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A meta-analysis on the association between obstructive sleep apnea and periodontitis

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Abstract

Purpose The present meta-analysis aimed to evaluate quantitively the recent scientific evidence regarding the association between obstructive sleep apnea (OSA) and periodontitis.

Methods Databases searched were PubMed, EMBASE, Scopus, and Web of Science. Publications were included according to the inclusion criteria. The following outcomes were evaluated: the prevalence of periodontitis, probing depth (PD), clinical attachment loss (CAL), the percentage of sites with bleeding on probing (BOP), plaque index (PI), and gingival index (GI). The statistical analysis was processed using the software STATA.

Results Thirteen eligible studies comprising a total of 31,800 patients were included. The meta-analysis showed an increased prevalence of periodontitis in OSA populations compared to controls. Both PD and CAL were increased in OSA populations compared with controls. (Prevalence of periodontitis: OR 2.348; 95%CI 2.221–2.482; PD: SMD = 0.681, 95% CI: 0.062–1.301, $Z = 2.61$, $P = 0.031$; CAL: SMD = 0.694, 95% CI: 0.167–1.22, $Z = 2.58$, $P = 0.01$). The study also found significantly increased BOP in patients with OSA after heterogeneity was clarified. (SMD = 0.357, 95% CI: 0.079–0.635, $Z = 2.52$, $P = 0.012$).

Conclusions The findings suggest that OSA was associated with an increased prevalence of periodontitis.

Keywords Periodontitis · Obstructive sleep apnea · Periodontal-systemic disease interactions · Meta-analysis

Introduction

Periodontitis is a chronic multifactorial inflammatory oral disorder that affects more than 50% of the adult population worldwide [1]. Patients with periodontitis suffer from diverse clinical manifestations ranging from gingival bleeding to tooth loss [2]. Periodontitis has been linked to a number of medical conditions including cardiovascular disease, diabetes mellitus, and autoimmune rheumatic disease [3]. In recent decades, the relationship between periodontitis and obstructive sleep apnea (OSA) has been investigated and a positive association between the two disorders has been hypothesized and explored [4].

OSA is a common sleep breathing disorder characterized by complete or partial pharyngeal obstruction, leading to reduced or absence of ventilation (hypopnea or apnea), hypercapnia as well as sleep fragmentation [5]. Also, OSA has been reported to be a risk factor of several systemic dysfunctions such as cardiovascular and metabolic morbidities [6]. The connection between OSA and inflammatory processes has been suggested to be due to cyclic hypoxia as well as dysfunction of the clock gene[7–9].

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Table 1 Characteristics of the included studies

Author and year	Study design	Country	OSA diagnostic	Sample size (OSA/Control)	Age	Outcomes
Ahmad (2013)	Cross-sectional	USA	STOP questionnaire	59/95	Mean:61	Periodontitis
Ai-Hammad (2015)	Case-controlled	Saudi Arabia	NA	30/30	3–8; mean ± SD: 4.3 ± 1.57	PI/GI
Al Habashneh (2016)	Cross-sectional	Jordan	Berlin questionnaire	44/252	30–60; Mean ± SD: 40 ± 8.5	Periodontitis/PD/PI/GI/CAL/BOP%
Durhan (2019)	Cross-sectional	Turkey	AHI > 1	11/7	7–14	PD/PI/GI/BOP%
Gamsiz-Isik (2017)	Case-controlled	Turkey	AHI > 5	83/80	OSA: 30–60; control: 30–68	Periodontitis/PD/PI/GI/CAL/BOP%
Kale (2018)	Cross-sectional	India	STOP questionnaire	130/130	21–72; mean ± SD: 43.67 ± 11.89	Periodontitis
Keller (2013)	Case-controlled	Taiwan China	Polysomnography	7673/21963	Mean ± SD: 47.6 ± 15.4)	Periodontitis
Latorre (2018)	Cross-sectional	Colombia	AHI > 5	141/58	30–85	Periodontitis
Loke (2015)	Cross-sectional	USA	AHI > 5	26/74	28–79; mean:52.6	Periodontitis/BOP%
Nizam (2016)	Case-controlled	Turkey	AHI > 5	39/13	Mean: 40–50	Periodontitis/PD/PI/CAL/BOP%
Sales-Peres (2016)	Cross-sectional	Brazil	Berlin questionnaire	47/61	30–60	Periodontitis/PD/CAL/BOP%
Seo (2013)	Cross-sectional	Korea	AHI > 5	320/367	Mean ± SD:55.85 ± 6.6	Periodontitis/PD/PI/GI/CAL/BOP%
Tamasas (2019)	Cross-sectional	USA	PSQ > 8	31/36	Mean ± SD:12.3 ± 2.7	PD

Although the association between OSA and periodontitis has not been firmly established, multiple observational studies have been published in this field [10–14]. In 2015, the first evidence-based research regarding the relationship between OSA and periodontitis was reported suggesting a plausible association between the two diseases. However, further evidence was still needed [15]. Therefore, the present study integrated the newly published study results with existing evidence, and a quantitative estimation was conducted through meta-analysis. The present study aimed to analyze the association between OSA and periodontitis, and the focused question was: Do patients with OSA have periodontal disease more frequently than subjects without OSA?

