neurotransmitters and medications in the association between SB and PD [121].

One intriguing phenomenon suggested by Abe et al. [64] is that in patients with RBD, the RMMA burst index during REM sleep is significantly higher than in controls, while it is widely recognized that most RMMA episodes occur in sleep stages N1 and N2 in otherwise healthy individuals [122,123]. So, elevated RMMA activity during REM could serve as a red flag for sleep specialists for a possible presence of RBD. Sleep physicians have to keep in mind that idiopathic RBD, a clinical manifestation in the absence of PD of multiple system atrophy, is a condition with a high risk of neurodegenerative disease conversion at 12 years post diagnosis [111].

To summarize, studies on the association between SB and RBD, and on the association between SB and PD are limited. SB occurrence in patients with RBD may be higher than that in the general population, while SB prevalence in patients with PD may be lower than that in the general population. Further, increased RMMA activity during REM could be an important sign for sleep specialists to further screen their patients for RBD. Future studies should enroll more patients, utilize PSG to evaluate SB, and diagnose RBD and PD by medical specialists to offer objective information on the prevalence of SB in patients with either RBD or PD, and on the mechanism of the association between SB and RBD as well as the association between SB and PD.

Sleep bruxism and sleep-related epilepsy

Khachatryan et al. [37] suggested that the SB prevalence in adult patients with epilepsy was 23.7%, which was significantly higher than that in healthy controls (5.4%). Despite the relatively large number of participants (175 patients with epilepsy and 130 healthy controls), SB was diagnosed based on self-report, which could potentially overestimate the prevalence of SB [47]. However, since questionnaires were used for both groups, the use of this tool does not affect the positive correlation between SB and epilepsy. Giuliano et al. [124] published an article after the search date of this review, suggesting that SB is significantly more frequent in the epilepsy group than healthy controls using PSG with audio and video recordings in a relatively large sample (100 patients with epilepsy and 62 healthy controls). The significantly higher prevalence of SB in patients with epilepsy calls for more SB-related screening of patients suspected of epilepsy. Besides, it has been speculated in a case report [33] that epileptic discharge could present a direct inductive effect on SB. So, there is a possibility that the treatment of epilepsy could improve the SB condition for patients with epilepsy.

There is no mention of the mechanism that could explain the association between SB and sleep-related epilepsy. However, a detailed review on epilepsy and motor events during sleep [125] found that major episodes of epilepsy, especially nocturnal frontal lobe epilepsy between 10 and 60 seconds, were preceded by a prolonged cyclic alternating pattern sequence which reflects a condition of sustained arousal instability. As previously mentioned, arousal was found to be associated with SB. Consequently, it could be speculated that the association between SB and sleep-related epilepsy is mediated by arousal.

To summarize, SB is positively associated with epilepsy. However, the precise SB prevalence in patients with epilepsy is yet to be determined in a larger population using a method of high validity. Based on the evidence available, the association between SB and epilepsy could be explained by the common association with arousals. Sleep physicians, when treating patients with epilepsy, should be more aware of the possible negative consequences caused by SB and seek collaboration with dental practitioners in their treatment planning.

Sleep bruxism and other sleep-related disorders

The identified two articles on SB and other sleep-related disorders were questionnaire studies

regarding SB and nightmare [68], as well as SB and sleep talking and sleepwalking [79]. More studies are needed to further understand the relationship between SB and nightmare, sleepwalking, and sleep talking. At the same time, sleep specialists need to be aware of these possible associations and seek collaborations with dentists when needed.

Strengths and Limitations

One of this review's strengths is that our article search was performed in four different databases. Two reviewers independently did the title and abstract screening and full-text reading to minimize the potential personal bias. On the other hand, despite the effort to select articles of higher quality, those selected articles still have one or two section(s) of high risks of bias, including a limited number of participants and relatively low validity of the diagnostic tools. Thus, the conclusions that were reached based on these studies should be considered with caution.

Different methods were used to assess SB as well as the other identified disorders. Some studies used questionnaires or interviews, and some other studies used clinical inspection. Even among those articles that used PSG to assess SB, different scoring methods were used to score sleep as well as SB. Some articles used the RMMA index of 4 as the cutoff between SB positive and negative, while others used the RMMA index of 2. All the articles related to PD or RBD had their participants' diagnoses by physicians, while none of the insomnia related articles involved the diagnosis by physicians. These differences in the assessment of all sleep-related disorders could potentially lead to different prevalence rates and associations. As each method has its own merits and demerits, standardized approaches for assessing SB and other sleep disorders with a global valuation of biopsychosocial and clinical data of a given individual are essential [126,127]. Future studies based on standardized and validated approaches to assess sleep-related disorders would provide more reliable evidence on the prevalence rates and associations between SB and other sleep-related disorders.

Despite these shortcomings, the review has identified and summarized all the sleep-related disorders in association with SB that are currently reported in the literature. Further, recommendations are made to medical specialists to raise awareness of SB as a potential indicator for these associated sleep-related disorders and to advocate the closer

collaboration between medical specialists and dental practitioners.

Even though there are a lot of studies supporting the association between SB and sleep arousal, few studies, if any, could prove the causal relationship. Carra et al. [32], using a cyclic alternating pattern, which is another marker of sleep instability [128] and part of the sleep microstructure, reported that cyclic alternating pattern phase A3 is a permissive window rather than a generator of RMMA/SB activity. Thus, SB generation could be influenced by other factors yet to be identified.

Conclusion

The systematic review identified sleep-related disorders that are possibly associated with SB, including OSA, RLS/PLMS, sleep-related GERD, insomnia, PD, RBD, and sleep-related epilepsy. Within the main limitation of this review (i.e., large methodological differences between the included studies in the assessment of SB and of other sleep disorders), the prevalence of SB in patients with OSA, RLS/PLMS, sleep-related GERD, RBD, and sleep-related epilepsy is higher than that in the general population, which sheds more light on the importance of routine SB screening in patients with aforementioned sleep-related disorders. Even though the specific mechanisms behind the associations between SB and other sleep-related disorders have not been identified yet, considering all the available evidence, sleep arousals could be a common factor with which all the identified disorders are associated, except RBD and PD.

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Supplement 3.A Search strategy

PubMed

PubMed could be reached at https://pubmed.ncbi.nlm.nih.gov/. The database is operated by National Center for Biotechnology Information, National Institute of Health, USA. The query below was used to deliver the search in PubMed. The reported numbers of items found were the results of the query on 15 May 2020.

Search	Query	Items found
#4	#3 NOT (("Adolescent"[Mesh] OR "Child"[Mesh] OR "Infant"[Mesh] OR adolescen*[tiab] OR child*[tiab] OR schoolchild*[tiab] OR infant*[tiab] OR girl*[tiab] OR boy*[tiab] OR teen[tiab] OR teens[tiab] OR teenager*[tiab] OR youth*[tiab] OR pediatr*[tiab] OR paediatr*[tiab] OR puber*[tiab]) NOT ("Adult"[Mesh] OR adult*[tiab] OR man[tiab] OR men[tiab] OR woman[tiab] OR women[tiab]))	825
#3	#1 AND #2	1,027
#2	"Sleep Wake Disorders"[Mesh] OR "Parkinsonian Disorders"[Mesh] OR "Epilepsy"[Mesh] OR "Gastroesophageal Reflux"[Mesh] OR "Stomach"[Mesh] OR "Comorbidity"[Mesh] OR comorbidity[tiab] OR multimorbidity[tiab] OR body rocking[tiab] OR stomach*[tiab] OR gastroesophageal refl*[tiab] OR gastro-esophageal refl*[tiab] OR gastrooesophageal refl*[tiab] OR gastro-oesophageal refl*[tiab] OR gastric*[tiab] OR GERD[tiab] OR laryngopharyngeal refl*[tiab] OR laryngo-pharyngeal refl*[tiab] OR parkinson*[tiab] OR epilep*[tiab] OR (("Sleep"[Mesh] OR sleep*[tiab] OR wake[tiab] OR awake[tiab] OR waking[tiab] OR awaking[tiab] OR somnolence*[tiab] OR somnolescent[tiab] OR REM[tiab] OR Circadian rhythm[tiab]) AND (disorder*[tiab] OR disturb*[tiab] OR problem*[tiab] OR difficult*[tiab] OR paroxysmal[tiab])) OR dyssomnia*[tiab] OR Sleep Deprivation*[tiab] OR Sleep Fragmentation*[tiab] OR Insufficient Sleep Syndrome*[tiab] OR Nyctohemeral Rhythm*[tiab] OR Sleep Phase Syndrome*[tiab] OR jet lag*[tiab] OR hypersomnolence*[tiab] OR hyper-somnolence*[tiab] OR hypersomnia*[tiab] OR hyper-somnia*[tiab] OR Kleine-Levin[tiab] OR narcoleps*[tiab] OR cataplex*[tiab] OR Gelineau*[tiab] OR nocturnal myoclonus syndrome*[tiab] OR Periodic Leg Movement*[tiab] OR Periodic Limb Movement*[tiab] OR ((Leg Movement*[tiab] OR Limb Movement*[tiab]) AND sleep*[tiab]) OR restless leg*[tiab] OR Willis Ekbom[tiab] OR Wittmaack Ekbom[tiab] OR sleep apnea*[tiab] OR nocturnal apnea*[tiab] OR sleep hypopnea*[tiab] OR sleep apnoea*[tiab] OR nocturnal apnoea*[tiab] OR sleep hypopnoea*[tiab] OR sleep-disordered breathing[tiab] OR insomnia*[tiab] OR parasomnia*[tiab] OR Nocturnal Dystonia*[tiab] OR Sleep paralys*[tiab] OR Night Terror*[tiab] OR Pavor Nocturnus[tiab] OR Somnambulis*[tiab] OR Sleepwalking[tiab] OR Sleep walking[tiab] OR Nocturnal Wandering*[tiab] OR Jactatio Capitis Nocturna[tiab] OR Nocturnal Leg Cramp*[tiab] OR Sleep talking[tiab] OR Sleep start*[tiab] OR ((periodic[tiab] OR repetitive[tiab]) AND movement*[tiab] AND sleep*[tiab]) OR plms[tiab] OR plmd[tiab]	945,613
#1	"Sleep Bruxism"[Mesh] OR (("Sleep"[Mesh] OR sleep[tiab] OR nocturnal[tiab] OR night[tiab]) AND ("Bruxism"[Mesh] OR brux*[tiab] OR grind*[tiab] OR clench*[tiab])) OR tooth tapping[tiab]	1,349

Embase

Embase could be reached at https://www.embase.com. The database is operated by Elsevier, an information and analytics company, based in the Netherlands. The query below was used to deliver the search in Embase. The reported numbers of items found were the results of the query on 15 May 2020.

Search	Query	Items found
#4	#3 NOT (('adolescent'/exp OR 'child'/exp OR adolescent*:ab,ti,kw OR child*:ab,ti,kw OR schoolchild*:ab,ti,kw OR infant*:ab,ti,kw OR girl*:ab,ti,kw OR boy*:ab,ti,kw OR teen:ab,ti,kw OR teens:ab,ti,kw OR teenager*:ab,ti,kw OR youth*:ab,ti,kw OR pediatr*:ab,ti,kw OR paediatr*:ab,ti,kw OR puber*:ab,ti,kw) NOT ('adult'/exp OR adult*:ab,ti,kw OR man:ab,ti,kw OR men:ab,ti,kw OR woman:ab,ti,kw OR women:ab,ti,kw))	1,030
#3	#1 AND #2	1,353
#2	'sleep disorder'/exp OR 'parkinsonism'/exp OR 'parkinson disease'/exp OR 'epilepsy'/exp OR 'gastroesophageal reflux'/exp OR 'stomach'/exp OR 'comorbidity'/exp OR 'multiple chronic conditions'/exp OR comorbidity:ab,ti,kw OR multimorbidity:ab,ti,kw OR 'body rocking'/exp OR 'body rocking':ab,ti,kw OR stomach*:ab,ti,kw OR 'gastroesophageal refl*':ab,ti,kw OR 'gastro-esophageal refl*':ab,ti,kw OR 'gastrooesophageal refl*':ab,ti,kw OR 'gastro-oesophageal refl*':ab,ti,kw OR gastric*:ab,ti,kw OR GERD:ab,ti,kw OR 'laryngopharyngeal refl*':ab,ti,kw OR 'laryngo-pharyngeal refl*':ab,ti,kw OR parkinson*:ab,ti,kw OR epilep*:ab,ti,kw OR (('sleep'/exp OR sleep*:ab,ti,kw OR wake:ab,ti,kw OR awake:ab,ti,kw OR waking:ab,ti,kw OR awaking:ab,ti,kw OR somnolence*:ab,ti,kw OR somnolescent:ab,ti,kw OR REM:ab,ti,kw OR 'Circadian rhythm':ab,ti,kw) AND (disorder*:ab,ti,kw OR disturb*:ab,ti,kw OR problem*:ab,ti,kw OR difficult*:ab,ti,kw OR paroxysmal:ab,ti,kw)) OR 'Sleep Deprivation*':ab,ti,kw OR 'Sleep Fragmentation*':ab,ti,kw OR 'Insufficient Sleep Syndrome*':ab,ti,kw OR 'Nyctohemeral Rhythm*':ab,ti,kw OR 'Sleep Phase Syndrome*':ab,ti,kw OR 'jet lag*':ab,ti,kw OR hypersomnolence*:ab,ti,kw OR 'hyper-somnolence*':ab,ti,kw OR hypersomnia*:ab,ti,kw OR 'hyper-somnia*':ab,ti,kw OR 'Kleine-Levin':ab,ti,kw OR narcoleps*:ab,ti,kw OR cataplex*:ab,ti,kw OR Gelineau*:ab,ti,kw OR 'nocturnal myoclonus syndrome*':ab,ti,kw OR 'Periodic Leg Movement*':ab,ti,kw OR 'Periodic Limb Movement*':ab,ti,kw OR (('Leg Movement*':ab,ti,kw OR 'Limb Movement*':ab,ti,kw) AND sleep*:ab,ti,kw) OR 'restless leg*':ab,ti,kw OR 'Willis Ekbom':ab,ti,kw OR 'Wittmaack Ekbom':ab,ti,kw OR 'sleep apnea*':ab,ti,kw OR 'nocturnal apnea*':ab,ti,kw OR 'sleep hypopnea*':ab,ti,kw OR 'sleep apnoea*':ab,ti,kw OR 'nocturnal apnoea*':ab,ti,kw OR 'sleep hypopnoea*':ab,ti,kw OR 'sleep-disordered breathing':ab,ti,kw OR insomnia*:ab,ti,kw OR parasomnia*:ab,ti,kw OR 'Nocturnal Dystonia*':ab,ti,kw OR 'Sleep paralys*':ab,ti,kw OR 'Night Terror*':ab,ti,kw OR 'Pavor Nocturnus':ab,ti,kw OR Somnambulis*:ab,ti,kw OR Sleepwalking:ab,ti,kw OR 'Sleep walking':ab,ti,kw OR 'Nocturnal Wandering*':ab,ti,kw OR 'Jactatio Capitis Nocturna':ab,ti,kw OR 'Nocturnal Leg Cramp*':ab,ti,kw OR 'Sleep talking':ab,ti,kw OR 'Sleep start*':ab,ti,kw OR ((periodic:ab,ti,kw OR repetitive:ab,ti,kw) AND movement*:ab,ti,kw AND sleep*:ab,ti,kw) OR plms:ab,ti,kw OR plmd:ab,ti,kw	1,588,592
#1	'sleep bruxism'/exp OR (('sleep'/exp OR sleep:ab,ti,kw OR nocturnal:ab,ti,kw OR night:ab,ti,kw) AND ('bruxism'/exp OR brux*:ab,ti,kw OR grind*:ab,ti,kw OR clench*:ab,ti,kw)) OR 'tooth tapping':ab,ti,kw	1,970

Cochrane Library

Cochrane Library could be reached at https://www.cochranelibrary.com/advanced-search. The database is operated by John Wiley & Sons, a multinational publishing company, headquartered in New Jersey, USA. The query below was used to deliver the search in Cochrane Library. The reported numbers of items found were the results of the query on 15 May 2020.

Search	Query	Items found
#4	#3 not ((adolescen*:ab,ti,kw or child*:ab,ti,kw or schoolchild*:ab,ti,kw or infant*:ab,ti,kw or girl*:ab,ti,kw or boy*:ab,ti,kw or teen:ab,ti,kw or teens:ab,ti,kw or teenager*:ab,ti,kw or youth*:ab,ti,kw or pediatr*:ab,ti,kw or paediatr*:ab,ti,kw or puber*:ab,ti,kw) not (adult*:ab,ti,kw or man:ab,ti,kw or men:ab,ti,kw or woman:ab,ti,kw or women:ab,ti,kw))	66
#3	#1 and #2	80
#2	comorbidity:ab,ti,kw OR multimorbidity:ab,ti,kw OR (body NEXT rocking):ab,ti,kw OR stomach*:ab,ti,kw OR (gastroesophageal NEXT refl*):ab,ti,kw OR (gastro NEXT esophageal NEXT refl*):ab,ti,kw OR (gastrooesophageal NEXT refl*):ab,ti,kw OR (gastro NEXT oesophageal NEXT refl*):ab,ti,kw OR gastric*:ab,ti,kw OR GERD:ab,ti,kw OR (laryngopharyngeal NEXT refl*):ab,ti,kw OR (laryngo NEXT pharyngeal NEXT refl*):ab,ti,kw OR parkinson*:ab,ti,kw OR epilep*:ab,ti,kw OR ((sleep*:ab,ti,kw or wake:ab,ti,kw or awake:ab,ti,kw or waking:ab,ti,kw or awaking:ab,ti,kw or somnolence*:ab,ti,kw or somnolescent:ab,ti,kw or REM:ab,ti,kw or (Circadian NEXT rhythm):ab,ti,kw) and (disorder*:ab,ti,kw or disturb*:ab,ti,kw or problem*:ab,ti,kw or difficult*:ab,ti,kw or paroxysmal:ab,ti,kw)) or (Sleep NEXT Deprivation*):ab,ti,kw or (Sleep NEXT Fragmentation*):ab,ti,kw or (Insufficient NEXT Sleep NEXT Syndrome*):ab,ti,kw or (Nyctohemeral NEXT Rhythm*):ab,ti,kw or (Sleep NEXT Phase NEXT Syndrome*):ab,ti,kw or (jet NEXT lag*):ab,ti,kw or hypersomnolence*:ab,ti,kw or (hyper NEXT somnolence*):ab,ti,kw or hypersomnia*:ab,ti,kw or (hyper NEXT somnia*):ab,ti,kw or (Kleine NEXT Levin):ab,ti,kw or narcoleps*:ab,ti,kw or cataplex*:ab,ti,kw or Gelineau*:ab,ti,kw or (nocturnal NEXT myoclonus NEXT syndrome*):ab,ti,kw or (Periodic NEXT Leg NEXT Movement*):ab,ti,kw or (Periodic NEXT Limb NEXT Movement*):ab,ti,kw or (((Leg NEXT Movement*):ab,ti,kw or (Limb NEXT Movement*):ab,ti,kw) and sleep*:ab,ti,kw) or (restless NEXT leg*):ab,ti,kw or (Willis NEXT Ekbom):ab,ti,kw or (Wittmaack NEXT Ekbom):ab,ti,kw or (sleep NEXT apnea*):ab,ti,kw or (nocturnal NEXT apnea*):ab,ti,kw or (sleep NEXT hypopnea*):ab,ti,kw or (sleep NEXT apnoea*):ab,ti,kw or (nocturnal NEXT apnoea*):ab,ti,kw or (sleep NEXT hypopnoea*):ab,ti,kw or (sleep NEXT disordered NEXT breathing):ab,ti,kw or insomnia*:ab,ti,kw or parasomnia*:ab,ti,kw or (Nocturnal NEXT Dystonia*):ab,ti,kw or (Sleep NEXT paralys*):ab,ti,kw or (Night NEXT Terror*):ab,ti,kw or (Pavor NEXT Nocturnus):ab,ti,kw or Somnambulis*:ab,ti,kw or Sleepwalking:ab,ti,kw or (Sleep NEXT walking):ab,ti,kw or (Nocturnal NEXT Wandering*):ab,ti,kw or (Jactatio NEXT Capitis NEXT Nocturna):ab,ti,kw or (Nocturnal NEXT Leg NEXT Cramp*):ab,ti,kw or (Sleep NEXT talking):ab,ti,kw or (Sleep NEXT start*):ab,ti,kw or ((periodic:ab,ti,kw or repetitive:ab,ti,kw) and movement*:ab,ti,kw and sleep*:ab,ti,kw) or plms:ab,ti,kw or plmd:ab,ti,kw	95,365
#1	((sleep:ab,ti,kw or nocturnal:ab,ti,kw or night:ab,ti,kw) and (brux*:ab,ti,kw or grind*:ab,ti,kw or clench*:ab,ti,kw)) OR (tooth NEXT tapping):ab,ti,kw	175

Web of Science

Web of Science could be reached at https://www.webofknowledge.com/. The database is operated by Clarivate Analytics, headquartered in London, UK. The query below was used to deliver the search in Web of Science. The reported numbers of items found were the results of the query on 15 May 2020.

