REVIEW ARTICLE

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Associations between obstructive sleep apnea and painful temporomandibular disorder: a systematic review

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Abstract (J Korean Assoc Oral Maxillofac Surg 2022;48:259-266)

The relationship between obstructive sleep apnea (OSA) and diverse types of pain conditions have been proposed. However, no consensus on the relationship between OSA and painful temporomandibular disorders (TMDs) has been established. Therefore, this systematic review has been conducted to review the existing literatures and provide comprehensive synthesis of such literatures about OSA and painful TMDs using the evidence-based methodology. A literature search was conducted using two electronic databases, Scopus, and PubMed. Risk of bias was assessed using the risk-of-bias assessment tool for non-randomized study version 2.0. A total of 158 articles were screened from the initial search and eventually, 5 articles were included in this systematic review. One study adopted both the longitudinal prospective cohort and case-control designs and other 4 articles adopted the cross-sectional design. Two studies employed polysomnography (PSG) for the diagnosis of OSA and mentioned the results from the PSG. All cross-sectional studies demonstrated higher OSA prevalence among patients with TMD, and one cohort study suggested OSA as a risk factor for TMD. OSA appears to have potential influences on the development of TMD; however, the role of TMD in the development of OSA remains to be unknown owing to the lack of high-quality evidences.

Key words: Obstructive sleep apnea, Temporomandibular disorder, Pain, Inflammation, Sleep fragmentation

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I. Introduction

Temporomandibular disorder (TMD) is a collective term which includes pain conditions and functional disabilities occurring in the temporomandibular joint, masticatory muscles, and their surrounding structures[1]. TMD can manifest high levels of its complexity via complicated pathophysiology and wide and variety spectrums of comorbidities including headache, chronic fatigue syndrome and so on[2,3].

Sleep disorders are among the well-known comorbidities of TMD, particularly painful TMDs[2,4-12]. Sleep quality deterioration and chronic pain seem to have a bi-directional association; however, the influences of poor sleep quality on chronic pain are greater than those of chronic pain on sleep quality. Several studies demonstrated that poor sleep quality greatly exacerbated pain but chronic pain only minimally leaded to poor sleep quality[13,14]. Therefore, for proper management of the painful TMD patients in TMD and orofacial pain clinics, thorough understanding of the complex pathophysiology of the sleep disorders and prompt diagnosis and treatment are necessary.

Obstructive sleep apnea (OSA) is one of the most prevalent sleep-related breathing disorders in the general population and it is accompanied by diverse types of comorbidities, such as cardiovascular diseases, cognitive impairment, traffic accident, depression, and increased risk of mortality[15-19]. OSA may cause sleep fragmentation and nocturnal hypoxemia which is related to hyperalgesia. Several studies have attempted previously to reveal interactions between pain modulating mechanisms and sleep disorders in terms of aforementioned factors[17,20,21]. It has also been reported that 36% of TMD patients that met the diagnostic criteria for insomnia and over 28% for OSA[22]. On the other hand, 51% of OSA pa-

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tients exhibited signs and symptoms of TMD compared with normal controls[23]. One prospective long-term cohort study suggested OSA as a risk factor for painful TMD in the long term[24]. Even though, several evidences have been proposed to clarify the association between OSA and painful TMDs, there is no consensus on the relationship between these two different entities. Therefore, the purpose of this systematic review was to review the existing literatures and provide comprehensive synthesis of such literatures about OSA and painful TMDs based on the evidence-based methodology.

II. Materials and Methods

1. Study design and registration

This systemic review was conducted in compliance with the Preferred Reporting Items for Systemic Review and Meta-Analysis (PRISMA) guidelines[25].

2. Eligibility criteria

This review included observation studies which evaluated the association between painful TMD and OSA in adults. Painful TMDs were assessed using validated diagnostic criteria and protocols including Diagnostic Criteria for TMD (DC/TMD) or Research Diagnostic Criteria for TMD (RDC/TMD). OSA was assessed through validated self-administered questionnaires, designed for screening OSA such as STOP-BANG questionnaires and/or level I-IV polysomnography (PSG).

The studies including pediatrics and/or adolescents, younger than 19 years old; studies with unvalidated diagnostic criteria for painful TMD and OSA; scoping, narrative and systematic literature reviews; case reports; animal studies; non-English language studies, and studies with confounding diagnosis including stroke, headache, bruxism, and/or depression were excluded.