Methods

This meta-analysis was conducted under the Preferred Reporting Items for Systematic Reviews and Meta-analysis checklist (PRISMA). Databases searched were PubMed, EMBASE, Scopus, and Web of Science (up to March 2021). The search algorithm is listed in Table 1. Additionally, bibliographies of the eligible studies and pertinent reviews were hand searched and screened for a complemented result.

Eligibility criteria

Publications were included if the following inclusion criteria were met: (1) case-controlled, cohort, or cross-sectional studies; (2) the exposure of interest was OSA, and the controls were absent of OSA; (3) the targeted outcomes included the prevalence of periodontitis, probing depth (PD), clinical attachment loss (CAL), the percentage of sites with bleeding on probing (BOP), plaque index (PI), gingival index (GI), and sufficient data were provided for the statistical analysis.

Publications were excluded if the studies repeated prior data, were reviews, case reports, letters, or conference abstracts.

Record screen and data extraction

Based on the eligibility criteria, titles and abstracts of the initially retrieved literature were screened and selected independently by two authors (SH Zhang and JF Zhu). The choices of the two authors were then discussed to reach a consensus according to suitability for full-text reading.

After the process of records screening, the data of the included studies were extracted by two independent authors (SH Zhang and JF Zhu), and disagreements were resolved through discussion. The following data were extracted: (1)

name of the first author and year of publication, (2) study design, (3) OSA diagnostic, (4) group size, (5) age.

The following periodontal outcome data were extracted for the meta-analysis: (1) prevalence of periodontitis, (2) PD, (3) CAL, (4) BOP, (5) PI, and (6) GI.

Risk of bias assessment

Two authors (JF Zhu and SH Zhang) independently assessed the quality and risk of bias of the included studies, and discrepancies were resolved through discussion. The assessment form for cross-sectional studies recommended by the Agency for Healthcare Research and Quality (AHRQ) was used for the risk of bias assessment of the cross-sectional studies. A total of 11 items were considered, and 1 point was given if the item was reflected in the study. The final scores ranged from 0 to 11. Studies with scores 0–4, 5–8, and 9–11 were considered as of low, moderate, and high quality, respectively [16]. The included case-controlled studies were evaluated through the Newcastle–Ottawa scale (NOS). Three