Search	Query	Items found
#4	#3 NOT TS= ((adolescen* OR child* OR schoolchild* OR infant* OR girl* OR boy* OR "teen" OR "teens" OR teenager* OR youth* OR pediatr* OR paediatr* OR puber*) NOT (adult* OR "man" OR "men" OR "woman" OR "women"))	714
#3	#1 AND #2	910
#2	TS=("comorbidity" OR "multimorbidity" OR "body rocking" OR stomach* OR "gastroesophageal refl*" OR "gastro-esophageal refl*" OR "gastrooesophageal refl*" OR "gastro-oesophageal refl*" OR gastric* OR "GERD" OR "laryngopharyngeal refl*" OR "laryngo-pharyngeal refl*" OR parkinson* OR epilep* OR ((sleep* OR "wake" OR "awake" OR "waking" OR "awaking" OR somnolence* OR "somnolescent" OR "REM" OR "Circadian rhythm") AND (disorder* OR disturb* OR problem* OR difficult* OR "paroxysmal")) OR "Sleep Deprivation*" OR "Sleep Fragmentation*" OR "Insufficient Sleep Syndrome*" OR "Nyctohemeral Rhythm*" OR "Sleep Phase Syndrome*" OR "jet lag*" OR hypersomnolence* OR "hyper-somnolence*" OR hypersomnia* OR "hyper-somnia*" OR "Kleine-Levin" OR narcoleps* OR cataplex* OR Gelineau* OR "nocturnal myoclonus syndrome*" OR "Periodic Leg Movement*" OR "Periodic Limb Movement*" OR (("Leg Movement*" OR "Limb Movement*") AND sleep*) OR "restless leg*" OR "Willis Ekbom" OR "Wittmaack Ekbom" OR "sleep apnea*" OR "nocturnal apnea*" OR "sleep hypopnea*" OR "sleep apnoea*" OR "nocturnal apnoea*" OR "sleep hypopnoea*" OR "sleep-disordered breathing" OR insomnia* OR parasomnia* OR "Nocturnal Dystonia*" OR "Sleep paralys*" OR "Night Terror*" OR "Pavor Nocturnus" OR Somnambulis* OR "Sleepwalking" OR "Sleep walking" OR "Nocturnal Wandering*" OR "Jactatio Capitis Nocturna" OR "Nocturnal Leg Cramp*" OR "Sleep talking" OR "Sleep start*" OR (("periodic" OR "repetitive") AND movement* AND sleep*) OR "plms" OR "plmd")	946,339
#1	TS=(((("sleep" OR "nocturnal" OR "night") AND (brux* OR grind* OR clench*)) OR "tooth tapping")	1,428

Supplement 3.B Quality assessment tool

The Risk of Bias Assessment tool for Non-randomized Studies (RoBANS)

1. The selection of participants Selection biases caused by the inadequate selection of participants	
Criteria for judgments of a 'Low risk' of bias	Sample size justified or large sample size (using questionnaire no less than 100; using PSG no less than 30) **Cohort study, Non-randomized controlled trial** Intervention (exposure) and control groups are the same population group (identical institution and period), and the absence of outcomes among the study participants was confirmed at the starting point of the study. **Case-control study** The case and control groups were selected from comparable population groups. The case group was clearly defined, and it was clearly demonstrated that the control group is not the patient group. **Before-after study** The study participants were consecutively recruited, and the data were collected prospectively.
Criteria for judgments of a 'High risk' of bias	Any one of the following conditions: No sample size calculation or small sample size (using questionnaire less than 100; using PSG less than 30); **Cohort study, Non-randomized controlled trial** ○ The intervention (exposure) and control groups were selected from different population groups (e.g., the intervention group differs from the control group with respect to study period or study center, or historical control groups were used). ○ The presence of outcomes among the study participants was not confirmed at the starting point of the study. **Case-control study** ○The case and control groups are not the comparable population groups. ○ The patient definitions were generated by self-reported or merged data. ○ It was not clearly confirmed that the control group excluded patients. **Before-after study** ○ The control group was not recruited consecutively. ○ Retrospective data collection was performed.
Criteria for judgments of an 'Unclear risk' of bias	It is uncertain whether the selection of participants resulted in a “high risk” or a “low risk” of bias

2. Confounding variables Selection biases caused by the inadequate confirmation and consideration of confounding variables

Criteria for judgments of a “Low risk” of bias	Any one of the following conditions: **Non-randomized studies (except for before-after studies)** ○ The major confounding variables were adequately confirmed and considered during the design phase (e.g., through matching, participation restriction, or other methods). ○ The major confounding variables were adequately confirmed and adjusted for during the analysis phase (e.g., through stratification, propensity score approaches, statistical adjustments, or other methods). **Before-after study** ○ A natural progression and learning effect* can be excluded during the consideration of diseases and interventions.
Criteria for judgments of a 'High risk' of bias	Any one of the following conditions: **Cohort study, Non-randomized controlled trial** ○ The intervention (exposure) and control groups were selected from different population groups (e.g., the intervention group differs from the control group with respect to study period or study center, or historical control groups were used). ○ The presence of outcomes among the study participants was not confirmed at the starting point of the study. **Case-control study** ○The case and control groups are not the comparable population groups. ○ The patient definitions were generated by self-reported or merged data. ○ It was not clearly confirmed that the control group excluded patients. **Before-after study** ○ The control group was not recruited consecutively. ○ Retrospective data collection was performed.
Criteria for judgments of an 'Unclear risk' of bias	It is uncertain whether the confounding variables resulted in a “high risk” or a “low risk” of bias
*This effect occurs if past experience improves future execution skills	

3. Measurement of exposure Performance biases caused by inadequate measurements of exposure	
Criteria for judgments of a “Low risk” of bias	If exposure data were described using at least one of the methods that are listed below: ○ Data were obtained from trustworthy sources, such as medical records. ○ Data were obtained from structured interviews. ○ Validated or widely accepted questionnaires or PSG were used.
Criteria for judgments of a “High risk” of bias	Any one of the following conditions: ○ Data were obtained through self-reported methods ○ Invalidated questionnaires were used ○ A clear case of interviewer bias* ○ A clear case of recall bias**
Criteria for judgments of	It is uncertain whether the exposure measurement resulted in a “high risk” or a “low

an “Unclear risk” of bias	risk” of bias

* “Interviewer bias” describes a situation in which the characteristics of the investigators cause the study data to be standardized in a manner that affects the study results. This phenomenon can be reduced through the training of investigators.

** “Recall bias” describes a situation in which the respondents' degree of recall can affect the study results.

4. Blinding of outcome assessments Detection biases caused by the inadequate blinding of outcome assessments	
Criteria for judgments of a “Low risk” of bias	Any one of the following conditions: ○ The outcome assessments were blinded ○ Although blinding was not present, its absence was judged to have no effect on the outcome measurements.
Criteria for judgments of a “High risk” of bias	Blinding was not performed or incomplete, and this lack of appropriate blinding appears likely to have affected the outcome measurements.
Criteria for judgments of an 'Unclear risk' of bias	It is uncertain whether the blinding of the outcome assessments resulted in a “high risk” or a “low risk” of bias

5. Incomplete outcome data Attrition biases caused by the inadequate handling of incomplete outcome data	
Criteria for judgments of a “Low risk” of bias	Any one of the following conditions: **Non-randomized studies (except for before-after studies)** ○ There are no missing data. ○ The causes of any missing data are considered to be relevant to the study outcomes (i.e., censoring does not create a bias in the survival data) ○ The quantity of missing data was a product of similar developments in both the intervention (exposure) and the control groups, and the causes of these developments are similar. **Before-after study** Information about the number of participants before and after the study exists, and the baseline did not differ with respect to completed and failed study participants.
Criteria for judgments of a “High risk” of bias	Any one of the following conditions: **Non-randomized studies (except for before-after studies)** The missing data could affect the study outcome. These effects may be attributed to the differences in the missing data between the intervention (exposure) group and the control group, or the effects may be caused by the absence of important measurements. **Before-after study** Differences exist with respect to the baseline for successful and failed participants.
Criteria for judgments of an 'Unclear risk' of bias	It is uncertain whether the incomplete outcome data resulted in a “high risk” or a “low risk” of bias

6. Selective outcome reporting Reporting biases caused by the selective reporting of outcomes	
Criteria for judgments of a 'Low risk' of bias	Any one of the following conditions: ○ The experimental protocol is available, and the pre-defined primary/secondary outcomes were described as planned. ○ All of the expected outcomes were included in the study descriptions (even in the absence of the experimental protocols).
Criteria for judgments of a 'High risk' of bias	Any one of the following conditions: ○ The pre-defined primary outcomes were not fully reported. ○ The outcomes were not reported in accordance with the previously defined standards. ○ Primary outcomes that were not pre-specified in the study existed (except for outcomes with clear explanations, such as unexpected adverse effects). ○ The existence of incomplete reporting regarding the primary outcome of interest. ○ The absence of reports on important outcomes that would be expected to be reported for studies in related fields.
Criteria for judgments of an 'Unclear risk' of bias	It is uncertain whether the selective outcome reporting resulted in a “high risk” or a “low risk” of bias. *

* Most of the examined studies were classified into this category.

Chapter 4

Sleep bruxism is highly prevalent in adults with obstructive sleep apnea: a large-scale polysomnographic study

Deshui Li, Boyuan Kuang, Frank Lobbezoo, Nico de Vries, Antonius A.J. Hilgevoord, Ghizlane Aarab

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Abstract

Study Objectives: To determine the prevalence and risk factors of sleep bruxism (SB); and to investigate the relationships between SB episodes, arousals, and respiratory events in adults with obstructive sleep apnea (OSA).

Methods: This prospective study included 914 adults with OSA (305 females, 609 males; age = 53 years [interquartile range = 17]; apnea-hypopnea index (AHI) = 13.9 events/hour [interquartile range = 21]). The diagnosis of SB was made when rhythmic masticatory muscle activity (RMMA) index was at least 2 episodes/hour sleep based on a full polysomnographic recording. Binary logistic regression was performed to identify risk factors for SB. Network analysis was performed to determine the relations between RMMA, respiratory event, sleep arousal, and other factors. Further, the percentage of RMMA time-related to arousal was calculated.

Results: The prevalence of SB in adults with OSA was 49.7%. Male gender, lower body mass index (BMI), and higher percentage of N1 increased the odds of having SB (odds ratios = 1.425, 0.951, 1.032, respectively, all $P < 0.05$). Network analysis showed that there were no direct associations between RMMA and AHI, nor between RMMA and arousal, although 85.7% of RMMA were time-related to arousals.

Conclusions: Nearly half of adults with OSA have comorbid SB. Male gender, lower BMI, higher percentage of light sleep increase the risk of having SB. Although RMMAs do not directly correlate with respiratory events and arousals, most RMMAs are time-related to arousals in adults with OSA.

Keywords: Sleep bruxism; Obstructive sleep apnea; Polysomnography; Prevalence; Risk factor; Arousal; Respiratory event

Introduction

Obstructive Sleep Apnea (OSA) is a sleep-related breathing disorder characterized by complete (apnea) or partial (hypopnea) collapse of the upper airway, which commonly leads to sleep arousal and oxygen desaturation.[1] OSA patients often complain of excessive daytime sleepiness, morning headache, and snoring.[1] Of the general population, 9%–38% experience OSA.[2] Male gender, advancing age, and overweight or obesity are risk factors for OSA.[2] Conversely, OSA can be an independent risk factor for many other medical conditions, such as diabetes, hypertension, stroke, depression, and sleep bruxism (SB).[3,4]

SB is characterized by rhythmic masticatory muscle activity (RMMA) during sleep, which manifests as clenching or grinding of the teeth and/or bracing or thrusting of the mandible.[5] In the general population, the prevalence of SB is approximately 13%.[6] The consequences of SB vary from person to person, and also from negative to positive. The negative consequences include tooth wear or fracture, orofacial pain, temporal mandibular disorders, and failure of dental prostheses and oral implants.[7,8] The suggested positive effects include clearing esophageal acid and lubricating the upper airway by promoting saliva secretion[9] and reinforcing the upper airway after respiratory events in OSA.[10]

Mandibular advancement appliances are considered a primary treatment option in mild to moderate OSA.[11] As a consequence of their SB, however, adults with OSA may break their mandibular advancement appliances during sleep and/or develop temporomandibular disorders.[12,13] Therefore, it is clinically relevant to determine the prevalence and risk factors of SB in adults with OSA. The prevalence of SB in adult patients with OSA is probably much higher than that in the general population.[14] However, since previous studies used different methods for diagnosing SB (e.g., self-report, clinical inspection, and polysomnography [PSG]) and included limited study samples, the occurrence rate of SB in the OSA population ranges widely, viz., from 26% to 100%.[15–18] Besides, age, gender, BMI, sleep stages, arousals, respiratory factors (e.g., oxygen desaturation), and some diseases or disorders (e.g., insomnia, periodic leg movement during sleep) have all been reported to be associated with SB in different studies.[14,19–22] However, while only a few previous studies took all these factors into consideration in a single study, the results of those previous studies were inconsistent. Tan et al. showed that respiratory arousal increases the odds of having SB, while apnea-hypopnea

index (AHI) and oxygen desaturation index had no effect on SB in 147 adults with OSA.[16] However, the diagnosis of SB in this study was made when the RMMA index was more than 4 episodes/hour. Thereof, low frequency SB (RMMA ≥ 2 episodes/hour) was included in the control group,[16] which makes this study difficult to interpret. In addition, Martynowicz et al. showed that higher AHI, male gender, and diabetes increased the RMMA index in a subgroup with AHI < 30, while sleep arousal did not have any effect on the RMMA index.[18] However, this study was performed in 110 adults with possible OSA, which included cases without OSA. Therefore, a large-scale PSG study that includes all potential risk factors is needed to determine the prevalence and risk factors of SB in adults with OSA. Based on previous findings, we hypothesized that SB is highly prevalent in adults with OSA, and that aging, obesity, and arousal will show a significant association with SB.

In addition, although OSA is considered a risk for SB, the cause-and-effect relationship between them is still inconclusive. Currently, the genesis of RMMA may involve, amongst others, several physiological factors that are related to OSA, such as sleep arousals and respiratory events.[7] Several studies reported that most RMMAs occur shortly after respiratory events in OSA, suggesting that SB may be secondary to respiratory events and play a protective role against OSA by restoring the upper airway.[4,23] However, other studies indicated that masticatory muscle activities after respiratory events are non-specific orofacial activities and not RMMA.[24] Further, some studies reported that RMMAs occurring after respiratory events are more like motor responses to respiratory arousals rather than to the preceding respiratory events per se.[25,26] Nonetheless, other studies showed that arousal has only a weak association with RMMA in OSA, and that it only acts as a permissive window for the occurrence of RMMA.[16,24,27] Considering all this evidence, the associations between RMMAs, arousals, and respiratory events in OSA are still inconclusive and need further studies to be clarified. Based on previous findings, we hypothesized that RMMA is not correlated with respiratory events, but rather with sleep arousals. Additionally, as mentioned above, the associations between RMMA, respiratory events, and arousals are interactive, thus the relationship between them maybe direct or indirect. Therefore, a novel approach, viz., network analysis would be suitable to show all associations between included factors and to identify bridge factors or common factors between them.

In short, this large-scale PSG study aimed: 1) to determine the prevalence and risk factors of SB; and 2) to investigate the relationships between RMMAs, arousals, and respiratory events in adults with OSA.

Methods

This is a prospective cross-sectional study. The protocol was approved by the institutional Medical Ethics Committee of the OLVG West, Amsterdam (WO 16-577). This study has also been registered on https://trialsearch.who.int (NL8516).

Participants

PSG recordings and profiles (see below) of all patients who were referred to the Department of Clinical Neurophysiology, OLVG West, Amsterdam, the Netherlands, between April 2017 to July 2018 were reviewed. Patients who met the following criteria were included in this study: 1) age ≥ 18 years; 2) diagnosed with OSA according to patients' profiles; and 3) AHI ≥ 5 events per hour of sleep. Exclusion criteria were: 1) total sleep time ≤ four hours;[28] 2) continuous artifacts or missing data on electroencephalography, electromyography (EMG), or respiratory channels (e.g., airflow, oxygen saturation) of PSG recordings; and/or 3) patients with OSA treatment in situ during PSG.

Patients' profiles

Patients' profiles, including their age, gender, primary diagnosis, secondary diagnoses, comorbidities, medication, and previous treatment history, were collected by one of us (A.H.) and colleagues at the Department of Clinical Neurophysiology.

Polysomnographic recordings

A potable PSG system (SOMNOscreen Plus, SOMNOmedics GmbH, Randersacker, Germany) was used to perform a full-night sleep recording. The following channels were recorded: electroencephalography (F4:C4, C4:O2, F3:C3, C3:O1), electrooculogram (E2:M1, E1:M2), electrocardiogram, bilateral masseter muscle EMG, anterior tibialis EMG, pressure airflow, snoring, abdominal and thoracic respiratory effort, oxygen saturation, heart rhythm, plethysmography, and sleep position.

Polysomnographic scoring

Prior to scoring, all PSG recordings were anonymized by removing patients' general information (name, gender, date of birth, and identity number). Subsequently, they were renamed by a series of numbers by a sleep technologist at the Department of Clinical Neurophysiology. Afterward, the PSG scoring was performed offline using DOMINO software (SOMNOmedics GmbH, Randersacker, Germany). Sleep stages and respiratory events (e.g., apnea, hypopnea) were scored manually by certified PSG technicians according to the American Academy of Sleep Medicine (AASM) scoring criteria.[29] Sleep arousals were analyzed according to the AASM scoring manual and were further classified as respiratory arousal and non-respiratory arousal by two of us (D.L. and B.K.).[29,30] Arousals occurring at the termination of respiratory events (i.e., apnea, hypopnea) were defined as respiratory arousal, while arousals without preceding respiratory events were defined as non-respiratory arousal.