Table 1. Strategies for electronic search

Database	No.	Query	Results
Scopus	4	#1 AND #2 AND #3	77
	3	TITLE-ABS-KEY (“pain” OR “pains”)	897,524
	2	TITLE-ABS-KEY (“temporomandibular pain disorder*” OR “temporo-mandibular pain disorder*” OR “temporomandibular disorder*” OR “temporomandibular disease*” OR “temporomandibular dysfunction*” OR “temporo-mandibular disorder*” OR “temporo-mandibular disease*” OR “temporo-mandibular dysfunction*” OR “TMD” OR “TMDs” OR “temporomandibular joint disorder*” OR “temporomandibular joint disease*” OR “temporomandibular joint dysfunction*” OR “temporo-mandibular joint disorder*” OR “temporo-mandibular joint disease*” OR “temporo-mandibular joint dysfunction*” OR “TMJ” OR “TMJ disorder*” OR “TMJD*” OR “jaw disease*” OR “jaw disorder*” OR “mandible injur*” OR “mandibular disease*” OR “mandibular injury*” OR “maxillary disease*”)	29,275
	1	TITLE-ABS-KEY (“sleep apnea*” OR “sleep apnoea*” OR “obstructive sleep apnea*” OR “obstructive sleep apnoea*” OR “nocturnal apnea” OR “nocturnal apnoea” OR “sleep-disordered breath*” OR “sleep-disorder breath*” OR ((“OSA” OR “OSAHS” OR “SDB” OR “OSDB”) AND “sleep*”) OR ((“upper airway resistant*” OR “upper airway obstruction*” OR “hypoxia”) AND “sleep*”))	55,174
PubMed	4	#1 AND #2 AND #3	148
	3	“Pain”[mesh] OR “pain”[tiab] OR “pains”[tiab]	1,329,334
	2	“Temporomandibular Joint Disorders”[mesh] OR “Temporomandibular Joint Dysfunction Syndrome”[mesh] OR “temporomandibular pain disorder*”[tiab] OR “temporo-mandibular pain disorder*”[tiab] OR “temporomandibular disorder*”[tiab] OR “temporomandibular disease*”[tiab] OR “temporomandibular dysfunction*”[tiab] OR “temporo-mandibular disorder*”[tiab] OR “temporo-mandibular disease*”[tiab] OR “temporo-mandibular dysfunction*”[tiab] OR “TMD”[tiab] OR “TMDs”[tiab] OR “temporomandibular joint disorder*”[tiab] OR “temporomandibular joint disease*”[tiab] OR “temporomandibular joint dysfunction*”[tiab] OR “temporo-mandibular joint disorder*”[tiab] OR “temporo-mandibular joint disease*”[tiab] OR “temporo-mandibular joint dysfunction*”[tiab] OR “TMJ”[tiab] OR “TMJ disorder*”[tiab] OR “TMJD*”[tiab] OR “jaw disease*”[tiab] OR “jaw disorder*”[tiab] OR “mandible injur*”[tiab] OR “mandibular disease*”[tiab] OR “mandibular injur*”[tiab] OR “maxillary disease*”[tiab]	57,120
	1	“Sleep Apnea Syndromes”[mesh:noexp] OR “Sleep Apnea, Obstructive”[mesh:noexp] OR “sleep apnea*”[tiab] OR “sleep apnoea*”[tiab] OR “obstructive sleep apnea*”[tiab] OR “obstructive sleep apnoea*”[tiab] OR “nocturnal apnea”[tiab] OR “nocturnal apnoea”[tiab] OR “sleep-disordered breath*”[tiab] OR “sleep-disorder breath*”[tiab] OR ((“OSA”[tiab] OR “OSAHS”[tiab] OR “SDB”[tiab] OR “OSDB”[tiab]) AND “sleep*”[tiab]) OR ((“upper airway resistan*”[tiab] OR “upper airway obstructi*”[tiab] OR “hypoxia”[tiab]) AND “sleep*”[tiab])	80,660

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3. Search strategies

A literature search was conducted using two electronic databases, namely, Scopus, and PubMed, from 1982 to 2022. Reference lists from relevant scoping, narrative, and systematic reviews or original articles were also search to identify further relevant literatures.