The EMG signals were filtered between 10 and 100 Hz.[29] A notch filter of 50 Hz was used to remove interference from nearby electrical sources. Also, the electrocardiogram elimination technique was applied to remove electrocardiogram contamination from EMG signals. RMMAs were scored by two of us (D.L. and B.K.) according to previously reported criteria.[31] Each EMG burst had a mean amplitude at least two times higher than the baseline EMG amplitude on bilateral masseter EMG traces. EMG bursts occurring within an interval shorter than 3 seconds were defined as a single EMG episode. RMMAs were classified into three subtypes: phasic RMMA, tonic RMMA, and mixed RMMA (phasic RMMA: three or more continuous EMG bursts lasting 0.25–2s; tonic RMMA: each EMG burst was longer than 2s; and mixed RMMA: both phasic and tonic EMG patterns were observed within a single EMG episode). In addition, RMMAs were considered to be related to arousals (respiratory arousal or non-respiratory arousal) when they occurred within 5 seconds of arousals.[26]

Statistical analysis

Before the start of masticatory muscle activity scoring, 30 PSG recordings were randomly selected to assess inter-scorer reliability. The inter-scorer reliability was tested by an average measure, absolute agreement, two-way mixed-effects model.

The diagnosis of SB was based on an RMMA index of at least 2 episodes per hour of sleep.[31] When the RMMA index was at least 4 episodes/hour, the individuals were diagnosed with severe SB. The normality of quantitative variables was tested by the Shapiro-Wilk test. For normally distributed variables, data are presented as mean with standard deviation. For non-normally distributed variables, data are presented in quartiles (25%|50% (median)|75%). According to the presence or absence of SB, the entire sample was divided into an SB group and a non-SB group. The comparison of variables between the SB group and the non-SB group were analyzed by independent samples t-test, Mann-Whitney U test, or $\chi 2$.

For the first aim, the prevalence of SB was expressed as the percentage of positive SB of the total sample. A binary logistic regression analysis, with SB (positive or negative) as the binary dependent variable, and with age, gender, BMI, sleep- and respiratory-related polysomnographic variables (i.e., N1, N2, supine position, AHI, respiratory arousal, non-respiratory arousal) as the independent variables was performed to identify the risk factors for SB in individuals with OSA. Although several OSA comorbidities have been reported to be possibly related to SB, only a few of them, e.g., insomnia and periodic leg movement during sleep, have been confirmed objectively by PSG studies. Moreover, the case numbers of insomnia and periodical leg movement during sleep in this study were quite small (4 and 2, respectively). Therefore, OSA comorbidities were excluded from the regression analysis.

For the second aim, the relationship between RMMAs, sleep arousals, respiratory events (e.g., AHI) and other factors were analyzed by a network analysis. The network analysis was performed using the Mixed Graphical Model of the R-package 'bootnet' (version 1.5) with conditional dependence relationships and network regularization (least absolute shrinkage and selection operator). The estimated relationships represent the unique association between two variables after controlling for other variables. R-package "qgraph" (version = 1.9) was used to visualize the network; all variables were presented as nodes, while the correlations between variables were displayed as edges. Finally, the robustness of the estimated network was analyzed by the bootstrapping method to investigate the network's accuracy. Bootstrapping would repeatedly estimate a model from simulated data (bootstrap = 1000 samples) and show 95% of bootstrapped confidence intervals. If the 95% confidence interval of an edge does not cover zero, this edge is strong enough to present in the network. The details of the methodology concerning the network analysis has been reported in a

previous publication of our research group.[32] The network analysis was performed in R (version 4.1.2, Vienna University of Economics and Business, Vienna, Austria).

In addition, the Wilcoxon signed-rank test was used to analyze the difference between the percentage of RMMA related to sleep arousal and that of RMMA unrelated to sleep arousal, and between the percentages of RMMA related to respiratory arousal and that of RMMA related to non-respiratory arousal. Statistical analyses, except for the network analysis, were performed using SPSS Statistics (version 26, SPSS Inc, Chicago, IL, USA); statistical significance was determined at $P < 0.05$.

Results

Participants

We reviewed 2639 patients who were referred to the sleep laboratory. Based on the inclusion and exclusion criteria, 1725 of them were excluded for various reasons. The screening of patients is shown in Figure 4.1. Finally, 914 patients (305 females and 609 males) were included in this study. Among them, 432 (47.3%) were diagnosed with mild OSA, 252 (27.6%) with moderate OSA, and 230 (25.2%) with severe OSA. The median age of the included participants was 53 years, with an interquartile range of 17 years. The median BMI was 29.1 kg/m^2, with an interquartile range of 6.9.

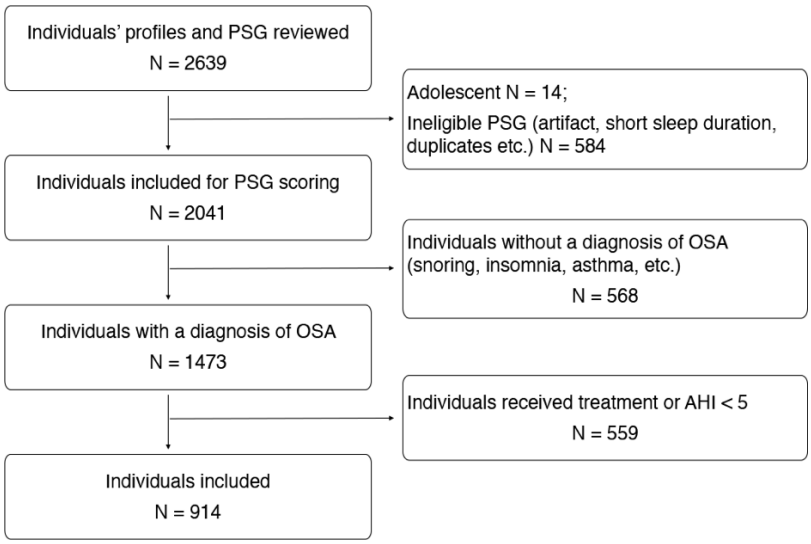

Figure 4.1 Flow diagram of participants screening. PSG: polysomnography; OSA: obstructive sleep apnea; AHI: apnea-hypopnea index

Table 4.1 Descriptive variables in individuals with obstructive sleep apnea without and with sleep bruxism [a]

		In total N = 914	Non-SB group N = 460	SB group N = 454	Test statistics b	P
Age, years		44.0|53.0|61.0	44.0|53.0|61.0	43.0|53.0|61.0	Z = -1.177	0.239
Gender	Female	305	179	126	$\chi 2$ =12.798	0.000*
	Male	609	281	328		
BMI, kg/m2		25.8|29.1|32.7	26.5|29.7|33.6	25.4|28.4|31.6	Z = -4.019	0.000*
Total sleep time, h		6.2|7.0|7.8	6.2|7.0|7.8	6.3|7.1|7.8	Z = -0.555	0.579
Sleep efficiency, %		82.2|90.1|94.8	82.0|90.1|94.9	82.3|90.0|94.5	Z = -0.267	0.790
N1, %		2.6|4.4|7.2	2.7|4.1|6.8	2.5|4.8|7.8	Z = -1.559	0.119
N2, %		45.2 ± 10.6	45.2 ± 10.9	45.1 ± 10.4	T = 0.202	0.840
N3, %		12.8|18.1|23.7	12.5|18.3|24.1	13.2|17.9|17.9	Z = -0.588	0.557
REM, %		17.8 ± 6.5	17.7 ± 6.4	17.9 ± 6.5	T = -0.339	0.735
Supine, h		1.0|2.3|3.8	1.0|2.4|3.8	1.0|2.3|3.6	Z = -0.198	0.843
Non-supine, h		3.1|4.5|5.7	3.0|4.5|5.7	3.1|4.6|5.6	Z = -0.408	0.683
Total arousal, N/h		5.8|10.3|19.0	4.9|10.2|18.6	6.5|10.4|10.4	Z = -1.681	0.093
nRAr, N/h		3.0|5.6|9.7	2.8|5.7|9.7	3.3|5.6|5.6	Z = -0.484	0.628
RAr, N/h		1.8|3.9|8.6	1.5|3.5|7.9	2.1|4.1|4.1	Z = -2.396	0.017*
AHI, N/h		9.0|15.9|30.4	9.0|15.1|29.8	9.3|16.7|16.7	Z = -0.451	0.652
ODI, N/h		12.8|20.7|34.9	12.5|20.4|36.6	13.1|21.0|21.0	Z = -0.128	0.898
RMMA, N/h		0.8|2.0|4.0	0.3|0.8|1.3	2.9|4.0|4.0	Z = -26.171	0.000*

[a] Data are presented as mean ± SD for normally distributed variables and 25%|median|75% for non-normally distributed variables; [b] Independent samples t-test for normally distributed data, Mann-Whitney U test for non-normally distributed data, chi-square test for categorical data; * Statistical significant at P < .05; SB: sleep bruxism; BMI: body mass index; N1-N3: non-rapid eye movement stage 1-3; REM: rapid eye movement stage; RAr: respiratory arousal; nRAr: non-respiratory arousal; AHI: apnea-hypopnea index; ODI: oxygen desaturation index; RMMA: rhythmic masticatory muscle activity.

Table 4.1 shows the descriptive information of the total sample, the SB group and the non-SB group. The SB group showed a significantly lower BMI than the non-SB group (P <0.001). Besides, SB was more prevalent in males than in females ($P < 0.001$). In addition, there was no significant difference in age between the two groups (P > 0.05). Similarly, the AHI and oxygen desaturation index did not show any significant between-group differences. In terms

of sleep arousal, the SB group had a significantly higher respiratory arousal index than the non-SB group (P = 0.017), while no such difference was found for the non-respiratory arousal index (P = 0.628) and for the total arousal index (P = 0.093). Additionally, total sleep time, sleep efficiency, sleep position duration, and percentages of sleep stages were similar between the two groups (all P > 0.05).

Prevalence and risk factors of SB

An excellent inter-rater agreement was achieved for RMMA scoring (0.925). Of the 914 adults with OSA, 454 (49.7%) were diagnosed with SB, and 223 (24.4%) were diagnosed with severe SB.

Table 4.2 shows the outcomes of the binary logistic regression. Compared with females, males had a significantly higher risk of having SB (OR = 1.425, *P* = 0.005). Lower BMI (OR = 0.951, *P* = 0.000) and higher percentage of N1 (OR = 1.032, *P* = 0.042) significantly increased the odds of having SB. There were no significant associations between SB and age, AHI, respiratory arousal, non-respiratory arousal, and the duration of supine position in the OSA population.

Table 4.2 Binary logistic regression model of factors related to sleep bruxism in adults with OSA

Predictors		***β*** **(SE)**	OR	95% CI for OR	P values
Age		-0.009 (0.006)	0.991	0.980–1.002	0.113
Gender	Female	Reference	–	–	–
	Male	0.354 (0.153)	1.425	1.055–1.924	0.021*
BMI		-0.050 (0.013)	0.951	0.926–0.976	0.000*
N1%		0.032 (0.016)	1.032	1.001–1.064	0.042*
N2%		-0.005 (0.007)	0.995	0.982–1.009	0.510
Supine		0.014 (0.036)	1.015	0.946–1.088	0.687
Respiratory arousal		0.001 (0.010)	1.001	0.981–1.021	0.954
Non-respiratory arousal		-0.002 (0.014)	0.998	0.971–1.025	0.868
AHI		0.003 (0.005)	1.003	0.992–1.014	0.586

β: regression coefficient; SE: standard error; OR: odds ratio; CI: confidence interval; OSA: obstructive sleep apnea; AHI: apnea-hypopnea index; BMI: body mass index.

Associations between RMMAs, arousals, and respiratory events

Figure 4.2 shows the visualization of the network analysis. As presented in the figure, the RMMA index has a negative correlation with BMI and a positive correlation with male gender. No direct association was found between RMMA and respiratory events. However, both RMMA and AHI were correlated with BMI, suggesting an indirect correlation between RMMA and respiratory events. Besides, neither respiratory arousal nor non-respiratory arousal had direct association with RMMA. In addition, the correlation between SB and N1 that was shown in the logistic regression analysis did not present in the network analysis after controlling for all the other factors. The bootstrapped confidence intervals of the network model are presented in the supplemental material (Supplement 4.1).

In addition, the majority of RMMAs (median = 85.7%) were time-related to sleep arousals, which was significantly higher than the percentage of RMMA unrelated to arousals (median = 14.3%, $P < 0.001$). Further, more RMMAs were related to non-respiratory arousal than to respiratory arousal (46.8% versus 25.0%, $P < 0.001$).

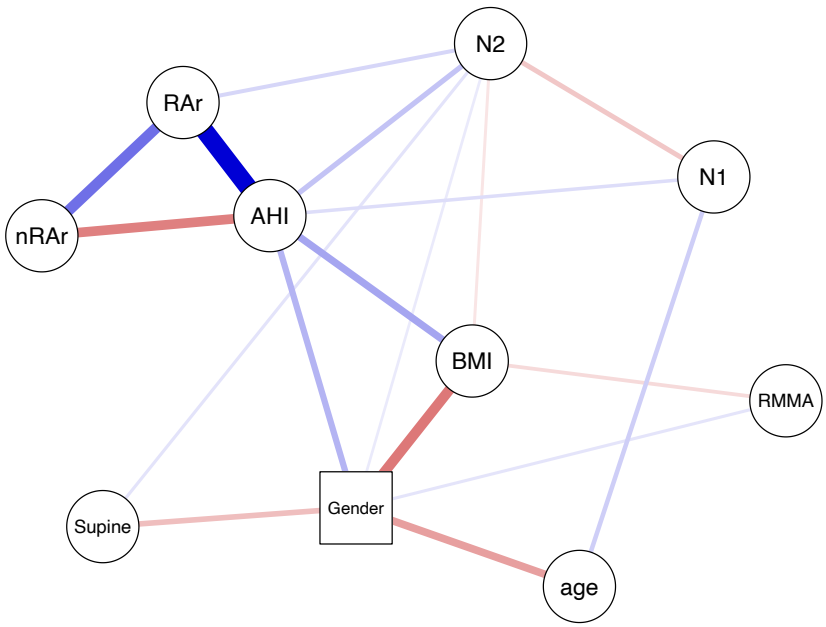

Figure 4.2 Network model of sleep bruxism in adults with obstructive sleep apnea. The squares represent categorical variables; the circles, continuous variables. The blue lines represent positive associations; the red lines, negative associations. Thicker and darker colored lines refer to stronger associations; RMMA: rhythmic masticatory muscle activity, biomarker of sleep bruxism; BMI: body mass index; AHI: apnea-hypopnea index; RAr: respiratory arousal; nRAr: non-respiratory arousal.

Discussion

This large-scale PSG study aimed to determine the prevalence and risk factors of SB in adults with OSA and to investigate the associations between RMMAs, arousals, and respiratory events in adults with OSA. Based on our results, 49.7% of adults with OSA had comorbid SB. Male gender, lower BMI, and higher percentage of N1 significantly increased the risk of having SB. Further, RMMA did not have a direct association with respiratory events and sleep arousals, however, most RMMAs were time-related to arousals.

Prevalence and risk factors of SB in adults with OSA

The present PSG study with a large-scale sample confirmed that nearly half (49.7%) of adults with OSA had comorbid SB. This result confirmed that SB is a common comorbidity of OSA that demands close attention. Further, it is important to note that the prevalence is much higher than that from studies in which SB was measured by self-report. As reported by a previous study, the prevalence of self-reported SB in individuals with OSA (n = 300) was 26%.[15] Another study showed that the prevalence of SB in OSA was 27.5% based on self-report, while in the same study, the prevalence became 52.4% when using PSG to measure SB.[33] These studies suggest that self-report or questionnaires may underestimate the prevalence of SB in the OSA population. Further, the underestimation of SB due to the use of self-report suggests that a large number of individuals with OSA are unaware of SB. With this, more attention on the negative consequences of SB is demanded from sleep doctors, dentists, as well as from the OSA individuals themselves.

Most studies that investigated the risk factors for SB did not show a significant difference between males and females in the prevalence of SB in the general population.[22,34] However, based on our analysis, male gender was a significant risk factor for SB in the OSA population (OR = 1.503), which is in line with another study that was composed of adults with OSA.[18] These contrary findings may due to the population that was under investigation. Male gender has been proved to be an independent risk factor for OSA.[35] Besides, previous studies considered SB to be secondary to sleep arousal.[27,36,37] At the same time, in individuals with OSA, males not only have more sleep arousals than females but also have a higher ventilatory response to sleep arousals, which might be related to the inherent gender differences in,

amongst others, the collapsibility of the upper airway, the neurochemical control mechanisms, and sex hormones. [38,39] Thus, the higher frequency of and response to sleep arousals in male than female could support that male gender is a risk factor for SB in adults with OSA.

Our results showed that patients with lower BMI had a higher risk of experiencing SB (OR = 0.954, $P < 0.001$). This is in accordance with the result of another large-scale PSG study (N = 1042).[40] That study reported that in the general population, individuals with normal weight had a significantly higher frequency of SB than those with obesity.[40] After controlling for other factors by the network analysis, RMMA also showed a negative correlation with BMI. However, the underlying mechanism for this association is still unclear. It may be attributed to the deleterious effects of obesity on skeletal muscle structure and performance, such as physical inactivity and inflammatory changes.[41,42] Future studies are warranted to investigate the underlying mechanism.

Previous findings suggest that most RMMAs and arousals occur in sleep stages 1 and 2, but rarely in stage 3 and REM.[43] The regression analysis in this study revealed that a higher percentage of sleep stage 1 increased the odds of SB. However, the percentage of N1 in this study was within the normal range[44] and the odds ratio for the percentage of N1 is quite close to 1.0 (1.032), suggesting that this finding may not have clinical relevance. This is supported by the result of the network analysis, that is, there is no (in-)direct association between SB and N1.

In summary, SB is highly prevalent in adults with OSA. It is recommended for sleep doctors to carry out a routine screening and monitoring of SB for adults with OSA, particularly for those with male gender and lower BMI. It would be better to refer those who report complaints about SB or show apparent negative consequences of SB (e.g., severe tooth wear and/or orofacial pain) to dentists for further examination and collaborative management. For individuals with OSA and SB, although oral appliances could relieve both OSA and SB in some cases, the elevated likelihood of oral appliance breakage should also be considered.

Association between RMMA, arousal and respiratory event

As presented in Figure 2, RMMA did not directly correlate to AHI. Moreover, some studies on the temporal relationship between RMMA and respiratory events demonstrated that a large

amount of RMMAs were time-unrelated to respiratory events.[45,46] These results are in line with some other studies which showed that masticatory muscle activities are more likely related to respiratory arousals rather than the respiratory events per se in individuals with OSA.[25,26] Moreover, our results showed that more RMMAs were related to non-respiratory arousals than to respiratory arousals. All these findings suggest that the occurrence of RMMA seems not rely on the presence of respiratory events.

Although RMMA is suggested to be related to sleep arousals, no direct link between RMMA and sleep arousals (including respiratory arousal and non-respiratory arousal) was found from the network analysis. These results suggest that there is not a linear correlation between the RMMA index and sleep arousal index. However, it is important to note that neither the regression analysis nor the network analysis takes the temporal relationship between variables into consideration.[14] Based on our results, most RMMAs (85.7%) were time-related to sleep arousals. Further, the proportion of RMMA in relation to sleep arousals in our sample—individuals with OSA—is quite close to that in individuals with SB without OSA (88%).[37] These results suggest that SB/RMMA is an arousal-related autonomic motor response during sleep without difference between in individuals with or without OSA. Moreover, these findings regarding the relationship between SB/RMMA and arousal supports the theory that arousal only acts as a permissive window for the occurrence of RMMA rather than a generator.[47]

Furthermore, with regard to the association between OSA and SB, it could be that OSA characterized by frequent sleep arousals provides more chances for the occurrence of SB. It is of importance to note that our findings cannot preclude other possible mechanisms for the association between OSA and SB. For example, studies have reported that some neurochemicals with direct activity in respiratory muscles' motor nuclei and arousal systems, such as glutamate, glycine, serotonin, acetylcholine, and gamma-aminobutyric acid, have also been reported to be related to the genesis of SB.[48,49] Therefore, OSA-related factors that influence the secretion or metabolism of these neurochemicals may also play an important role in the occurrence of SB in OSA.

Strengths and limitations

This study has several strengths. Firstly, this study was performed in a large-scale sample of individuals with OSA, which ensures the statistical power and reliability of our results. Secondly, compared with univariate analysis and logistic regression analysis, network analysis takes all variables into account in a single model, which controlled the influence of other covariates on the association between pairwise variables. Also, the network analysis and its graphical representation showed direct and indirect associations between variables, which helps understanding the intertwined correlations between factors, and identify the independent risk factors for RMMA and SB.

Apart from the strengths, several limitations should be kept in mind during the interpretation of the results. Firstly, although SB was assessed objectively by PSG, the absence of audio and video recordings may, to some extent, overestimate the RMMA index.[31] Nonetheless, as reported by previous studies, the accuracy of RMMA scoring with PSG systems without audio and video remains relatively good for research and clinical aims.[31,50] Moreover, the prevalence of SB in adult patients with OSA found in this study is similar to that of previous PSG studies which had audio and video,[4,18] suggesting that our results remain reliable. Secondly, the participants of this study were those who received PSG recordings in the hospital. Thus, the OSA sample might deviate from a representative OSA group in the general population.

Conclusions

This study demonstrated that nearly half of patients with obstructive sleep apnea have comorbid sleep bruxism. Male gender, lower BMI, and a higher percentage of sleep stage 1 increase the odds of having sleep bruxism. However, the clinical relevance of the latter is doubtful given the low odds ratio and lack of other supportive evidence. Further, although sleep bruxism was not directly correlated with respiratory events and sleep arousals, the majority of sleep bruxism events were time-related to sleep arousals.

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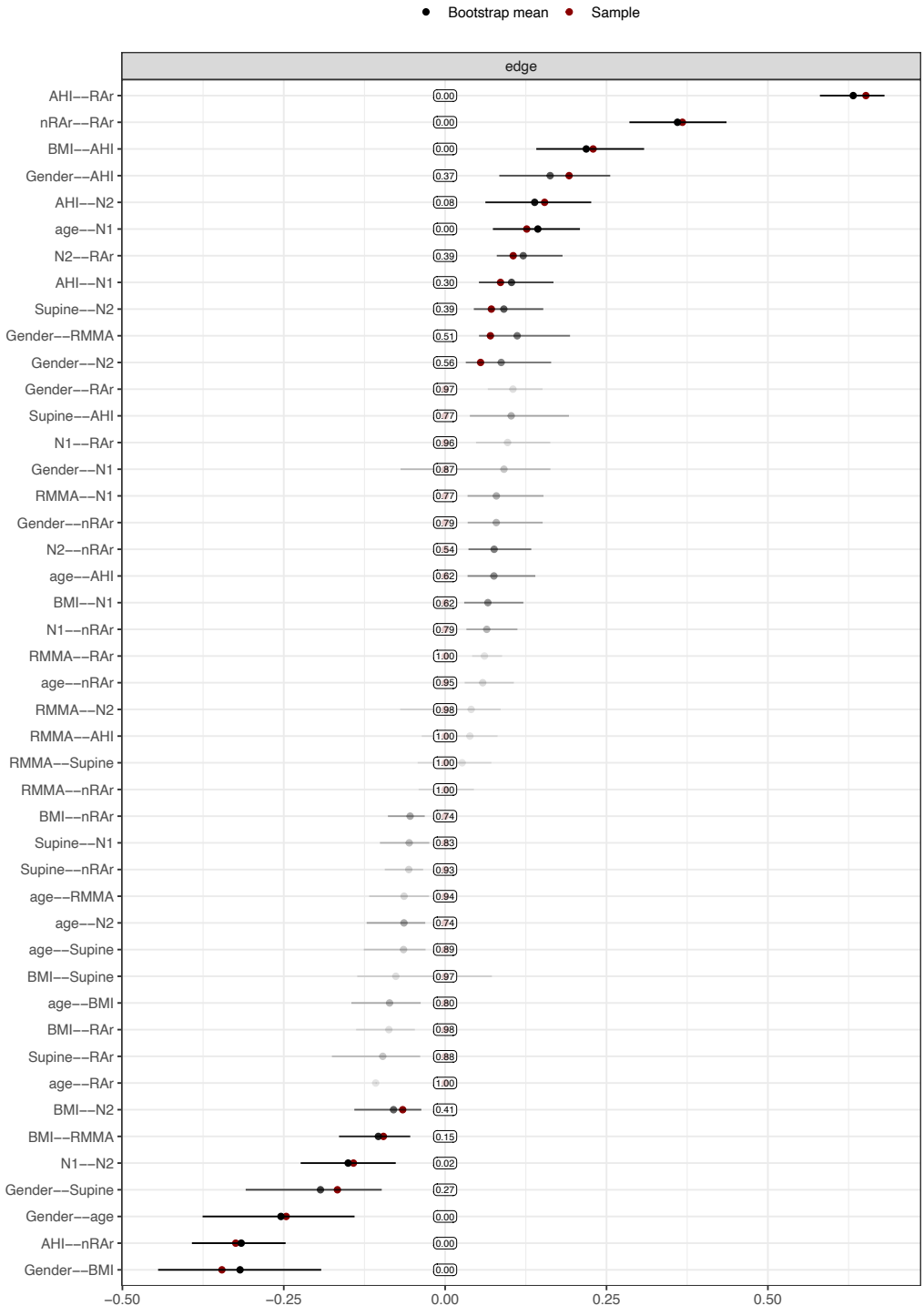
Supplement 4.1



Bootstrapped confidence intervals of network model. Note: Bootstrapped CIs showed accuracy of the edges in the network model. Only the black confidence intervals (CIs) were the edges in the network model. The gray CIs represent that these edges were not significant and did not appear in the network model. The strongest edge was at the top of the plot and followed by the weaker edges. The left side of y-axis refers to negative edges, and the right side of the y-axis refers to positive edges.

Chapter 5

The effects of mandibular advancement appliance on the sequence of jaw-closing muscle activity and respiratory events in individuals with obstructive sleep apnea

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Abstract

Purpose: To determine the effects of mandibular advancement appliance (MAA) on sequences of jaw-closing muscle activity (JCMA) and apneic or hypopneic event (AHE) in individuals with obstructive sleep apnea.

Methods: Sixteen individuals with obstructive sleep apnea (6 women and 10 men, 51.3 ± 8.5 years) were included in a secondary analysis of a randomized controlled crossover trial, in which two ambulatory polysomnographic recordings were performed: one with MAA in situ and the other without MAA. A time span of 16 seconds between JCMA and AHE was applied to classify JCMAs into four sequences: 1. JCMA occurs before AHE (B-type); 2. both events occur simultaneously (S-type); 3. JCMA occurs after AHE (A-type); and 4. JCMA is time-unrelated to AHE (U-type). The effects of MAA on the distribution of these sequences were analyzed by Wilcoxon signed-rank test.

Results: The baseline apnea-hypopnea index and JCMA index were 23.8 ± 16.0 events/h and 10.8 ± 10.3 events/h, respectively. In both conditions, i.e., without and with MAA, most JCMAs were U-type (48.3% and 64.6%, respectively), followed by A-type (40.5% and 21.6%), B-type (25.1% and 21.0%), and S-type (1.6% and 1.0%). With MAA in situ, only the A-type JCMA index decreased significantly ($P = 0.005$), while B-type, S-type and U-type JCMA indices did not change significantly (all $P > 0.05$).

Conclusion: MAA therapy only significantly reduces the jaw-closing muscle activities that occur after apneic or hypopneic events in individuals with obstructive sleep apnea.

Keywords: obstructive sleep apnea; jaw-closing muscle activity; respiratory event; sequence; mandibular advancement appliance

Introduction

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder characterized by repetitive obstructions of the upper airway that may result in oxygen desaturations and arousals from sleep [1]. OSA is usually accompanied by loud snoring, morning headache, and excessive daytime sleepiness [1,2]. The overall population prevalence of OSA ranges from 9% to 38%, and is higher in individuals with male gender, higher age, and obesity [3]. OSA has been reported to be a risk factor for several metabolic (e.g., diabetes, glucose dysregulation), cardiovascular (e.g., hypertension, stroke), psychiatric (e.g., depression), and sleep-related disorders (e.g., sleep bruxism, insomnia) [4,5].

Jaw-closing muscle activity (JCMA) is an increased electromyography activity that commonly occurs during sleep in individuals with OSA [6]. JCMA includes rhythmic masticatory muscle activity (RMMA, i.e., muscle activity characterizing sleep bruxism) and orofacial activity (e.g., swallowing, yawning, lip movement, and sleep talking).

Previous studies suggested that in OSA individuals, respiratory events (apneic or hypopneic events [AHEs]) are frequently followed by JCMA [7,8], and JCMAs' onset may be triggered by the AHEs [9,10]. Two studies reported that the majority of RMMAs occurred after AHEs in individuals with OSA [11,12], supporting a theory that JCMA in association with the termination of AHE may play a protective role by re-opening the upper airway [13]. However, some other studies showed that most RMMAs were time-unrelated to AHEs [14,15]. Therefore, the temporal relationship between JCMA and AHE in individuals with OSA is probably not characterized by one specific sequence of events at the level of the individual patient [13].

Besides, some studies suggested that JCMA is a general motor response to sleep arousals [16–18]. In our primary study [19], in which the same sample was used as in the present study, we observed that the effect of a mandibular advancement appliance (MAA) significantly reduces JCMAs related to respiratory arousals in participants with OSA [19]. Based on this, we hypothesized that only JCMAs occurring after AHEs would decrease with MAA treatment, while JCMAs occurring before AHEs, during AHEs, and those time-unrelated to AHEs would not change. Further, we hypothesized that only JCMAs occurring after AHEs in relation to respiratory arousals would decrease. Therefore, the primary aim of this study was to

determine the effects of MAA on the distribution of sequences of JCMAs and AHEs. The secondary aim was to determine the effect of MAA on JCMA occurring after AHE in relation to arousal.

Methods

Study design

This study is a secondary analysis of a prospective randomized controlled crossover trial in which the effects of MAA therapy on JCMA in individuals with OSA were investigated [19]. This clinical study is registered at www.clinicaltrials.gov (NCT02011425). The scientific and ethical aspects of this study were approved by the Medical Ethics Committee of the Université de Montréal (13-105-CERES-D).

Participants

Individuals who were prescribed MAA therapy by a physician for their OSA were recruited in the primary study. The criteria of participants' recruitment were described in detail by Aarab et al. [19]. In summary, participants aged between 30 and 65 years with an apnea-hypopnea index (AHI) of 15-45 events/hour of sleep and OSA signs or symptoms (e.g., choking or gasping during sleep, daytime fatigue) were included. The exclusion criteria were: presence of other respiratory or sleep disorders (except sleep bruxism), ongoing periodontal problems, reversible upper airway abnormalities, severe orofacial pain or temporomandibular disorders; usage of medications that could influence respiratory or sleep; and lack of retention possibilities for an MAA.

Polysomnography

After a 3 to 6 months' habituation period of wearing MAA (SomnoDent Flex; SomnoMed, Ontario, Canada), polysomnographic (PSG) recordings were made for participants at two conditions, i.e., without and with MAA in situ, in random order with an interval of one week to eliminate possible carryover effects. An ambulatory type II PSG system, Embla Titanium hardware (Embla, Ontario, Canada), was used to record the following channels: electroencephalography (F3M2, F4M1, C3M2, C4M1, O1M2, O2M1), electrooculography (left and right), electromyography (EMG; mentalis, masseter, temporalis, and tibialis muscles),

airflow (nasal cannula), respiratory effort (abdominal and thoracic), oximetry, and sleep position.

PSG recordings, including standard sleep variables, respiratory events (e.g., apnea, hypopnea), and sleep arousals, were scored manually by an experienced and registered polysomnographic technologist from an independent company (Sleep Strategies, Ottawa, Canada), following the criteria of the American Academy of Sleep Medicine [20]. JCMAs (i.e., RMMA and orofacial activity) were scored by the first author (D.L.) according to previously published criteria [21]. EMG burst was scored when the mean amplitude was two times higher than the baseline EMG signal on at least three of the four EMG channels of the bilateral masseter and temporalis muscles. EMG burst was classified as phasic (duration: 0.25–2s) or tonic (duration ≥ 2s). EMG bursts occurring with an interval of shorter than 3 seconds were considered belonging to a single episode. Subsequently, an RMMA episode was scored as phasic (three or more continuous phasic EMG bursts), tonic (one or more tonic EMG bursts), or mixed (at least one phasic and one tonic EMG bursts). Orofacial activity was scored when EMG bursts did not meet the criteria for RMMA. The number of JCMA was defined as the sum of RMMA and orofacial activity.

The sequence of JCMA and AHE

Scored JCMAs were categorized into four possible sequences in association with AHE (see Figure 5.1a): 1. JCMA occurs before AHE (B-type); 2. JCMA and AHE occur simultaneously (S-type); 3. JCMA occurs after AHE (A-type); and 4. JCMA is time-unrelated to AHE (U-type). A time span of 16 seconds [16,22–24] was applied for the relation between the two events, starting at the termination of the preceding AHE or JCMA. When JCMA occurred between two AHEs and both time spans were within 16 seconds, the JCMA was scored twice, i.e., B-type and A-type. Consequently, the total percentages of the four types may be over 100%.

A-type JCMAs were considered in relation to arousal when they occurred within 5 seconds of the arousal [16,19]. If the arousal occurred at the termination of or immediately after a respiratory event (i.e., AHE), the arousal was scored as respiratory arousal [25], and the JCMA was then scored as respiratory arousal-related JCMA [16,19.] In contrast, if the arousal was

scored as non-respiratory arousal, the JCMA was scored as non-respiratory arousal-related JCMA (see Figure 5.1b).

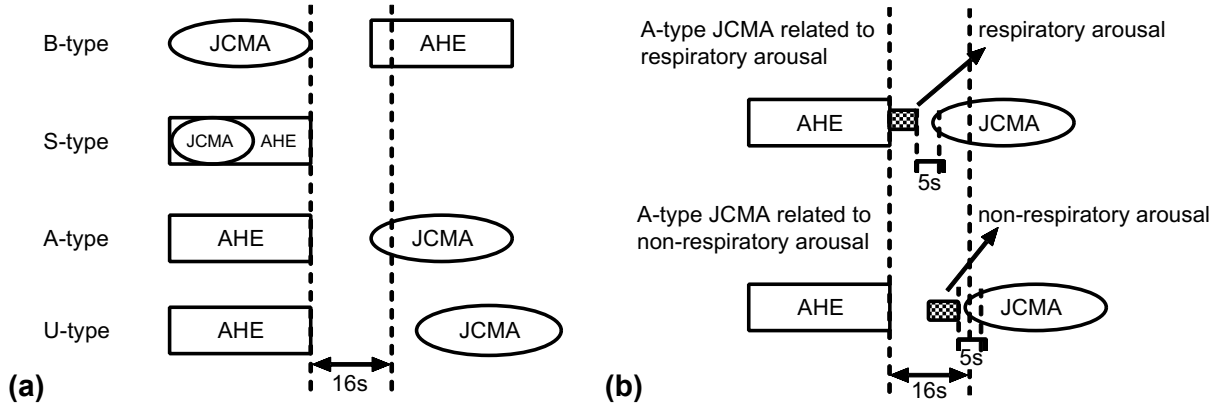

Figure 5.1 Relationship between jaw-closing muscle activity (JCMA), arousal, and apneic or hypopneic event (AHE) (a) Sequences of JCMA and AHE; (b) Respiratory or non-respiratory arousal-related JCMA. B-type: JCMA occurs before AHE; S-type: JCMA and AHE occur simultaneously; A-type: JCMA occurs after AHE; U-type: JCMA occurs before or after AHE but is time-unrelated to AHE.

Outcome variables

Some variables were transformed into indices, defined as the number of events per hour of sleep, such as the JCMA index. The primary outcome variables of this study were the indices of each sequence of JCMA, viz., B-type JCMA index, S-type JCMA index, A-type JCMA index, and U-type JCMA index. In order to compare our results with other studies, the number of JCMAs for each sequence was also expressed as a percentage of the total number of JCMAs. Secondary outcome variables were the index of A-type JCMA in relation to respiratory and non-respiratory arousal.

Statistical analysis

The normality of variables was tested by the Shapiro-Wilk test. Paired-samples t-tests or Wilcoxon signed-rank tests were used to compare variables between PSG recordings without and with MAA in situ. The effects of MAA on the indices of the four sequences of JCMA and the indices of A-type JCMA in relation to arousals were analyzed by the Wilcoxon signed-rank

test. Statistical significance was set at 0.05. Statistical analysis was performed using SPSS Statistics (version 26, SPSS Inc, Chicago, IL, USA).

Results

Participants

Thirty-two OSA individuals were initially invited to participate. For various reasons, fourteen individuals were excluded in the primary study of Aarab et al. [19]. Besides, in two participants, the scored AHEs were invisible on the respiratory traces of their PSG recordings. Hence, in this study, we included 16 participants, including 6 women and 10 men. Their mean age was 51.3 ± 8.5 years; their mean body mass index was 29.1 ± 3.6 kg/m^2. Although all the participants met the AHI criteria (i.e., 15–45 events/hour) during their recruitment, 6 cases showed an AHI below 15 events/hour in the PSG recordings without MAA in situ.

Descriptive analyses

Table 5.1 shows the descriptive analyses of the sleep, respiratory, and JCMA variables in PSG recordings without and with MAA in situ. The total sleep time and sleep efficiency did not show a significant difference between PSG recordings without and with MAA in situ. The percentage of sleep stage N2 decreased significantly with MAA in situ, while the percentage of stage N3 and REM increased significantly ($P < 0.05$). The AHI, oxygen desaturation index, total arousal index, and respiratory arousal index decreased significantly with MAA in situ ($P < 0.05$).

Sequences of JCMA and AHE

Table 5.2 shows the distribution of each sequence of JCMA and AHE without and with MAA in situ. In both conditions, i.e., without and with MAA in situ, the majority of JCMAs were classified as U-type (mean = 48.3% and 64.6%, respectively), followed by A-type (mean = 40.5% and 21.6%) and B-type (mean = 25.1% and 21.0%). Only a few JCMAs were scored as S-type (mean = 1.6% and 1.0%). In addition, without MAA, 15.5% (mean) of JCMAs were scored as both A-type and B-type, while with MAA in situ, the percentage of the double-scored JCMAs decreased to 8.3%.