Multiple keywords and MeSH (Medical Subject Headings) terms related to OSA and painful TMD were used for the electronic search. The search strategies for Scopus and PubMed were listed in Table 1. Two reviewers (J.H.K. and J.K.L.) independently screened the title and abstract of the identified appropriate studies included in this systematic review. If both reviewer had inconsistent decisions regarding an article, such an article was excluded.

4. Risk of bias assessment

One orofacial pain specialist (J.H.K.) and one librarian who as expertise in methodology and literature search evaluated the methodological quality of the eligible articles using the risk-of-bias assessment tool for non-randomized study (RoBANS) version 2.0[26]. The RoBANS covers six areas; the selection of participants, confounding variables, the measurement of exposure, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting. Each area of the RoBANS tool was judged as either 'low', 'high', or 'unclear' risk of bias. Two assessors independently evaluated the risk of bias of the articles based on the RoBANS tool, and items inconsistent with each other were determined via thorough discussion.

III. Results

1. Literature selection and characteristics of the selective studies

A total of 77 articles from Scopus and 148 articles from PubMed database were identified. After removing duplicated articles, 158 articles were identified from the initial search. After the title and abstract screening and full-text assessment, 5 studies were finally included in this systematic review.(Fig. 1, Table 2) One study adopted both prospective cohort and case-control design[27], two studies used the cross-sectional case-control study design[22,28], and the other two studies adopted the cross-sectional study design[23,29]. TMDs were diagnosed using the RDC/TMD[22,27,28] or DC/TMD criteria[23,29]. Three studies employed overnight full-channel PSG to evaluate respiratory events and the sleep qualities whereas other two studies used self-administered questionnaires[23,29].

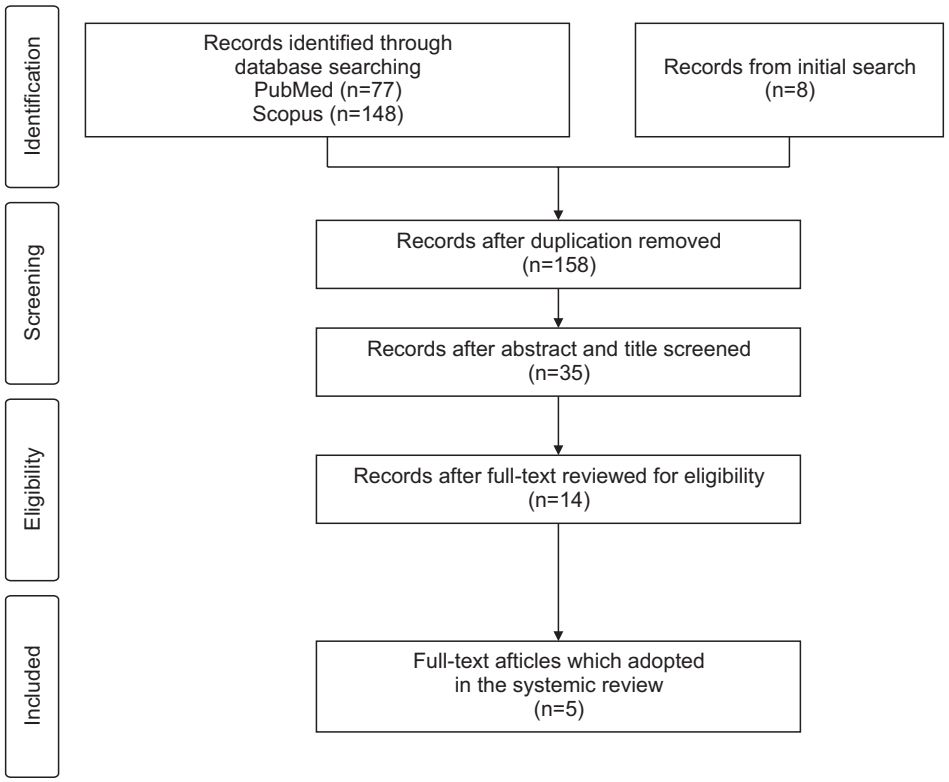

Fig. 1. The PRISMA (Preferred Reporting Items for Systemic Review and Meta-Analysis) flow chart.
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Table 2. Descriptive characteristics of the included studies (n=5)