Table 5.1 Polysomnographic variables of 16 patients with OSA without and with MAA in situ

	Without MAA [a]	With MAA [a]	Statistics	*P* value
Sleep variables				
Total sleep time (minutes)	359.6|392.8|434.5	357.8|391.5|447.7	Z = -0.259	0.796 [b]
Sleep efficiency (%)	88.5 ± 7.0	87.0 ± 6.0	T = 0.643	0.530 [c]
N1 (%)	87.0 ± 6.0	10.2 ± 3.8	T = 1.565	0.138 [c]
N2 (%)	66.2 ± 4.5	61.8 ± 5.9	T = 2.710	0.016 [c,*]
N3 (%)	0.3|2.7|6.8	2.6|7.2|9.4	Z = -2.166	0.030 [b,*]
REM (%)	18.7 ± 4.0	21.5 ± 5.5	T = -2.210	0.043 [c,*]
Total arousal	14.2 ± 5.6	18.7 ± 7.5	T = 2.726	0.016 [c,*]
Respiratory arousal	4.0|7.7|14.5	2.5|3.8|8.0	Z = -2.844	0.004 [b,*]
Non-respiratory arousal	6.2|8.2|9.3	6.6|8.0|10.5	Z = -0.233	0.816 [b]
Respiratory variables (events/hour)				
AHI	14.3|19.8|31.7	6.4|13.9|23.9	Z = -2.947	0.003 [b,*]
Oxygen desaturation index	14.2|22.8|28.8	6.8|14.9|26.6	Z = -2.443	0.015 [b,*]
JCMA variables (events/hour)				
Total JCMA	4.1|6.7|9.4	2.5|3.9|6.4	Z = 1.215	0.234 [b]
RMMA	0.8|2.0|3.6	0.6|1.0|2.0	Z = 1.034	0.277 [b]
Orofacial activity	2.3|4.5|5.8	1.5|2.7|4.6	Z = 1.212	0.061 [b]

[a] For normally distributed variables, data are presented as mean ± one standard deviation; for non-normally distributed variables, the 25%|50% (median)|75% percentiles are given; [b] Wilcoxon signed-rank test; [c] Paired samples t-test; * Statistically significant at the 0.05 probability level; OSA: obstructive sleep apnea; MAA: mandibular advancement appliance; AHI: apnea-hypopnea index; RMMA: rhythmic masticatory muscle activity; JCMA: jaw-closing muscle activity (JCMA = RMMA + orofacial activity).

With MAA in situ, only the A-type JCMA index decreased significantly compared with that without MAA (*P* = 0.005), while B-type, S-type, and U-type JCMA showed no significant difference (*P* = 0.069, 0.401, and 0.501, respectively, see Table 5.2). This finding still holds after removing the double-scored JCMAs from A-type and B-type (for A-type, P = 0.023; for B-type, P = 0.326). Although the reduction of the B-type JCMA index was not significant, 10 of the 16 participants showed a decrease (Figure 5.2). Also, in a few cases, the A-type, B-type, and U-type JCMA index increased with MAA in situ.

In addition, for the A-type JCMA index, only the respiratory arousal-related JCMA index decreased significantly with MAA in situ (0.40|2.15|3.67 vs 0.16|0.57|0.75, *P* = 0.001),

whereas the non-respiratory arousal-related JCMA index did not show a significant difference (0.00|0.21|0.71 vs 0.00|0.06|0.37, *P* = 0.170).

Table 5.2 Distribution of sequences of jaw-closing muscle activity and apneic or hypopneic events in patients with OSA

Sequences	Without MAA		With MAA		Z [c]	*P* value
	Index [a] (events/hour)	Percentage [b] (%)	Index [a] (events/hour)	Percentage [b] (%)		
B-type	0.2|1.4|3.9	25.1 ± 21.5	0.3|0.8|1.5	21.0 ± 16.5	-1.817	0.069
S-type	0.0|0.0|0.2	1.6 ± 2.6	0.0|0.0|0.2	1.0 ± 1.9	-0.840	0.401
A-type	0.5|2.7|5.6	40.5 ± 24.8	0.2|1.2|1.8	21.6 ± 14.8	-2.783	0.005*
U-type	1.2|3.1|4.0	48.3 ± 28.0	1.5|2.2|5.7	64.6 ± 21.7	-0.672	0.501

[a] Data are presented as percentiles (25%|50% (median)|75%); [b] Data are presented as mean ± one standard deviation; [c] Statistical analysis was performed by the Wilcoxon signed-rank test based on the indices of each sequence; * Statistically significant at the 0.05 probability level; MAA: mandibular advancement appliance; JCMA: jaw-closing muscle activity; B-type: JCMA occurs before apneic or hypopneic event (AHE); S-type: JCMA and AHE occur simultaneously; A-type: JCMA occurs after AHE; U-type: JCMA is time-unrelated to AHE.

Discussion

This study aimed to determine the effects of MAA on the distribution of the sequences of JCMA and AHE in participants with OSA. Our results showed that MAA therapy only significantly reduced the JCMAs that occurred after AHEs in relation to respiratory arousals; not those that occurred after AHEs in relation to non-respiratory arousals, nor those that occurred before AHEs, during AHEs, or were time unrelated to AHEs.

A recent study demonstrated that both RMMA and other orofacial activities are involved in a cascade of arousal-related motor responses during sleep.[26] Considering that sleep arousals commonly follow AHEs in OSA, it can be assumed that RMMA and other orofacial activities have similar temporal relationship to AHEs. Also, the reliable distinction between RMMA and orofacial activities relies on audio-video recordings.[21] However, the PSG used in this study did not include such recordings. In addition, as previous studies on the temporal relationship

between RMMAs/orofacial activities and AHEs are rare, especially for orofacial activity, comparisons between our study and others would be limited. For these reasons, in this study, we combined both types of oromotor events as JCMA to avoid potential bias as well as to analyze their temporal relationship to AHEs.

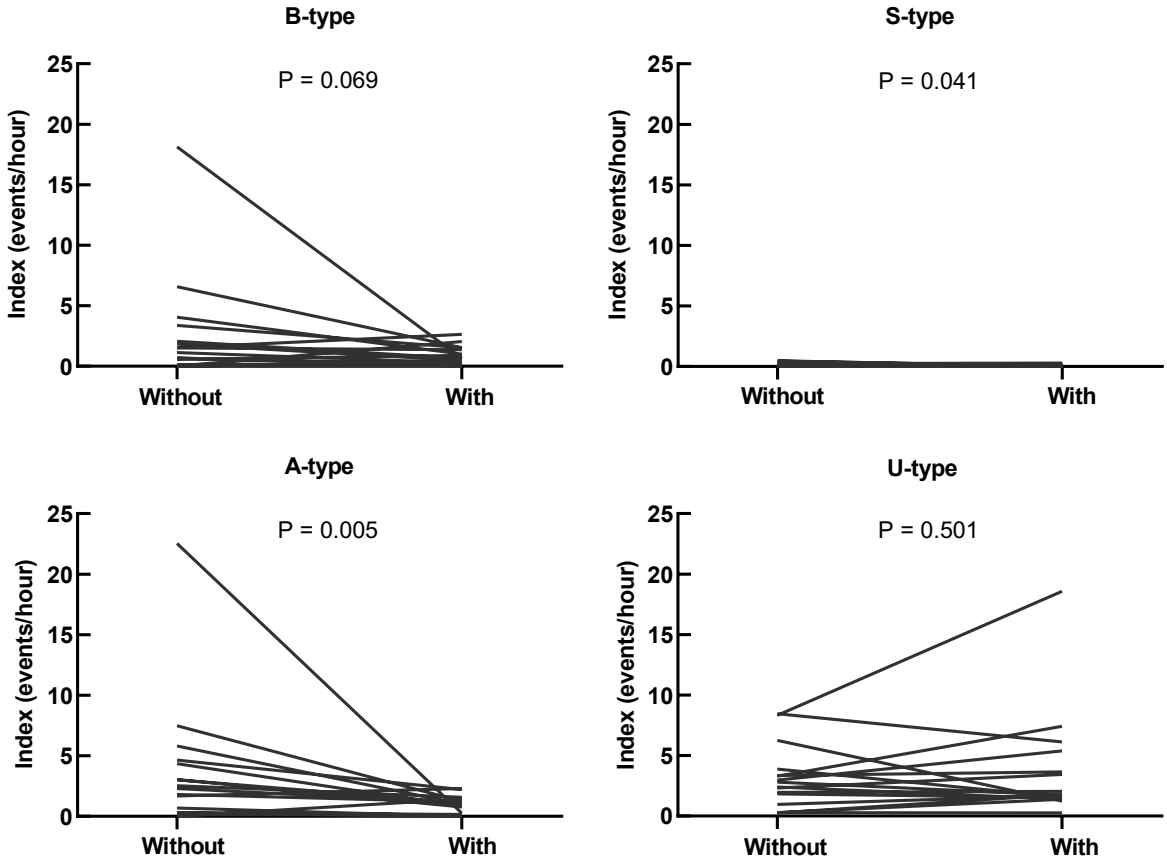

Figure 5.2 Individual values of JCMA index for each sequence without and with MAA in individuals with obstructive sleep apnea *A P value of < 0.05 is considered statistically significant; MAA: mandibular advancement appliance; JCMA: jaw-closing muscle activity; B-type: JCMA occurs before AHE; S-type: JCMA and AHE occur simultaneously; A-type: JCMA occurs after AHE; U-type: JCMA occurs before or after AHE but is time-unrelated to AHE.

Currently, there is no evidence pointing out an appropriate time span to consider JCMA and AHE as being related [13]. Based on evidence gathered from several sources, we set the time span at 16 seconds. Hosoya et al. performed a PSG study to investigate the relationship between sleep bruxism and OSA, which concluded that RMMA is secondary to arousal that occurs after AHE [22]. Based on this, the time span between AHE and RMMA was regarded as involving three periods: 1) the time span between AHE and arousal; 2) the duration of arousal;

and 3) the time span between arousal and RMMA. Based on the results of three studies, the time of the three periods were determined at 0.9s [23], 10.8s [24] and 4s [16], respectively. Thus, by adding up the times of the three periods, the time span of AHE to RMMA was estimated to be 16 seconds. Based on this, when RMMA occurred after AHE within 16 seconds, we took these two events as being related and classified this RMMA into A-type. Unfortunately, to the best of our knowledge, available evidence regarding the possible time span between AHE and JCMA seems to be only available for RMMA that occur after AHE; not for RMMA that occur before AHE. Similarly, such evidence seems to be unavailable for orofacial activities. Therefore, in this study, we applied the 16-second rule to all types of JCMA and all possible sequences.

Theoretically, a longer time span would result in more JCMAs classified as AHE-related, i.e., B-type and A-type. This is indeed the case when comparing our results with those from Tsujisaka et al. [15] and those from Saito et al [11]. In the study of Tsujisaka et al. [15], the 10-seconds rule resulted in around 40% of RMMAs and 18% of orofacial activities being related to AHEs, while the 16-seconds rule in our study resulted in 52% of JCMAs and the 5-minutes rule in the study of Saito et al. [11] even resulted in 80% of RMMA being related to AHEs.

Another possible reason for the discrepancy between these studies may be the participants' OSA severity. The present study was composed of participants with OSA ranging from moderate to severe, while in the study of Tsujisaka et al. [15], that had a time-span setting comparable to ours, only mild cases were included. Besides, our study showed more JCMAs that were associated with AHEs than the study of Tsujisaka et al [15]. Based on this, we can speculate that in severe cases, more JCMAs would be related to AHEs than in mild cases. This notion could support, at least partially, the expert opinion that the relative predominance of one specific sequence of events varies at the level of the individual patient [13]. Future studies are needed to confirm this hypothesis.

Corresponding to the four possible sequences of JCMA and AHE, four theories of the role of JCMA in OSA were hypothesized [13], viz., 1. B-type: JCMA may have an OSA-inducing effect; 2. S-type: the genesis of two events may share the same stimulus and mechanism; 3. A-type: JCMA may have a potential OSA-protective role; and 4. U-type: two events are unrelated. Further, a possible predominant sequence would support one of these four theories.

According to our results (Table 5.2), the most common JCMA was U-type (48.3%). On the one hand, the result means that around half of the JCMAs were time-unrelated to AHEs. On the other hand, it indicates that the other half of JCMAs were time-related to AHEs (i.e., B-type, A-type, or S-type). Thus, we could not conclude that these two events are unrelated. Since only a few JCMAs were scored as S-type, the presence of S-type seems like a coincidental occurrence of JCMA and AHE. Besides, 25.1% of JCMAs were scored as B-type. However, considering that part of B-type had an overlap with A-type JCMAs and that 10 of the 16 participants showed a reduction in B-type JCMA index with MAA therapy, these overlapping B-type JCMAs were more likely responses to the preceding AHEs and respiratory arousals. Given this, if we subtract the number of overlapping JCMAs (15.5%), the percentage of remaining B-type JCMA will be around 10%, which weakens the rationality of the hypothesis that JCMA has an OSA-inducing effect. Finally, 40.1% of JCMAs were scored as A-type, and most A-type JCMAs were related to respiratory arousals. These results suggest that A-type JCMA is a response to preceding AHE and respiratory arousal, supporting the hypothesis that some JCMAs may have a positive protective role against OSA [13].

Based on our results, we accepted the hypothesis that only A-type JCMA would decrease with MAA therapy, while B-type, S-type, and U-type JCMA would not change. Also, we accepted our second hypothesis that only JCMA occurring after AHE in relation to respiratory arousal would decrease with MAA treatment. These results imply that with MAA therapy, the reduction of the A-type JCMA index is mainly due to the decrease of respiratory arousal-related A-type JCMA. Besides, our results showed that with MAA in situ, only respiratory arousals decreased significantly; not non-respiratory arousals. Considering all this evidence, we can speculate that successful MAA treatment may effectively reduce JCMA through decreasing respiratory arousal. Further, the efficacy of MAA in reducing JCMA in individuals with OSA may vary at an individual level depending on the proportion of A-type JCMA related to respiratory arousal in the total JCMA.

Additionally, previous studies reported that in some cases, MAA might not be effective in managing OSA, or even aggravate the condition of OSA [26,27]. Given this, it is not surprising that a few cases in our sample showed an increase in the A-type JCMA index. Further, it could be hypothesized that MAA responders may show a higher reduction in the JCMA index than non-responders in individuals with OSA. Similar to A-type, the U-type JCMA index also displayed

an increase in several cases with MAA in situ, suggesting that MAA may increase the frequency of JCMA, even in individuals without OSA. This has also been reported in previous studies [28,29].

Although this study was performed in participants with OSA and not in a population with comorbid sleep bruxism, based on our results and considering the fact that RMMA is a common muscle activity observed in both OSA and healthy individuals [30], we hypothesize that only RMMAs that occur after AHEs in relation to arousals would be improved by MAA therapy in individuals with OSA. Also, the proportion of respiratory arousal-related A-type RMMAs may be able to predict the efficacy of MAA on reducing the comorbid sleep bruxism in individuals with OSA. Future studies are needed to verify these hypotheses in individuals with both OSA and sleep bruxism.

Although this study provides new findings on the relationship between JCMA and AHE, several limitations should be noted. Firstly, we did not perform an a priori sample size calculation. However, based on the post hoc power analysis, a sample of 11 would be enough to detect the difference in the A-type JCMA index with MAA therapy. Thus, the significant reduction of A-type JCMA with MAA in situ found in this study is considered reliable. Secondly, the time span setting for scoring sequences was based on limited and indirect evidence. A specifically designed study is needed to define a solid evidence-based time span at which JCMA or RMMA and AHE can be considered being related.

Conclusions

This study showed that effective mandibular advancement appliance therapy in individuals with obstructive sleep apnea only reduces the jaw-closing muscle activities that occur after respiratory events with arousals; not those that occurred after AHEs in relation to non-respiratory arousals, nor those that occurred before AHEs, during AHEs, or were time-unrelated to AHEs. These results suggest that mandibular advancement appliance can relieve jaw-closing muscle activities that are secondary to obstructive sleep apnea, and that the efficacy may vary at the level of individual patients depending on the distribution of jaw-closing muscle activities that occur after respiratory events.

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Chapter 6

Effects of continuous positive airway pressure and mandibular advancement appliance therapy on sleep bruxism in adults with obstructive sleep apnea

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Submitted for publication

Abstract

Study objectives: This study aimed to investigate the effects of continuous positive airway pressure (CPAP) and mandibular advancement appliance (MAA) therapy on rhythmic masticatory muscle activity (RMMA), a biomarker of sleep bruxism (SB), and to compare the effects of CPAP with MAA in adults with obstructive sleep apnea (OSA).

Methods: This cohort study included 38 individuals with OSA (32 males, 6 females; mean ± SD age = 52.6 ± 10.6 years; mean ± SD baseline apnea-hypopnea index = 26.5 ± 15.2 events/hour; mean ± SD RMMA index = 3.5 ± 3.1 events/hour) who received treatment with CPAP (N = 13) or MAA (N = 25). Polysomnographic recordings with and without therapy were performed in each individual. Statistical analyses were performed with repeated measures ANOVA.

Results: In the total group, the RMMA index decreased significantly with CPAP and MAA therapies ($P < 0.05$). The changes in the RMMA index with therapy did not differ significantly between CPAP and MAA ($P > 0.05$). Besides, the RMMA index decreased in 60% of the individuals with OSA, and the changes ranged widely, with a median of 52% and an interquartile of 107%.

Conclusions: Both CPAP and MAA therapies significantly reduce SB in individuals with OSA. However, the interindividual differences in the effects of these therapies on SB are large.

Keywords: Obstructive sleep apnea; Sleep bruxism; Polysomnography; Continuous positive airway pressure; Mandibular advancement appliance

Introduction

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder characterized by apneic (absent airflow) or hypopneic (reduced airflow) events that result from repetitive narrowing and/or collapsing of the upper airway and that commonly result in oxygen desaturations and arousals from sleep [1]. Individuals with OSA commonly have symptoms of morning headache, daytime sleepiness, and loud snoring [1]. The prevalence of OSA ranges from 2% to 14% in community-screened populations to a higher prevalence in certain subgroups (*e.g.,* in males and in obese individuals) [2,3]. OSA has been reported to be associated with many other health conditions such as stroke, hypertension, depression, diabetes, coronary artery disease, and sleep-related movement disorders, such as periodic leg movement during sleep and sleep bruxism (SB) [4–6].

SB is a masticatory muscle activity during sleep that is characterized by rhythmic masticatory muscle activity (RMMA) and may induce severe tooth wear, orofacial pain, and temporomandibular disorder [7]. Previous study has reported that OSA could be an independent risk factor for SB [8]. Furthermore, some studies reported that around half of individuals with OSA also have SB, suggesting that SB is a common comorbidity of OSA and that there is a close association between the two conditions [9,10].

Although the underlying mechanism of the association between OSA and SB is still unclear, previous studies suggested that the occurrence of RMMA might be related to recurrent respiratory events and sleep arousals in OSA. Based on this, we hypothesized that effective OSA therapies will decrease the frequency of RMMA in individuals with OSA. This has been reported in two cases with concomitant OSA and SB [11,12]. RMMA episodes in these two cases disappeared during continuous positive airway pressure (CPAP) therapy, while RMMA recurred when CPAP was removed [11,12]. Similarly, other studies have demonstrated that mandibular advancement appliances (MAA) significantly reduced RMMA episodes in individuals with SB [13,14]. However, a few studies have been performed to investigate the effects of OSA therapies on SB in adults with OSA. Therefore, the first aim of this study was to determine the effects of OSA therapies (CPAP and MAA) on SB in adults with OSA and in a subgroup of those with comorbid SB. We hypothesized that both CPAP and MAA therapies will significantly reduce RMMA in adults with OSA as well as in those with comorbid SB. In

addition, since a growing number of studies indicated that the occurrence of RMMA was related to arousals rather than to respiratory events [15,16], we hypothesized that both OSA therapies would significantly reduce RMMA related to respiratory arousals (RMMA-RAr), while having no effect on RMMA related to non-respiratory arousals (RMMA-nRAr). Therefore, the second aim of this study was to investigate the effect of CPAP and MAA on the RMMA-RAr and RMMA-nRAr in individuals with OSA and in those with comorbid SB.

Methods

This cohort study is part of a large-scale prospective polysomnographic (PSG) study on the associations between SB and other sleep-related disorders. The protocol was approved by the institutional Medical Ethics Committee of the OLVG West, Amsterdam (WO 16-577). This study has also been registered on trialsearch.who.int (Trial NL8516).

Participants

The sample was collected on the basis of the medical history of patients who were referred to the Department of Clinical Neurophysiology, OLVG West, Amsterdam, the Netherlands, between April 2017 to July 2018. Individuals who met the following criteria were included in this study: 1) age >18 years; 2) diagnosed with OSA; 3) baseline apnea-hypopnea index (AHI) ≥ 5 events/hour; 4) received treatment with CPAP or MAA; 5) received two PSG recordings, one without treatment and one with treatment; 6) the PSG recordings had bilateral masseter muscle electromyographic (EMG) traces [17]. Individuals were excluded: 1) with < 4 hours of sleep during the recording; 2) with missing data on electroencephalography or masseter EMG; 1) with other sleep-related breathing disorders (e.g., asthma, chronic obstructive pulmonary disease), neurological disorders (e.g., epilepsy), or sleep-related movement disorders except for SB (e.g., periodic limb movement disorder); 2) received other OSA treatments, such as bariatric surgery, oral and maxillofacial surgery, and positional therapy.

Polysomnography and scoring criteria

Full night PSG recordings were performed by a portable compact PSG system (SOMNOscreen Plus, SOMNOmedics GmbH, Germany). The PSG system consisted of electroencephalography (F4C4, C4O2, F3C3, C3O1), electrooculogram (E1M2, E2M1), electrocardiogram, EMG

(bilateral masseter muscles, anterior tibialis, mentalis and submentalis), pressure airflow, abdominal/thoracic respiratory effort, oxygen saturation, plethysmograph, heart rhythm, and sleep position. The mounting was performed by certified sleep technicians at the Department of Clinical Neurophysiology, OLVG West, Amsterdam, the Netherlands.

PSG recordings were analyzed offline using Domino software (SOMNOmedics GmbH, Germany). Sleep stages and respiratory events (viz., apnea, hypopnea, and respiratory effort-related arousal) were scored manually by sleep technicians from OLVG according to the American Academy of Sleep Medicine (AASM) scoring manual of sleep and associated events [18]. Sleep arousals were scored by two of us (D.L. and B.K.), following the scoring rules of AASM [18]. Sleep arousals were classified as respiratory arousals (RAr) or non-respiratory arousals (nRAr) [19]. Arousals occurring at the termination of respiratory events were defined as RAr, while those without preceding respiratory events were defined as nRAr.

The masseter EMG signals were filtered according to the AASM scoring manual (50 Hz notch; 10 Hz high pass; 100 Hz low pass) [18]. RMMA was scored according to previously reported criteria [17]. Each RMMA burst must exceed twice the amplitude of background EMG and be present simultaneously on the bilateral masseter muscles EMG traces. RMMA bursts occurring at an interval shorter than 3 seconds were regarded as a single episode. RMMA episodes were classified into three subtypes: phasic RMMA (three or more continuous RMMA bursts that are 0.25-2s in the duration), tonic RMMA (one or more RMMA bursts ≥ 2s), and mixed RMMA (if both phasic and tonic RMMA bursts are present within an episode). In addition, RMMA was considered to be related to arousal (RMMA-RAr or RMMA-nRAr) when they occurred within 5 seconds of an arousal [20].

Statistical analysis

The number of RMMA episodes was transformed into an index, defined as the number of events per hour of sleep. Individuals with an RMMA index of at least two episodes per hour of sleep were diagnosed with SB [17]. Individuals with concomitant OSA and SB were included in a subgroup for subgroup analysis.

The normality of outcome variables was assessed by using the Shapiro-Wilk test. Normally distributed data are presented as mean with standard deviation (SD). Non-normally

distributed data are presented as quartiles (25%|median|75%). The comparisons of baseline characteristics of the two therapy groups, including sleep variables and respiratory variables, were analyzed using the independent sample t-test (for normally distributed variables), Mann-Whitney U test (for non-normally distributed variables), or Chi-square test (for nominal variables).

Two-way repeated measures analyses of variance (ANOVA) were applied to analyze the mean difference of RMMA variables (i.e., RMMA index, RMMA-RAr index, and RMMA-nRAr index) separately for within-subjects factor (with versus without therapy) and to assess the interaction effect between the two factors (treatment effect of CPAP versus that of MAA). The baseline characteristics that showed significant differences between the two therapy groups were included as covariates of the two-way repeated measures ANOVA. Further, when CPAP and MAA showed significantly different effects on the RMMA variables, paired sample t-test or Wilcoxon signed-rank test were performed for each therapy group separately. The statistical analyses were performed in the total group as well as in individuals with comorbid SB. The significance level α of all statistical tests was set at 5%. All statistical analyses were performed using the SPSS statistics software package (version 26.0, SPSS Inc., Chicago, IL).

Results

Figure 6.1 shows a flow diagram of participants. We reviewed the medical history and PSG recordings of 2639 patients. According to the inclusion and exclusion criteria, 38 patients with OSA (6 females and 32 males) were included in this study. Among them, 6 were diagnosed with mild OSA, 23 with moderate OSA, and 9 with severe OSA. Their median AHI was 23.7 episodes (range from 8.6 to 75.9); their mean ±SD age was 52.6 ± 10.6 years; and their mean± SD BMI was 25. 4 ± 6.3 kg/m^2. Thirteen individuals received CPAP; 25 individuals received MAA therapy. In addition, 21 individuals (4 females and 17 males) were diagnosed with comorbid SB (6 received CPAP and 15 received MAA).

Sleep variables, including total sleep time, sleep efficiency, and percentages of sleep positions, did not change significantly with CPAP or MAA therapy (see Table 6.1). Both therapies reduced the AHI and ODI significantly (both $P < 0.01$). With regard to arousal-related variables,

CPAP significantly decreased the total arousal index and RAr index (both $P < 0.01$), while MAA only reduced the RAr index ($P = 0.006$). Both therapies did not affect the nRAr index ($P > 0.05$).

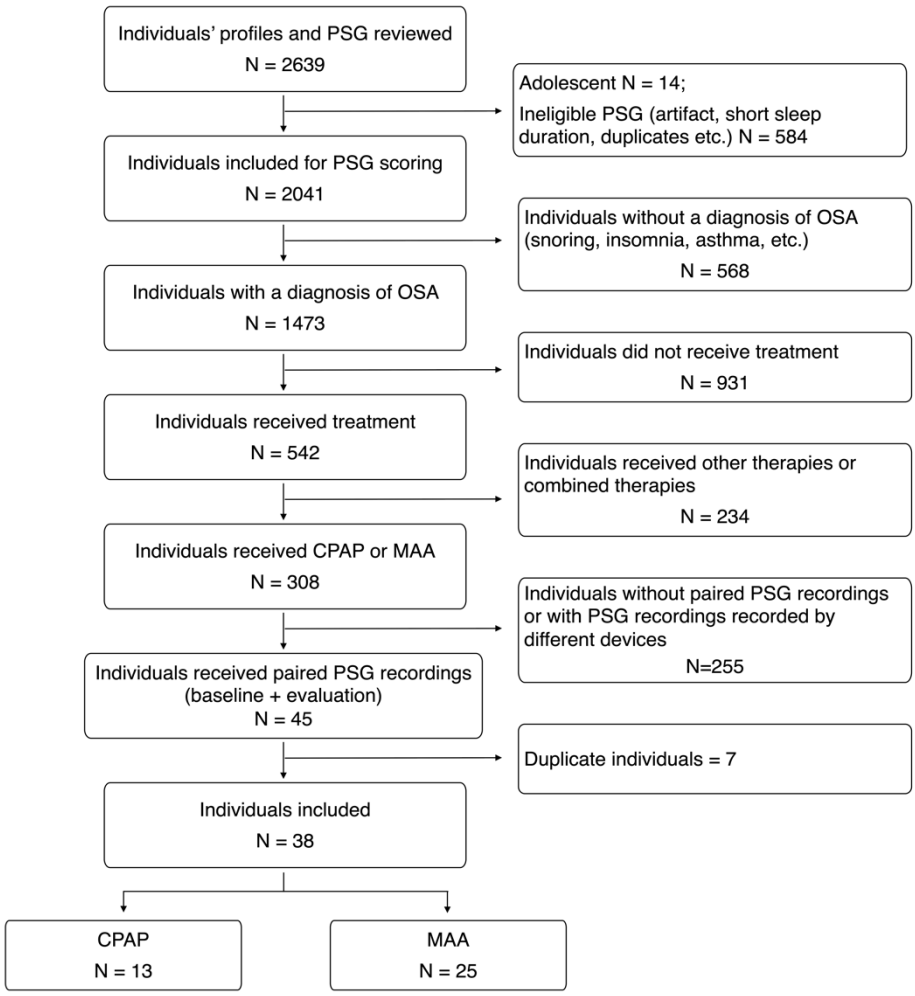

Figure 6.1 Flow diagram of participants in this study. PSG: polysomnography; OSA: obstructive sleep apnea; CPAP: continuous positive airway pressure; MAA: mandibular advancement appliance.

The baseline characteristics and PSG variables of participants are presented in Table 6.1. None of the variables differed significantly between the CPAP and MAA therapy groups. Therefore, no variable was taken as a covariate in ANOVA. Table 6.2 shows the values of RMMA variables in the total group and in the subgroup (i.e., OSA individuals with comorbid SB). Both in the total group and in the subgroup, the RMMA index decreased significantly with OSA therapies ($P < 0.05$ and 0.01, respectively). In addition, based on the interaction effect, the changes in

the RMMA index between PSG recordings without and with therapy did not differ significantly between CPAP and MAA (P > 0.05).

Table 6.1 Characteristics and polysomnographic variables of two therapy groups

	CPAP [a] (N=13)		P [b]	MAA [a] (N=25)		P [b]	P [c]
	Without	With		Without	With		
Age, years	50.8±11.3	-	-	53.6±10.3	-	-	0.447
Gender, female/male	0/13	-	-	6/19	-	-	0.054
BMI	27.4±4.5	-	-	27.5±3.9	-	-	0.942
Total sleep time, h	6.9±0.9	6.4±0.7	0.113	6.4|6.7|7.3	6.3|6.8|7.9	0.627	0.878
Sleep efficiency, %	88.6±8.2	86.3±9.9	0.571	84.8|90.8|95.1	86.6|90.8|94.6	0.946	0.939
N1, %	5.7±3.7	4.4±2.8	0.291	2.3|4.1|6.4	2.5|4.3|7.3	0.798	0.433
N2, %	43.7±12.1	41.7±7.4	0.500	45.2±11.3	46.4±9.8	0.617	0.706
N3, %	19.2±6.0	22.0±7.7	0.256	18.2±8.3	16.9±6.7	0.516	0.695
REM, %	18.4|19.6|21.6	14.2|14.9|24.0	0.345	17.3±7.3	19.2±6.6	0.249	0.214
Supine, min	32.3|104.4|125.1	59.5|87.5|174.0	0.421	68.4|132.4|173.0	12.5|101.1|258.7	0.443	0.236
Non-supine, min	297.2±128.6	264.2±107.7	0.244	252.4±104.6	277.8±139.3	0.311	0.640
Total arousal, N/h	30.7±12.1	14.9±8.0	0.000*	25.5±12.4	21.7±10.5	0.152	0.222
RAr, N/h	8.9|12.7|17.1	0.0|0.2|0.9	0.001*	6.6|8.8|14.9	2.5|4.6|9.4	0.006*	0.249
nRAr, N/h	14.3±6.5	13.7±7.8	0.715	9.1|10.8|18.5	9.2|14.3|20.8	0.968	0.770
AHI, N/hour	23.5|24.4|31.3	0.3|0.7|4.0	0.001*	16.9|21.7|27.1	8.5|11.1|21.5	0.002*	0.103
ODI, N/hour	37.6±19.1	10.3±7.5	0.000*	18.7|25.6|32.7	12.4|14.7|28.2	0.003*	0.054

[a] Data are presented as mean±standard deviation for normally distributed variables and as 25%|median|75% percentiles for non-normally distributed variables; [b] Comparisons between PSG recordings without and with therapy were performed by paired t-test for normally distributed data, by Wilcoxon signed-rank test for non-normally distributed data; [c] Comparisons of baseline characteristics between CPAP and MAA were performed by Independent t-test for normally distributed data, Mann-Whitney U test for non-normally distributed data, and by χ^2 test for nominal variables; * Statistically significant values at the 0.05 probability level; CPAP: continuous positive airway pressure; MAA: mandibular advancement appliance; BMI: body mass index; N1-3: non-rapid eye movement sleep stage 1-3; REM: rapid eye movement sleep stage; RAr: respiratory arousal index; nRAr: nonrespiratory arousal index; AHI: apnea-hypopnea index; ODI: oxygen desaturation index.

Figure 6.2 shows the individual values of RMMA indices in PSG recordings with and without therapy. Among individuals who received CPAP (n=13), six (46.2%) showed a decrease in the RMMA index, while seven (53.8%) showed an increase. For MAA, the RMMA index decreased in 17 individuals (68%), while it increased in seven individuals (28%), and one case (4%)

showed no difference in the RMMA index. In OSA individuals with comorbid SB, the RMMA index decreased in four of the six cases who received CPAP (66.7%) and in 12 of the 15 cases who received MAA therapy (80%).

Table 6.2 Effects of OSA therapies on sleep bruxism [a]

	CPAP		MAA		Without vs. with therapy		CPAP vs. MAA	
Total group: OSA individuals (N =38)								
	Without	With	Without	With	F (1, 36)	P	F(1,36)	P
RMMA index	2.9±2.8	2.1±2.0	3.7±3.2	2.1±2.8	6.423	0.016*	0.646	0.427
RMMA-RAr index	1.6±1.6	1.7±1.8	1.6±1.5	0.7±1.4	16.571	0.000*	1.005	0.323
RMMA-nRAr index	1.0±1.0	1.7±1.8	1.7±1.6	1.2±1.4	0.141	0.710	8.240	0.007*
Subgroup: OSA individuals with SB (N = 25)								
	Without	With	Without	With	F (1, 23)	P	F(1,23)	P
RMMA index	5.1±3.0	3.0±2.7	5.6±2.8	2.7±3.4	11.041	0.004*	0.323	0.577
RMMA-RAr index	2.8±1.7	0.1±0.1	2.5±1.5	1.0±1.8	17.262	0.001*	1.651	0.214
RMMA-nRAr index	1.5±1.2	2.5±2.4	2.6±1.5	1.5±1.7	0.023	0.882	9.233	0.007*

[a] Two-way repeated measures analyses of variance was applied to analyze the difference between CPAP and MAA; * Statistically significant values at the 0.05 probability level; OSA: obstructive sleep apnea; CPAP: continuous positive airway pressure; MAA: mandibular advancement appliance; RMMA: rhythmic masticatory muscle activity; RMMA-RAr: RMMA related to respiratory arousal; RMMA-nRAr: RMMA related to nonrespiratory arousal.

In addition, in the total group, the decrease of the percentage of the RMMA index was (-24.8%|51.5%|82.2%). For CPAP and MAA, it was (-33.7%|-13.2%|61.2%) and (-1.9%|58.8%|85.8%), respectively. The changes of the percentage of the RMMA index showed no significant difference between CPAP and MAA (P = 0.159). In individuals with OSA and comorbid SB, the decrease of the percentage of the RMMA index was (16.1%|61.2%|83.6%). For CPAP and MAA, it was (-13.2%|47.6%|77.0%) and (46.6%|61.7%|88.1%), respectively. The changes of the percentage of the RMMA index showed no significant difference between CPAP and MAA (P = 0.381).

During CPAP and MAA therapy, the RMMA-RAr index reduced significantly, and no significant difference in the changes of the RMMA-RAr index was found between the two therapies. The RMMA-nRAr index showed no significant changes in the total group and in the subgroup. However, CPAP and MAA showed a significantly different effect on the changes in the RMMA-nRAr index (P < 0.05). For this, a post-hoc analysis was conducted to analyze the effect of

CPAP and MAA separately. In the total group, the RMMA-nRAr index increased significantly with CPAP treatment (Z = -2.027, P = 0.043), while it did not change significantly with MAA in situ (Z = 1.786, P = 0.074). To the contrary, in individuals with OSA and SB, CPAP did not affect the RMMA-nRAr index (T = -1.644, P = 0.161), but MAA decreased the RMMA-nRAr index significantly (Z = - 2.385, P = 0.017).

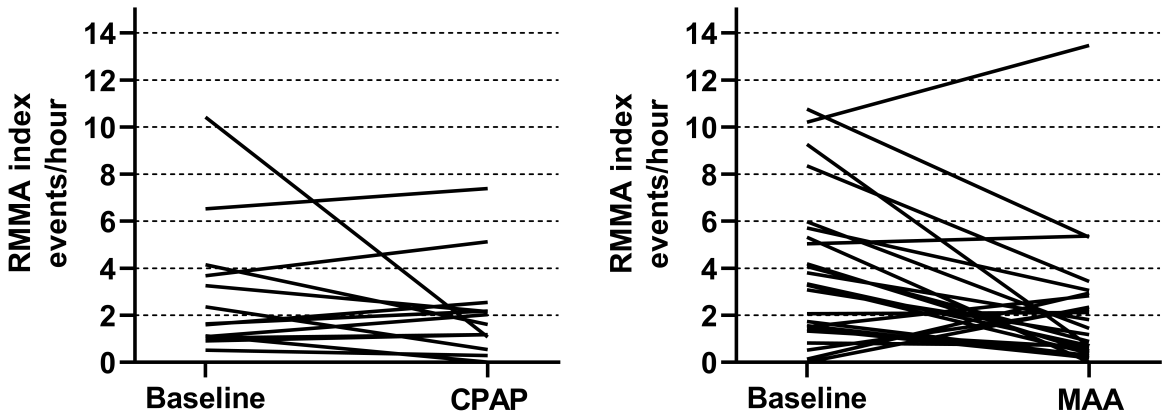

Figure 6.2 Individual values of RMMA indices in polysomnographic recordings without and with CPAP and MAA. RMMA: rhythmic masticatory muscle activity; CPAP: continuous positive airway pressure (N=13); MAA: mandibular advancement appliance (N=25).

Discussion

Previous case reports showed that CPAP could relieve SB in cases with severe OSA, and several studies showed that MAA could do so in otherwise healthy individuals with SB [11–13,21]. However, the effects of OSA therapies on SB has rarely been investigated in adults with OSA. Since SB could be primary, i.e., without clear cause, or secondary to other disorders [22], the underlying mechanism for the genesis of different phenotypes of SB might be different. Subsequently, the treatment effects of CPAP and MAA on SB may also vary depending on the characteristics of the population under investigation. Considering SB is highly prevalent in individuals with OSA (30%–50%) [10], it is clinically relevant to understand the effects of these therapies on SB in the OSA population. The primary aim of this study was to investigate and compare the effects of CPAP and MAA therapies on RMMA in individuals with OSA and in a subgroup of those comorbid with SB. This study showed that CPAP and MAA decreased the

frequency of RMMA in the total group as well as in those with comorbid SB, and no significant difference in the reduction of RMMA index was found between CPAP and MAA. The second aim of this study was to investigate the effects of CPAP and MAA on RMMA related to arousal. In the present study, with CPAP and MAA treatment, RMMA-RAr decreased significantly in the total group as well as in those with comorbid SB, and no significant difference in the changes of the RMMA-RAr index was found between the two therapies. Overall, both CPAP and MAA did not affect RMMA-nRAr, but the effects were different between both groups. In the total group, CPAP slightly increased the RMMA-nRAr index, while MAA showed no significant effect. In individuals with comorbid SB, the RMMA-nRAr index was not influenced by CPAP, but decreased with MAA.

As expected, both CPAP and MAA decreased the RMMA index in OSA individuals as well as in those with comorbid SB. Therefore, we accepted our hypothesis for the primary aim that both CPAP and MAA will reduce the frequency of RMMA in individuals with OSA. These results are consistent with previous studies in individuals with primary SB [11,13,21]. Further, the results support that in individuals with comorbid OSA and SB, OSA therapies can improve both conditions [10]. Based on this, for individuals with concomitant OSA and SB, OSA therapies should be adopted in the first step. Then, sleep physicians should evaluate if the negative consequences of SB, such as jaw muscle pain, temporomandibular joint disorder or teeth wear, are still severe enough to necessitate a collaborative management by sleep physicians and dentists.