Study	Study design	Cases	Controls	Diagnostic criterial for painful TMD	Evaluation of sleep apnea and sleep quality	Major study findings
Alessandri-Bonetti et al.[23] (2021)	Cross-sectional	41 consecutive patients with OSA	41 healthy controls	DC/TMD	PSG, site of obstruction observed by DISE	• 51% of consecutive OSA patients presented TMD signs and/or symptoms and 32% of controls showed TMD signs and/or symptoms.
Dubrovsky et al.[28] (2014)	Case-control	124 females with myofascial TMD	46 females without myofascial TMD	RDC/TMD criteria	PSG, ESS	• TMD cases demonstrated higher levels of respiratory events and arousal. • TMD cases with chronic myofascial TMD presented mild sleep disturbance and mild increase in upper airway resistance. • The degree of sleep disturbance and upper airway resistance were associated with acute myofascial pain levels.
Lee et al.[29] (2022)	Cross-sectional	503 chronic TMD patients	180 healthy controls	DC/TMD axis I	PSQI, STOP-BANG, ESS	• PSQI scores were higher in patients compared to controls and poor sleep was more prevalent in TMD patients. • Patients with chronic TMD had a higher likelihood of OSA and showed higher daytime sleepiness.
Sanders et al.[27] (2013)	Prospective cohort Case-control	2,604 participants in cohort study 1,614 participants in the case-control study	Random sample of 102 controls with low likelihood of OSA	RDC/TMD criteria	PSQI, 4-itmes STOP screening questionnaire	• Prospective cohort study: 1st onset TMD was two times higher in the 60% participants with high likelihood of OSA. • Case control study: chronic TMD cases had 3-fold higher odd ratios of high likelihood of OSA.
Smith et al.[22] (2009)	Cross-sectional	53 patients with myofascial TMD	-	RDC/TMD axis I	ISI, PSG, PSQI, ESS	• 89% of participants with myofascial TMD met the criteria for at least one sleep disorder and 43.4% of participants with myofascial TMD were diagnosed with more than 2 sleep disorders. • Prevalence of primary insomnia and sleep apnea was high in myofascial TMD patients. • The primary insomnia bay play a role in hyperalgesia in myofascial TMD patients.

(OSA: obstructive sleep apnea, DC/TMD: Diagnostic Criteria for Temporomandibular Disorders, PSG: polysomnography, DISE: drug induced sleep endoscopy, TMD: temporomandibular disorder, RDC/TMD: Research Diagnostic Criteria for TMD, ESS: excessive daytime sleepiness, PSQI: Pittsburg Sleep Quality Index, ISI: Insomnia Severity Index)

2. Methodological quality assessment of the included articles

Four studies clearly mentioned the inclusion criteria[22,27-29], whereas one study did not clearly state the inclusion criteria and basement assessment for controls[23]. Two studies measured and controlled confounding factors[22,27], whereas three studies did not[23,28,29]. All studies were conducted without employing blindness between the observers and participants, and between observers and evaluators[22,23,27-29].(Fig. 2, 3)

3. Results from individual studies

Three studies which employed overnight full channel PSG for assessing OSA showed that myofascial TMD patients presented higher levels of sleep disturbances, respiratory events and arousals[22,23,28]. Two of the three studies reported precise PSG data about sleep quality, oxygen desaturation, and respiratory events[22,28] but the other study did not[23]. One study suggested the primary insomnia as a potential risk factor for hyperalgesia and central sensitization in patients with myofascial TMD which was diagnosed using the RDC/TMD criteria[22]. Primary insomnia was found to be correlated with mechanical and thermal thresholds on the masseter muscle and forearm and the respiratory disturbance index with increased pressure pain thresholds on the forearm[22]. Another study demonstrated that patients with TMD had higher levels of respiratory events and arousal compared with controls and that the levels of sleep disturbance and upper airway resistance were associated with acute myofascial pain levels[23]. One study that employed both cross-sectional and prospective cohort designs suggested that OSA was a potential risk factor for TMD but could not determine role of TMD on onset of OSA[27]. The results from the longitudinal prospective cohort study demonstrated that 1st onset TMD was two times higher in the 60% participants with high likelihood OSA[27]. This study also presented the results from the cross-sectional study indicating that chronic TMD cases exhibited 3-fold higher odds of high likelihood of OSA[27]. However, this study used self-administered questionnaires to screen the risk of OSA and did not used the PSG. One cross-sectional study demonstrated that consecutive patients with OSA had increased risk of TMD. Conversely, another cross-sectional study showed that patients with chronic TMD had deteriorated sleep quality and increased risk of OSA[29]. Hence, OSA appears to have potential influences on the development of TMD; however,