In addition, our results showed that there was no significant difference in the changes of the RMMA index between CPAP and MAA. This could be explained by several reasons. Firstly, most of the participants in our sample were diagnosed with mild to moderate OSA. As reported in previous studies, CPAP and MAA did not show significant difference in the treatment of mild to moderate OSA [23,24]. Thus, the possible difference between CPAP and MAA in the changes of RMMA that benefited from the improvement of OSA may not be present in individuals with mild to moderate OSA. Further studies are recommended to confirm whether CPAP is more effective than MAA in relieving SB in individuals with severe OSA. Secondly, although SB may be a motor response to sleep arousals during sleep [25], some studies demonstrated that sleep arousal only acts as a permissive window for the occurrence of SB rather than a trigger [26]. Therefore, the reduction of sleep arousal may not have a linear

relationship with that of RMMA. Based on this, although CPAP reduced more RAr than MAA (Table 6.1), it is possible that CPAP did not show a better effect on reducing the RMMA index than MAA. In addition, MAA has been reported to be able to relieve SB in individuals with SB but without OSA, implying that MAA may have other mechanisms for reducing RMMA except by reducing arousals. Currently, the possible mechanisms by which RMMA was reduced with MAA may include 1) a "novelty effect" or psychological effect of MAA (this may also apply to CPAP); 2) reducing contractile properties of masseter muscles when the mandible is advanced by MAA; 3) reducing the freedom of mandibular movement; and 4) inducing masticatory muscle pain which then decreases RMMA [27].

Although both CPAP and MAA showed a consistent effect on the total RMMA index and RMMA-RAr index, the two therapies showed different effects on the RMMA-nRAr index. In the total group, the RMMA-nRAr index increased with CPAP therapy, but no change was found with MAA in situ. In OSA individuals with SB, CPAP did not affect the RMMA-nRAr index, while MAA decreased the RMMA-nRAr index significantly. In short, MAA seems to have an additional effect on RMMA related to non-respiratory arousal compared with CPAP. This might be due to the possible mechanisms of MAA for reducing RMMA.

It is noteworthy that the effect of OSA therapy on SB seems to vary at an individual level. In the present study, around 60% of OSA individuals (6/13 in CPAP, 17/25 in MAA) showed an decrease in the RMMA index with OSA treatment. In addition, the percentage of the changes of the RMMA index with OSA therapies among individuals had a wide range. This phenomenon has been reported in previous study [28]. There may be several reasons for such variances. Firstly, previous study demonstrated that RMMA index has a time-variant nature across nights (22%-37%) [29]. Thus, the changes of the RMMA index in this study may be partially due to the natural fluctuation of RMMA. Secondly, although the anterior tongue position under the treatment of CPAP and MAA can improve the upper airway patency and result in a decrease in masticatory muscle activity, the anterior positioning of the tongue might also increase masticatory muscle activity in some cases [30]. Thirdly, according to the etiology of SB, SB could be primary or secondary related to other medical conditions or other stimuli [22]. Thus, we can speculate that RMMA episodes may have a mixed pathogenesis both between and within individuals. Based on this, combined therapies, involving a primary

therapy for OSA and supplementary therapies for the remaining signs or symptoms of SB, would be better to improve patients' quality of life.

Limitations

Several limitations should be taken into consideration when interpreting the results of this study. Firstly, since this is not a randomized controlled trial (RCT), the comparison of the effects of CPAP and MAA on SB may be biased. Nevertheless, our results show that both CPAP and MAA can effectively relief SB in most cases. Future studies are recommended to adopt RCT design to compare the effects of OSA therapies, thus supplying solid evidence for treatment of cases with concomitant OSA and SB. Secondly, this study did not involve a healthy control group so that the observed effect of CPAP and MAA on SB cannot be definitively attributed to the therapies themselves. Thirdly, a limited sample was included in this study, especially for the CPAP group. Besides, as shown in Fig. 2, two cases showed substantial decreases with CPAP and MAA therapies, which could be considered as outliers. However, possibly, these purported outliers may be common observations in a large sample study. This could be supported by the large interindividual discrepancy in the effects of CPAP and MAA on SB that was presented in this study and by previous case reports which showed that SB episodes could disappear completely with CPAP treatment [11,12]. For that reason, we did not remove these cases from analysis. Fourthly, it is a pity that the signs and symptoms of SB before and after treatment were not collected at the moment of data collection. Future studies with large samples and prospective, RCTs are needed to confirm our findings in individuals with OSA and to compare the effects of different treatment modalities with different configurations.

Conclusions

Within the limitations of this study, we concluded that both continuous positive airway pressure and mandibular advancement appliance significantly reduce sleep bruxism in individuals with obstructive sleep apnea and in those with comorbid sleep bruxism. No significant difference regarding the effects on sleep bruxism was found between the two therapies. In addition, the two therapies can reduce sleep bruxism episodes related to respiratory arousal but may have different effects on those related to non-respiratory arousal.

It is noteworthy that the interindividual differences in the effects of both therapies on sleep bruxism are large.

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Chapter 7

General discussion

The general aim of this thesis was to gain insight into the associations between OSA and SB from an assessment and management point of view. This chapter discusses the main findings of the studies included in the thesis from four perspectives, namely: (1) SB assessment in OSA; (2) prevalence and risk factors of SB in adults with OSA; (3) association between SB and OSA; and (4) treatment effects of OSA therapies on SB in OSA. Where appropriate, the clinical implications and recommendations for future research are given. The chapter ends by providing a general conclusion.

Assessment of SB

SB assessment and treatment evaluation requires a valid SB scoring method. Currently, the gold standard for SB measurement is full-night PSG recordings with audio-video recordings.[1] According to the AASM scoring manual,[2] bruxism could be analyzed on chin EMG or masseter muscle EMG. Other studies recommended scoring bruxism on bilateral masseter and temporalis muscles EMG.[1] However, the accuracy and discrepancy in SB scoring based on different jaw muscles have not been studied so far. Therefore, **chapter 2** presents a study comparing the accuracy of SB scoring between different jaw muscles, namely, masseter, temporalis, and (sub)mentalis muscles.[3] The study concluded that PSG with bilateral masseter and/or temporalis EMG yield good accuracy in SB scoring, while PSG with unilateral masseter or temporalis EMG showed fair accuracy, and chin EMG displayed poor accuracy. Based on these findings we recommend that clinicians and researchers should use at least the bilateral masseter muscles or bilateral temporalis muscles EMG channels for the assessment of SB.

Besides instrumental assessments of SB, self-report is commonly used in clinics and research. However, the SB prevalence based on self-report (26%[4]) is much lower than that on PSG (49% in **chapter 4**), suggesting that SB may be underestimated by self-report. However, it is of importance to note that both instrumental and non-instrumental methods for SB assessment have their advantages and disadvantages.[5] Self-report mainly depends on the report of tooth-grinding sound, indicating the condition of SB in a past period.[6,7] However, studies have proved that not all RMMAs (around 50%) are accompanied by tooth grinding sounds.[8,9] Clinical inspection, such as tooth wear and jaw muscle pain or fatigue, generally reflects long-

term consequences that possibly result from sleep and/or awake bruxism, which, however, can hardly be used as an indicator of ongoing SB.[10] In contrast, a full-night PSG or EMG can objectively demonstrate the condition of SB at the time of the recording, while it cannot directly reflect the clinical manifestation of SB.[10] Moreover, although the cut-off point of the RMMA index for SB diagnosis (RMMA ≥ 2 or 4 episodes/hour) was established to maximumly match the EMG data with the clinical signs of SB based on a selected sample, studies demonstrated that the RMMA index has a time-variant nature and poorly reflects the severity of SB and its negative consequences, making such approach not optimal for establishing the status of clinically relevant SB or non-SB. [11–15] Based on current knowledge, it is probable that no single method will adequately characterize all aspects of SB. A prediction model for SB based on longitudinal data of a large population sample would be promising to reflect and predict the symptoms and consequences of SB and responses to SB treatment.

In addition, although studies stated that RMMA and other oromotor activities (e.g. swallowing, chewing) have different EMG patterns and represent distinct activations of the brainstem, studies reported that the majority of masticatory muscle activities have a close temporal relationship with bodily movements (e.g., legs, arms), and that no difference was noted in the association with bodily movements between the two types of masticatory muscle activities (RMMA vs other oromotor activities).[16] This finding suggests that bodily movements and oromotor activities during sleep may have a similar or same neurophysiological process. Besides, other oromotor activities, which do not meet the EMG pattern of RMMA, may not be distinct from RMMA episodes in nature. Considering the poor correlation between the frequency of RMMA and the clinical signs and symptoms in relation to masticatory muscle activities (e.g., orofacial pain, tooth wear), it is probable that the intensity (including the frequency, the peak amplitude, and the total duration) of all types of masticatory muscle activities that contribute to the clinical manifestation. Future studies on the consequences of SB or masticatory muscle activities are recommended to take SB as well as other orofacial activities into considerations.

Prevalence and risk factors of SB

Studies have shown that SB is highly prevalent in adults with OSA. As a consequence of SB, adults with OSA may break their MAAs during sleep and/or develop temporomandibular

disorders.[17,18] Therefore, it is clinically relevant to determine the prevalence and risk factors of SB in adults with OSA. Both **chapter 3** and **chapter 4** deal with the prevalence and risk factors of SB in adults with OSA.

Chapter 3 systematically reviewed previous studies that reported the prevalence of SB in adults with other sleep-related disorders. Based on the included articles, the prevalence of SB in adults with OSA, restless leg syndrome, periodic limb movement during sleep, sleep-related gastroesophageal reflux disease, REM behavior disorder (RBD), and sleep-related epilepsy was found to be higher than that in the general population.[19–22] These findings suggest that SB may be a common comorbidity of many other sleep-related disorders, thus SB could not be regarded as an isolated phenomenon with only dental implications. Further, symptomatic alleviation of just the muscle activity (e.g., with botulinum toxin) may not be the most sensible approach for SB. Additionally, these findings also imply that some common factors or bridging factors that contribute to the higher prevalence of SB in these disorders may exist. In **chapter 4**, a large-scale PSG study was performed to determine the prevalence of SB in the adult OSA population. In a sample of 914 adults with OSA, the SB prevalence in adults with OSA turned out to be 49.7%. It is important to note that the prevalence validated by PSG is nearly two times higher than in self-report studies (26%-28%),[4,19] implying that a large number of adults with OSA are unaware of their SB condition. This phenomenon may also be present in adults with the abovementioned sleep-related disorders.

In addition, it is noteworthy that a recent debate on the status of SB, based on current evidence, reached a consensus that bruxism should be considered a common behavior that could be a risk factor, a protective factor, and/or a harmless behavior, rather than a disorder that is inherently causing harm to the person and representing a dysfunction in normal biopsychosocial processes.[23] In some cases, SB may increase the risk of some negative health consequences, such as severe mechanical tooth wear and muscle pain or fatigue, while it has also been reported to have some potentially protective consequences, such as reducing the chemical tooth wear by increasing salivation in individuals with gastroesophageal reflux, and restoring the patency of the upper airway in individuals with OSA.[24–26] It is also possible that SB may play both protective and harmful roles simultaneously in individual cases. For example, SB may help restore upper airway patency in individuals with OSA, while at the same time frequent SB episodes will increase the risk of severe tooth wear.

Considering the high prevalence of SB in adults with OSA and the possible negative consequences of SB, sleep physicians should be aware of SB in adults with OSA and/or with other sleep-related conditions, and refer those who report complaints related to SB (e.g., bruxism sound, severe tooth wear, and orofacial pain), to dentists for further examination and collaborative management.

The study in **chapter 4** also analyzed the risk factors for SB in adults with OSA. The logistic regression analysis showed that male gender, lower BMI, and a higher percentage of N1 increased the odds of having SB. Besides, a network analysis was performed in the study, which can present the direct and indirect associations between variables by a graph. The graph displayed that there is no direct link between the RMMA index and AHI or sleep arousal, but they can be connected by bridging factors, viz., BMI and gender. Based on this, future studies that investigate the association between SB and other disorders are recommended to take BMI and gender into consideration. In addition, these findings imply that associations between SB and other health conditions may be indirect, i.e., that they are linked by some bridging factors. This can be supported by a recent study from our group, which showed that the indirect association between SB and insomnia could be connected via anxiety.[27]

It is important to acknowledge that the study in **chapter 4** only considered limited factors. Other risk indicators or factors that have been reported to be related to SB, such as insomnia, periodic leg movement during sleep, stress, and anxiety, were not included in the analyses.[28,29] These factors may be directly related to SB, or act as bridging factors to connect SB and OSA. Therefore, a larger sample study including more potential risk factors and using network analysis or deep learning based on big data are promising to explore the complicated associations between SB and OSA, as well as the associations between SB and other health conditions.

Associations between OSA and SB

The association between OSA and SB could also shed light on the pathophysiology of SB in OSA. Although this topic has been investigated and discussed for decades, no consensus has been reached yet.[20,22,25,30–34]

Several chapters in this thesis investigated the association between masticatory muscle activity, sleep arousal, and respiratory event in adults with OSA. Previous studies on the sequences of respiratory and SB events suggest that the temporal relationship between the two events may vary at the individual level.[19,25,35,36] This is confirmed by a pilot study in **chapter 5** of this thesis. Besides, based on the large sample PSG study in **chapter 4**, no significant correlation between the RMMA index and AHI was found either. All these results support that the occurrence of SB in OSA does not rely on the presence of respiratory events. At the same time, most RMMAs (85.7%) were time-related to sleep arousals (**chapter 4**), regardless of their temporal relationships with respiratory events. Interestingly, this proportion of RMMA in relation to sleep arousals in adults with OSA is quite close to that in individuals with SB without OSA (88%).[37] These findings support that RMMA occurring after respiratory events is a response to sleep arousal rather than to the respiratory events per se.[38–40]

Notably, the frequencies of sleep arousal and RMMA are not linearly correlated as shown in previous studies and the one in **chapter 4**.[21,41] These seemingly contrasting findings regarding the associations between SB and arousal can be explained by the theory that sleep arousals only act as a permissive window for RMMA occurrence rather than being a trigger.[42,43] This can be supported by a study which showed that experimental arousals (induced by vibrotactile and auditory stimuli) can evoke RMMA in individuals with SB, but rarely in controls without SB.[44] These findings suggest that some endotypic traits in adults with SB must be present, making their jaw-motor system more responsive to arousals.[44] For example, as studies suggested that SB and respiratory muscle responses are associated with sleep arousal intensity,[40,45] it is worth identifying the common traits of arousal (e.g., peak amplitude, frequency, and duration) that are related to the occurrence of SB in future studies. Such studies would provide a deeper insight into the role of arousal in the genesis of SB.

By summarizing the evidence concerning the genesis of SB, a cause-conditions-effect model may be appropriate to describe the pathophysiology of SB. 1) Cause: individuals with SB are highly likely to have neurophysiological dysfunction in relation to masticatory muscle activity, which could be congenital (including genetic) or results from chronic diseases or disorders, such as OSA. This is in line with a study by Lobbezoo et al, which concluded that bruxism is mainly regulated centrally, not peripherally.[46] 2) Conditions: currently, sleep arousal is

considered the permissive window for the occurrence of SB, although available evidence shows that there are still around 10-15% of RMMAs that are not related to arousals. This might be attributed to the scoring rules for arousal, which only take the changes in EEG activity that are longer than three seconds into consideration.[47] Thus, the remainder of SB events might be related to those mini-arousals. 3) Effect: only when the cause and conditions are all present, do the RMMAs occur.

The cause-conditions-effect model could be used to elucidate the relationship between OSA and SB. On the one hand, untreated OSA may result in neurodegeneration and brain impairment,[48–50] which may in turn result in a malfunction of nuclei or nerves that are related to the generation of SB. In this case, OSA could be regarded as the cause for SB. However, whether OSA-induced brain changes contribute to the genesis of SB should be tested in future studies. Functional magnetic resonance imaging and transcranial magnetic stimulation might contribute to better understanding the pathophysiological mechanisms for both OSA and SB, as well as for their association. On the other hand: as we mentioned above, sleep arousal may act as a permissive window for the occurrence of SB. In this case, OSA could simply act as an arousal supplier, which has no direct association with SB. Besides, as mentioned above, SB may promote saliva secretion, and the latter could lubricate the upper airway and then reduce the upper airway resistance in OSA. This can be supported by evidence that more than 50% of RMMA is followed by swallowing episodes.[51,52] In this case, SB might be co-activated with pharyngeal muscles by factors in relation to oral dryness, such as increased levels of sympathetic nervous system activity, reduced vagal tone, or increased surface tension of the upper airway.[53] Similarly, SB may help restore upper airway patency by reinforcing the upper airway dilators in individuals with OSA. Studies have shown that there is a coactivation pattern of jaw-closing muscles, jaw-opening muscles, and muscles that dilate the upper airway after apneic or hypopneic events in OSA.[54–58] From this point, SB may be stimulated by factors in relation to respiratory muscles, such as respiratory effort, upper airway pressure, and tension of the upper airway in individuals with OSA.

Management of SB

Case reports showed that OSA therapies, such as CPAP, could relieve comorbid SB in adult cases with severe OSA.[59,60] However, this finding has not been investigated in previous studies.

The effects of OSA therapies on SB will yield evidence-based information for designing a comprehensive treatment procedure for adults with concomitant OSA and SB.

Chapter 6 presented a cohort study on the effects of CPAP and MAA on SB. The study showed that both CPAP and MAA significantly reduced the RMMA index in adults with OSA as well as in a subgroup of those with comorbid SB. Moreover, the results showed that there was no significant difference in the changes in the RMMA index between CPAP and MAA. These findings suggest that the treatment of OSA could relieve a comorbid SB, regardless of the therapies that patients received. In addition, since this is a retrospective study without a control group, the effect of CPAP and MAA on SB in OSA individuals should be confirmed in randomized controlled trials with an appropriate sample.

It is of importance to note that the effects of OSA therapies on SB vary at the individual level. For those who continuously report complaints about SB after (or during) OSA therapies, alternative and/or additional therapy is necessary to prevent and relieve the negative consequence of SB, e.g., severe tooth wear, jaw-muscle pain or fatigue, and headache. The multiple-P approach is also applicable for individuals with concomitant SB and OSA, including pep talk (counseling), psychotherapy, physiotherapy, and pills (medicine).[61]

Conclusions

SB is a common comorbidity of adults with OSA. The associations between OSA and SB may have different patterns that vary at the individual level. This may explain why the effectiveness of OSA therapy on SB varies at an individual level.

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Chapter 8

Summary

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder, manifesting as apnea or hypopnea during sleep, which generally results in oxygen desaturation and sleep arousal. Sleep bruxism (SB) is a masticatory muscle activity occurring during sleep that is characterized as rhythmic or non-rhythmic. Both OSA and SB are common sleep-related conditions. Many studies reported that a large proportion of individuals with OSA were diagnosed with SB, suggesting a possible positive association between OSA and SB. However, due to the limited sample and different assessment methods used in previous studies, the reported occurrence rates of SB in OSA vary widely, from 26% to 100%. Also, evidence regarding the mechanism to support their association is lacking and inconclusive. Therefore, this thesis aimed to determine the essential number and type of jaw muscles for valid SB scoring in adults with OSA (chapter 2), to investigate the prevalence and risk factors of SB in adults with OSA (chapters 3 and 4), to explore the underlying mechanism of the association between OSA and SB (chapters 3, 4 and 5), and to identify the effects of OSA therapies on SB (chapter 5 and 6).