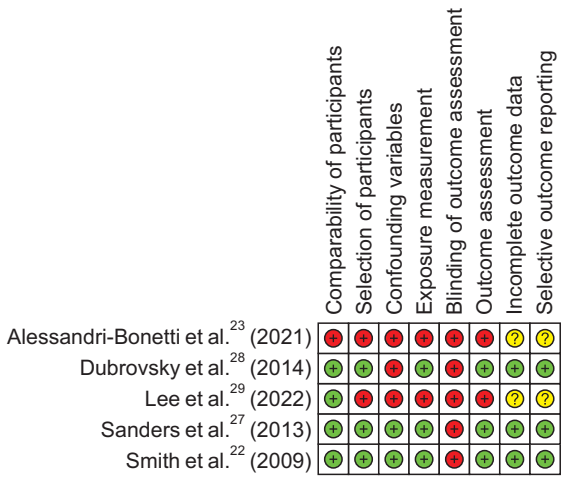

Fig. 3. RoBANS (risk-of-bias assessment tool for non-randomized study) summary. Green: low risk of bias, Yellow: unclear risk of bias, Red: high risk of bias.
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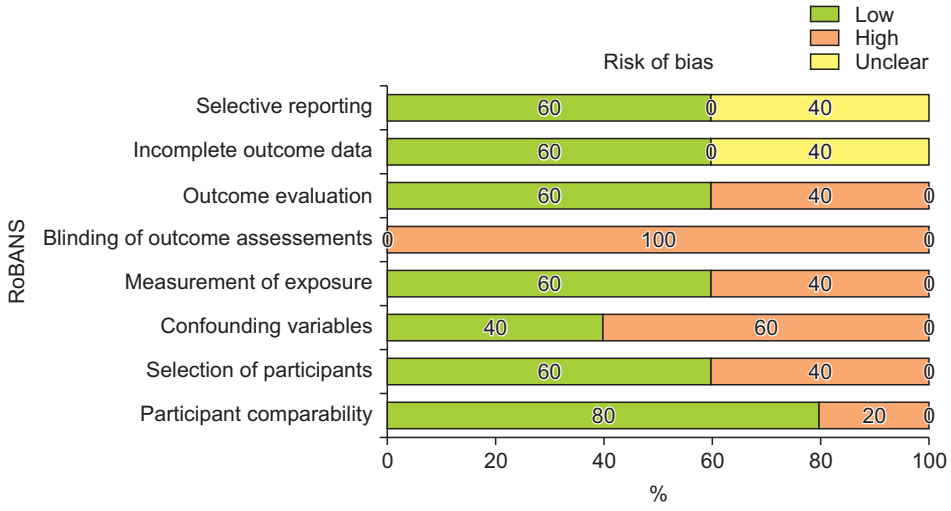

Fig. 2. RoBANS (risk-of-bias assessment tool for non-randomized study) graph.
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the role of TMD in the development of OSA still remains unknown.

IV. Discussion

The potential bi-directional association between pain and sleep-related breathing disorders has been a topic of interest for researchers and clinicians for the past decades. Co-occurrence of pain and OSA has been previously reported[30,31]. Furthermore, it has been postulated that OSA patients experienced hyperalgesia due to fragmented sleep and hypoxemia, which enhanced peripheral and central pain sensitization, thus promoting inflammation, and increasing spontaneous pain[32,33]. To the best of our knowledge, there have been sparse studies which tried to integrate the fragmented knowledge about the relationship between painful TMD and OSA. Therefore, the aim of this systematic review was to review the existing literatures which dealt with related topics and provide comprehensive and integrated knowledge about OSA and painful TMDs accordance with the evidence-based methodology.

The aforementioned results indicated that OSA could be one of the risk factors for painful TMD; however, the role of TMD in the development of OSA remained obscure. Increased respiratory arousal and sleep disturbance, particularly during slow-wave non-rapid eye movement (NREM) sleep, in OSA patients have been reported, previously[34,35]. Sleep deprivation can cause myalgia and chronic fatigue and impairs descending pain-inhibition pathways that are crucial for controlling and coping with pain[36]. Slow-wave NREM sleep seems to play a role in the suppression of cortisol activity in the feedback loop of the hypothalamus-pituitary-adrenal (HPA) axis[37]. The chronic TMD patients exhibited altered HPA axis feedback mechanisms and increased pain intensity and pain-related jaw disability[38]. Therefore, disrupted sleep architectures, especially, slow-wave sleep structure owing to OSA may have negative impacts on the maintenance of endocrinological homeostasis and descending pain inhibitory pathway, which may play a role in the pain-modulating mechanisms in chronic TMD. Altered HPA axis homeostasis could have interactions with the amplification of pain intensity and limited jaw function in patients with painful TMD.

Nocturnal oxygen desaturation in patients with OSA showed increased analgesic sensitivity to opioid[39]. Oxygen desaturation during sleep seemed to play a role in the increased expression of pro-inflammatory cytokines, especially interkeukin-6 and tumor necrosis factor-α[21]. These pro-inflammatory cytokines are associated with the enhancement of transient receptor potential vanilloid 1 activity which may play a role in the development of hyperalgesia[40,41]. Furthermore, some evidences have indicated that interleukin-6 could enhance of N-methyl-D-aspartate receptor activity which may result in impaired descending pain inhibitory pathways[42,43]. Hence, the nocturnal hypoxic condition in patients with painful TMD can increase pain sensitivity and alter descending pain inhibitory pathway and which can eventually influence the occurrence of peripheral and central pain sensitization.

The majorities of studies dealing with pain disorders and OSA focused on the aforementioned two mechanisms, activity of pro-inflammatory cytokines and sleep fragmentation. However, one study suggested the other possibility. This study demonstrated that nocturnal arterial desaturation was related with an increased pain in subject with sleep-disordered breathing; however, such as association was not related to sleep fragmentation and inflammation. Owing to complicated pain modulating mechanisms, further investigations are warranted.

The influence of OSA management on pain outcome has been proposed in previous reports. The delivery of continuous positive airway pressure (CPAP) may improve pain intensity and tolerance[44-46], and the use of oral appliance can lessen the systemic inflammatory cytokine levels in patients with TMD[47]. However, the use of CPAP and oral appliance to manage OSA in patients with painful TMD should be carefully considered as both may cause mask discomfort and orofacial pain at the initial stage of the therapy[48,49]. Because no long-term well-designed randomized controlled trial has been conducted, the therapeutic effects of OSA treatment on painful TMD remains to be obscure.

To date, there has been no sufficient evidence proving the association between OSA and painful TMD. Furthermore, studies employing PSG, the gold standard for OSA diagnosis are scares and questionnaires for screening the risk of OSA are commonly used instead. Three studies included in this systematic review were published before 2016[22,27,28], therefore the DC/TMD criteria, the most current validated diagnostic criteria for TMD, could not be applied. Only one prospective cohort study has been conducted and majorities of the studies included in this review adopted cross-sectional design. In addition, quantitative sensory test data for the diagnosis of hyperalgesia was performed in only one cross-sectional study. Hence, to elucidate this topic, more longitudinal prospective cohort studies using full-channel overnight PSG data, TMD diagnosis based on the DC/TMD criteria, and quantitative

sensory testing would be required.

V. Conclusion

Evidences of the potential relationships between painful TMDs and OSA are inconclusive. In addition, due to the small number of well-designed prospective studies using proper diagnostic criteria for TMD and PSG, the causal relationships remain unclear. Furthermore, the therapeutic effects of OSA treatment on improvement of pain in TMD or vice versa have not been revealed. Future well-structured prospective cohort studies which include large sample size as well as randomized controlled trials would be warranted.

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Authors' Contributions

J.H.K. and J.K.L. participated in conception and design of the study. J.H.K. analysis the data and performed statistical analysis. J.H.K. and J.K.L. wrote the manuscript. J.H.K. and J.K.L. edited and finally approved the manuscript. All authors approved the final version of the manuscript.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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