Chapter 1 is a general introduction to this thesis, in which the background knowledge, the general aims, as well as a brief description of each chapter are provided.

In **Chapter 2**, the accuracy of chin, masseter and temporalis EMG in SB scoring was analyzed, aiming to determine the essential number and type of jaw muscles for a valid SB scoring in adults with OSA. Ten adults with OSA, who received PSG and had eligible chin, masseter, and temporalis EMG traces, were admitted into this study. The accuracies of six scoring setups, namely, the unilateral or bilateral chin, masseter, or temporalis EMG traces, were analyzed by comparing them with a reference standard (bilateral masseter and temporalis EMG traces). Bilateral masseter or temporalis EMG traces displayed good accuracy in SB scoring (sensitivity: 87% and 72%; positive predictive value: 83% and 76%), while PSG with unilateral masseter or temporalis EMG trace had good sensitivity (88% and 88%) but only a fair positive predictive value (60% and 53%). In contrast, chin EMG, regardless of unilateral or bilateral, showed poor to fair accuracy (ICC: 0.662, 0.657; sensitivity: 41%, 40%; positive predictive value: 63% and 61%). Based on these results, PSG with bilateral masseter or temporalis muscle EMG traces is regarded as valid in SB scoring in individuals with OSA.

Chapter 3 provides a systematic review on the association between SB and other sleep-related disorders in adults, including OSA. A systematic search was performed in PubMed,

Embase, Cochrane Library, and Web of Science, using search terms and synonyms of “sleep bruxism” and all the other sleep-related disorders, such as “sleep-wake disorder”, “obstructive sleep apnea” and “insomnia”. Finally, 37 eligible articles that reported the prevalence of SB in adults with other sleep-related disorders or investigated the underlying mechanism of the association between SB and other sleep-related disorders were included in this review. The prevalence of SB in adult patients with OSA, restless leg syndrome, periodic limb movement during sleep, sleep-related gastroesophageal reflux disease, REM behavior disorder, and sleep-related epilepsy was higher than that in the general population. The specific mechanisms behind these positive associations could not be identified. Nonetheless, sleep arousals seem to be a common factor to which both SB and these sleep-related disorders are related. Among the included articles, 14 articles dealt with SB and OSA. Of these articles, one reported that the prevalence of possible SB (based on self-report) in adults with OSA was 26%, and five articles showed that the prevalence of definite SB, validated by PSG, ranges from 33% to 53.7%. Thirteen out of the 14 articles explored the possible mechanism of the association between SB and OSA, mainly by analyzing the association between SB and respiratory events, and between SB and sleep arousal. However, the evidence did not allow us to draw a definitive conclusion regarding the association between SB and OSA.

In **Chapter 4,** a large-scale PSG study was performed to determine the prevalence and risk factors of SB in adults with OSA. In addition, this study investigated the correlation between SB episodes, sleep arousals, and respiratory events. Through reviewing 2639 OSA individuals’ medical profiles and PSG recordings, 914 individuals who had eligible PSG recordings without any interventions were eventually included in the analysis of this study. The diagnosis of SB was made when the RMMA index was at least two episodes per hour of sleep. As a result, 49.7% of the adults with OSA were diagnosed with comorbid SB. Besides, based on a binary logistic regression analysis, male gender (OR=1.425) and lower body mass index (OR=0.951) were significant risk factors for SB in adults with OSA. In addition, a network analysis was performed to investigate the association between RMMA, AHI, sleep arousal, and other SB-relevant factors. Although no direct association was found between RMMA and AHI, and between RMMA and sleep arousals, 85.7% of RMMA episodes were associated with sleep arousals, with more RMMAs related to non-respiratory arousals than to respiratory arousals.

These results further confirmed that SB has a weak association with respiratory events, and that SB is more like a motor response to sleep arousal.

The study in **Chapter 5** investigated the effects of mandibular advancement appliance (MAA) on sequences of jaw-closing muscle activity (JCMA) and respiratory events in individuals with OSA. Sixteen individuals with OSA who received MAA therapy and two ambulatory PSG recordings (one with MAA *in situ* and the other without MAA) were included in this randomized crossover study. Based on the temporal relationship between JCMA and respiratory events, JCMAs were classified into four possible sequences by employing a 16-second rule: before (JCMA occurs before the respiratory event), during (JCMA occurs during the respiratory event), after (JCMA occurs after a respiratory event) and time-unrelated (JCMA occurs before or after respiratory event beyond the 16-second window). In both conditions, without and with MAA *in situ*, most JCMAs were time-unrelated to respiratory events (48% and 65%, respectively). The second common sequence was the after-type (41% and 22%), followed by the before-type (25% and 21%). The least common sequence was the during type (2% and 1%). These results suggest that all four sequences are possible and that the occurrence of JCMA does not rely on the presence of respiratory events in OSA. In addition, with MAA *in situ*, only the after-type JCMA decreased significantly ($P<0.05$), while other sequence-type JCMA did not change significantly ($P>0.05$). These results allow us to conclude that effective MAA therapy only significantly reduces the JCMA that occurs after apneic or hypopneic events in adults with OSA.

Chapter 6 displays a cohort study that aimed to investigate the effects of continuous positive airway pressure (CPAP) and MAA therapy on RMMA, and to compare the effects of CPAP with MAA in adults with OSA. Thirty-eight adults with OSA who received therapy of CPAP (n=13) or MAA (n=25) were included in this study. The RMMA index decreased significantly with CPAP and MAA therapies ($P < 0.05$). This result suggests that OSA therapies could relieve the comorbid SB in the OSA population. Moreover, no difference in the changes of the RMMA index was found between CPAP and MAA, probably suggesting that the comorbid SB would not influence OSA patients' choice between CPAP and MAA. It is of importance to note that the RMMA index decreased in only 60% of the individuals with OSA. Further, in line with previous studies, the effects of OSA therapies on SB varied at an individual level.

Chapter 8 summary

Chapter 7 presents a general discussion of the main findings of this thesis. In addition, it discusses the clinical implications of these findings and provides recommendations for future research.

Conclusions

Valid SB scoring should be based on bilateral masseter and/or temporalis muscle EMG. SB is a common comorbidity of OSA, especially in those with male gender and low body mass index. The associations between OSA and SB may have different patterns that vary between individuals. This may explain why the effectiveness of OSA therapy on SB varies at an individual level.

Chapter 9

Samenvatting

Obstructieve slaapapneu (OSA) is een slaapgerelateerde ademhalingsstoornis, die zich manifesteert als apneu of hypopneu tijdens de slaap, wat meestal leidt tot zuurstofdesaturatie en slaap-arousals. Slaapbruxisme (SB) is een kauwspieractiviteit tijdens de slaap die wordt gekenmerkt als ritmisch of niet-ritmisch. Zowel OSA als SB zijn veel voorkomende slaapgerelateerde aandoeningen. Veel studies meldden dat bij een groot deel van de personen met OSA SB werd vastgesteld, wat wijst op een mogelijk positief verband tussen OSA en SB. Vanwege de beperkte steekproefgroottes en de verschillende beoordelingsmethoden die in eerdere studies werden gebruikt, lopen de gerapporteerde percentages van SB bij OSA echter sterk uiteen, van 26% tot 100%. Ook ontbreekt het bewijs voor het onderliggende mechanisme van deze associatie. Daarom was dit proefschrift gericht op: het bepalen van het essentiële aantal en type kaakspieren voor een valide SB-score bij volwassenen met OSA (hoofdstuk 2), het onderzoeken van de prevalentie en risicofactoren van SB bij volwassenen met OSA (hoofdstukken 3 en 4), het onderzoeken van het onderliggende mechanisme van de associatie tussen OSA en SB (hoofdstukken 3, 4 en 5), en het vaststellen van de effecten van OSA-therapieën op SB (hoofdstuk 6).

Hoofdstuk 1 is een algemene inleiding tot dit proefschrift, waarin de achtergrondkennis, de algemene doelstellingen en een korte beschrijving van elk hoofdstuk worden gegeven.

In **hoofdstuk 2** werd de nauwkeurigheid van het EMG van de kin, de m. masseter en m. temporalis bij het scoren van SB geanalyseerd, met als doel het bepalen van het essentiële aantal en type kaakspieren voor een valide SB-score bij volwassenen met OSA. Tien volwassenen met OSA die PSG ondergingen met EMG-kanalen van kin, masseter en temporalis, werden in deze studie opgenomen. De nauwkeurigheid van zes score-methoden, namelijk de unilaterale of bilaterale kin-, masseter- of temporalis EMG-kanalen, werd geanalyseerd door vergelijking met een referentiestandaard (bilaterale masseter- en temporalis EMG-kanalen). Bilaterale masseter of temporalis EMG-kanalen vertoonden een goede nauwkeurigheid in SB-score (gevoeligheid: 87% en 72%; positief voorspellende waarde: 83% en 76%), terwijl PSG met een unilateraal masseter of temporalis EMG-kanaal een goede gevoeligheid had (88% en 88%) maar slechts een redelijke positief voorspellende waarde (60% en 53%). Daarentegen vertoonde kin-EMG, ongeacht of het unilateraal of bilateraal was, een slechte tot redelijke nauwkeurigheid (ICC: 0.662, 0.657; gevoeligheid: 41%, 40%; positief

voorspellende waarde: 63% en 61%). Op basis van deze resultaten wordt PSG met bilaterale masseter of temporalis EMG-kanalen als valide beschouwd in de SB-scoring bij personen met OSA.

Hoofdstuk 3 geeft een systematisch overzicht van de associatie tussen SB en andere slaapgerelateerde aandoeningen bij volwassenen, waaronder OSA. Er werd systematisch gezocht in PubMed, Embase, Cochrane Library en Web of Science, met zoektermen en synoniemen van "slaapbruxisme" en alle andere slaapgerelateerde stoornissen, zoals "slaap-waakstoornis", "obstructief slaapapneu" en "slapeloosheid". Tenslotte werden 37 in aanmerking komende artikelen, die de prevalentie van SB bij volwassenen met andere slaapgerelateerde stoornissen rapporteerden of het onderliggende mechanisme van de associatie tussen SB en andere slaapgerelateerde stoornissen onderzochten, opgenomen in deze review. De prevalentie van SB bij volwassen patiënten met OSA, rusteloze-beensyndroom, periodieke ledematenbeweging tijdens de slaap, slaapgerelateerde gastrooesofageale refluxziekte, REM-gedragsstoornis en slaapgerelateerde epilepsie was hoger dan die in de algemene bevolking. De specifieke mechanismen achter deze positieve associaties konden niet worden geïdentificeerd. Niettemin lijkt slaap-arousal een gemeenschappelijke factor te zijn die zowel bij SB als bij deze slaapgerelateerde aandoeningen relevant is. Van de opgenomen artikelen hadden er 14 betrekking op SB en OSA. Van deze artikelen meldde er één dat de prevalentie van mogelijke SB (gebaseerd op zelfrapportage) bij volwassenen met OSA 26% was, en vijf artikelen toonden aan dat de prevalentie van ‘definite’ SB, gevalideerd door PSG, varieert van 33% tot 53.7%. 13 van de 14 artikelen onderzochten het mogelijke mechanisme van de associatie tussen SB en OSA, voornamelijk door de associatie tussen SB en ademhalingsgebeurtenissen en tussen SB en slaap-arousal te analyseren. De bewijslast liet echter niet toe een definitieve conclusie te trekken over de associatie tussen SB en OSA.

In **hoofdstuk 4** werd een grootschalig PSG-onderzoek uitgevoerd om de prevalentie en de risicofactoren van SB bij volwassenen met OSA te bepalen. Bovendien onderzocht deze studie de correlatie tussen SB-episodes, slaap-arousals en ademhalingsgebeurtenissen. Door de medische profielen en PSG-opnames van 2639 OSA-personen te bekijken, werden uiteindelijk 914 personen zonder enige interventie die in aanmerking kwamen voor PSG-registraties opgenomen in de analyse van deze studie. De diagnose SB werd gesteld wanneer de RMMA-

index ten minste twee episodes per uur slaap bedroeg. Bijgevolg werd bij 49.7% van de volwassenen met OSA de diagnose comorbide SB gesteld. Op basis van een binaire logistische regressieanalyse waren mannelijk geslacht (OR=1.425) en een lagere 'body mass index' (OR=0.951) significante risicofactoren voor SB bij volwassenen met OSA. Daarnaast werd een netwerkanalyse uitgevoerd om de associatie tussen RMMA, AHI, slaap-arousal en andere SB-relevante factoren te onderzoeken. Hoewel er geen direct verband werd gevonden tussen RMMA en AHI, en tussen RMMA en slaap-arousal, was 85.7% van de RMMA-episodes geassocieerd met slaap-arousal, waarbij meer RMMA's gerelateerd waren aan niet-respiratoire dan aan respiratoire arousals. Deze resultaten bevestigden verder dat SB een zwakke associatie heeft met respiratoire gebeurtenissen, en dat SB meer lijkt op een motorische respons op slaap-arousal.

De studie in **hoofdstuk 5** onderzocht de effecten van het mandibulair repositieapparaat (MRA) op de opeenvolging van kaaksluitspieractiviteit (JCMA) en ademhalingsgebeurtenissen bij personen met OSA. Zestien personen met OSA die MRA-therapieën kregen en twee ambulante PSG opnames (één met MRA in situ en de andere zonder MRA) werden geïncludeerd in deze gerandomiseerde cross-over studie. Op basis van de tijdsrelatie tussen JCMA en ademhalingsgebeurtenissen werden JCMA's ingedeeld in vier mogelijke volgordes door een 16-secondenregel toe te passen: vóór (JCMA treedt op vóór de ademhalingsgebeurtenis), tijdens (JCMA treedt op tijdens de ademhalingsgebeurtenis), na (JCMA treedt op na een ademhalingsgebeurtenis) en tijd-ongerelateerd (JCMA treedt op vóór of na een ademhalingsgebeurtenis, buiten het 16-secondenvenster). In beide omstandigheden, zonder en met MRA in situ, waren de meeste JCMA's niet-tijdgebonden aan ademhalingsgebeurtenissen (respectievelijk 48% en 65%). De op één na meest voorkomende volgorde was het na-type (41% en 22%), gevolgd door het voor-type (25% en 21%). Het minst voorkomend was het tijdens-type (2% en 1%). Deze resultaten suggereren dat alle vier de volgordes mogelijk zijn, en dat het optreden van JCMA niet afhankelijk is van de aanwezigheid van ademhalingsgebeurtenissen bij OSA. Bovendien nam, met MRA in situ, alleen het na-type significant af ($P<0.05$), terwijl andere JCMA-volgorde-types niet significant veranderden ($P>0.05$). Deze resultaten laten ons concluderen dat effectieve MRA-therapie alleen de JCMA's die optreden na apneus of hypopneus bij volwassenen met OSA significant vermindert.

Hoofdstuk 6 beschrijft een cohortstudie die tot doel had de effecten van continue positieve luchtwegdruk (CPAP) en MRA-therapie op RMMA te onderzoeken, en de effecten van CPAP met MRA te vergelijken bij volwassenen met OSA. Achtendertig volwassenen met OSA die een behandeling kregen met CPAP (n=13) of MRA (n=25) werden in deze studie geïncludeerd. De RMMA-index daalde significant met CPAP- en MRA-therapieën ($P < 0.05$). Dit resultaat suggereert dat OSA-therapieën de comorbide SB in de OSA-populatie kunnen verlichten. Bovendien werd geen verschil in de veranderingen van de RMMA-index gevonden tussen CPAP en MAA, wat impliceert dat de comorbide SB de keuze van OSA-patiënten tussen CPAP en MAA niet zou hoeven te beïnvloeden. Het is van belang op te merken dat de RMMA-index daalde bij slechts 60% van de personen met OSA. Verder variëren, in overeenstemming met eerdere studies, de effecten van OSA-therapieën op SB op individueel niveau.

Hoofdstuk 7 betreft een algemene bespreking van de belangrijkste bevindingen van dit proefschrift, evenals de klinische implicaties van deze bevindingen en aanbevelingen voor toekomstig onderzoek.

Conclusies

Valide SB-scores moeten gebaseerd zijn op bilaterale masseter en/of temporalis EMG-registraties. SB is een veel voorkomende comorbiditeit van OSA, vooral bij mannen en bij een lage ‘body mass index’. De associaties tussen OSA en SB kunnen verschillende patronen vertonen die tussen individuen variëren. Dit kan verklaren waarom de effectiviteit van OSA-therapie op SB op individueel niveau varieert.

APPENDICES

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Chapter 2 Accuracy of sleep bruxism scoring based on electromyography traces of different jaw muscles in individuals with obstructive sleep apnea

- Study design: DL, FL, GA
- Data collection: DL, GA, NH, PA
- Data analysis: DL, FL, GA
- Interpretation of results: DL, FL, GA, GL, NH
- Preparation of the manuscript: DL, FL, GA, GL, NH, PA

Chapter 3 Associations between sleep bruxism and other sleep-related disorders in adults: a systematic review

- Study design: BK, DL, FL, GL, NH, GA
- Data collection: BK, DL, RV
- Data analysis: BK, DL
- Interpretation of results: AH, BK, DL, FL, GA, GL, NH, NV
- Preparation of the manuscript: AH, BK, DL, FL, GA, GL, RV, NH, NV

Chapter 4 The effects of mandibular advancement appliance therapy on the sequence of jaw-closing muscle activity and respiratory events in individuals with obstructive sleep apnea

- Study design: DL, FL, GA
- Data collection: DL, GA, NH, PA
- Data analysis: DL, FL, GA
- Interpretation of results: DL, FL, GA, GL, NH
- Preparation of the manuscript: DL, FL, GA, GL, NH, PA

Chapter 5 Sleep bruxism is highly prevalent in adults with obstructive sleep apnea: a large-scale polysomnographic study

- Study design: DL, FL, GA
- Data collection: AH, BK, DL
- Data analysis: DL, FL, GA
- Interpretation of results: AH, BK, DL, FL, GA, NV
- Preparation of the manuscript: AH, BK, DL, FL, GA, NV

Chapter 6 Effects of continuous positive airway pressure and mandibular advancement appliance therapy on sleep bruxism in adults with obstructive sleep apnea

- Study design: DL, FL, GA
- Data collection: AH, BK, DL
- Data analysis: DL, FL, GA
- Interpretation of results: AH, DL, FL, GA, NV
- Preparation of the manuscript: AH, BK, DL, FL, GA, NV

Publications

- Li D, Aarab G, Lobbezoo F, Arcache P, Lavigne GJ, Huynh N. Accuracy of sleep bruxism scoring based on electromyography traces of different jaw muscles in individuals with obstructive sleep apnea. *J Clin Sleep Med*. 2022;18(6):1609-1615. doi:10.5664/jcsm.9940
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Deshui Li was born in 1989 in Dezhou, China. In 2008, he started studying Dentistry at Binzhou Medical University, Shandong, China. In June 2016, he graduated as a dentist and obtained his master's degree in orthodontics. After that, he started his clinical work as an orthodontist in the Department of Orthodontics at the Stomatological Hospital of Shandong University, Jinan, China. One year later (2017), he received a Ph.D. position at the department of Orofacial Pain and Dysfunction at Academic Centre for Dentistry Amsterdam (ACTA) in The Netherlands, and he obtained financial support from the China Scholarship Council (CSC), China. In March 2022, he restarted his clinical work at the Stomatological Hospital of Shandong University, while finalizing his PhD thesis.

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prevalence
events
RMMA
BMI
Jaw closing muscle activity
N1
Masticatory
male
Therapy
Scoring
Bruxism
AHI
accuracy
Risk factor
EMG
sleep
discreapncy
Arousal
PSG
chin
airway
respiratory
clinical
OSA
Association
disorder
CPAP
Treatment
Adult
Masseter
bilateral
Oral applicance
Temporalis
individual
sequence