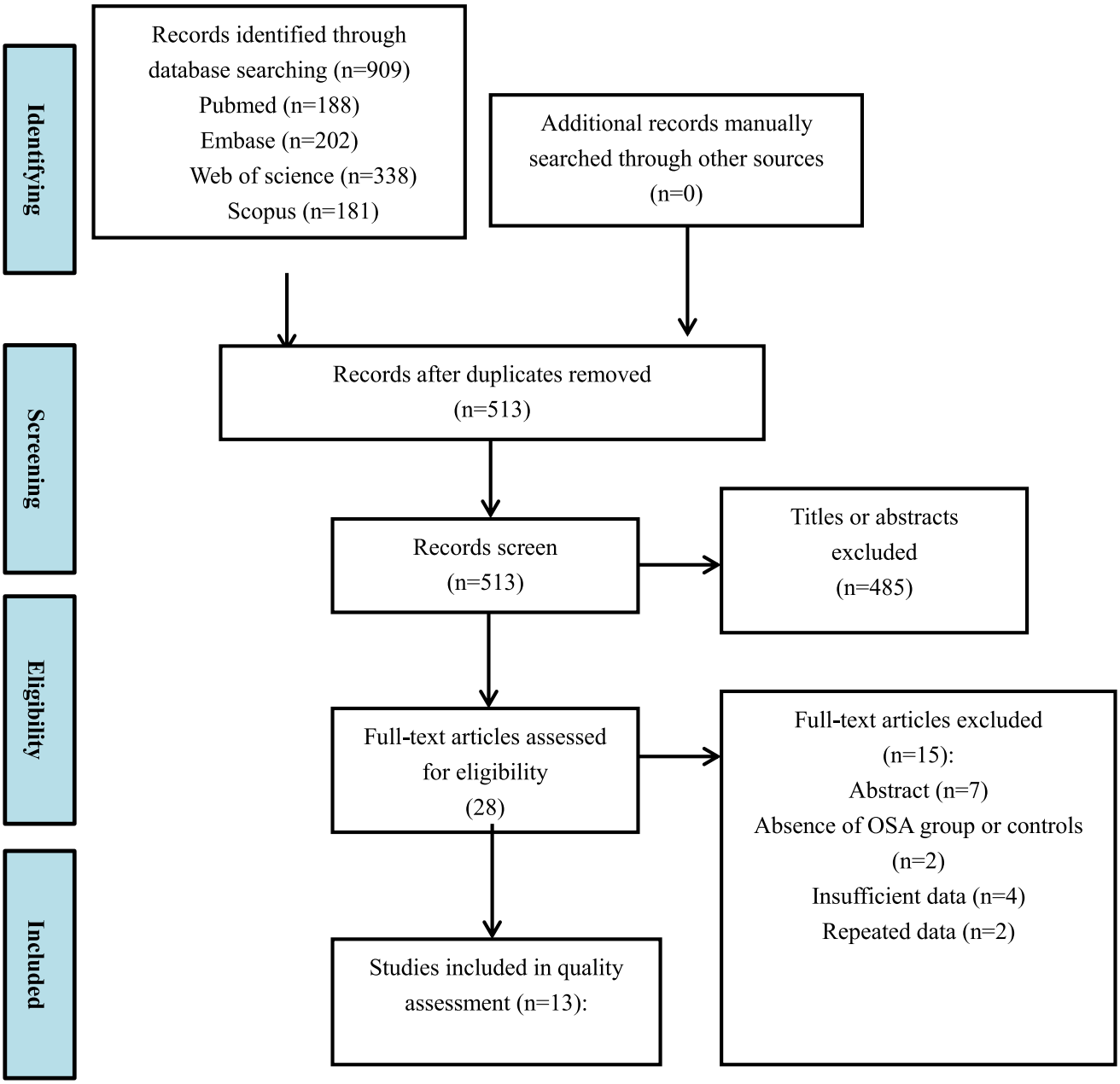

Fig. 1 Flow diagram of literature selection according to PRISMA

Table 2 Quality assessment for cross-sectional studies

Author and year	Item1	Item2	Item3	Item4	Item5	Item6	Item7	Item8	Item9	Item10	Item11	Total
Ahmad (2013)	●	●	●	◌	●	●	◌	◌	●	●	●	8/11
Al Habashneh (2016)	●	●	●	●	●	●	●	●	●	●	●	11/11
Durhan (2019)	●	●	●	●	◌	◌	◌	◌	●	●	●	7/11
Kale (2018)	●	●	●	◌	●	◌	●	●	●	●	●	9/11
Latorre (2018)	●	●	◌	◌	●	●	◌	◌	●	●	●	7/11
Loke (2015)	●	●	●	●	●	◌	●	●	●	●	●	10/11
Sales-Peres (2016)	●	●	●	●	●	●	●	●	●	●	●	11/11
Seo (2013)	●	●	●	●	●	◌	●	◌	●	●	●	9/11
Tamasas (2019)	●	●	◌	●	◌	●	●	◌	●	●	●	8/11

● The item was achieved, ◌ the item was not achieved or unclear.

chapters were involved which were "Selection" (0–4 points), "Comparability" (0–2 points), and "Exposure" (0–3 points). The final scores were calculated ranging from 0 to 9. Studies with scores of 0–3, 4–6, and 7–9 points were considered of low, moderate, and high quality [17].

Meta-analysis

The software STATA 15.0 was used for the statistical analysis. The data of continuous variables were presented in mean (M) ± standard deviation (SD). The mean difference (MD), standard mean difference (SMD), and corresponding 95% confidence interval (CI) were used for the meta-analysis on PD, CAL, BOP, PI, and GI. ORs and CIs were calculated to evaluate the prevalence of periodontitis. Additionally, meta-regression was conducted to explore the potential sources of heterogeneity.

Results

Characteristics of the included studies

Figure 1 demonstrates the selection process. Thirteen studies involving 31,800 participants were included. Four of the included studies were case-controlled and 9 were cross-sectional. The origin of the studies included the USA, Brazil, Columbia, China, India, Jordan, Korea, Saudi Arabia, and Turkey. Most of the included studies employed polysomnography to perform the diagnostic of OSA, 4 studies applied self-reported questionnaires, including the Berlin questionnaire and STOP questionnaire; however, 1 of the studies failed to mention the exact method of OSA diagnostic (Table 1).

Table 3 Quality assessment for case-controlled studies

Author and year	Selection	Comparability	Exposure	Total
Ai-Hammad (2015)	●◌●	●●	●●●	8/9
Gamsiz-Isik (2017)	●◌◌	●●	●●●	7/9
Keller (2013)	●●◌	●●	●●◌	7/9
Nizam (2016)	●◌◌	●◌	●●●	6/9

● The star (*) was achieved, ◌ the star (*) was not achieved.

Risk of bias assessment

NOS was used to evaluate the methodological quality of the included case-controlled studies. Four studies were evaluated. The study conducted by Nizam et al. was considered to be of medium quality (6 points), and the other 3 studies were of high quality (Table 2). The 9 included cross-sectional studies were assessed through AHRQ, and the final scores were ranged from 7 to 11. Therefore, all cross-sectional studies were of high quality (Table 3).

Meta-analysis

A total of 10 studies reported the prevalence of periodontitis [10, 12–14, 18–24]. The overall meta-analysis showed an increased prevalence of periodontitis in OSA populations compared with controls (Fig. 2A; OR 2.348; 95%CI 2.221–2.482; $Z = 30.98$ $P < 0.05$; $I^2 = 47.3\%$, $P = 0.047$). However, the study reported by Keller et al. [20] presented a considerably large sample size, contributing 92% of the weight in the result. Subsequently, the study was deleted in the meta-analysis and the result was not significantly changed (Fig. 2B; OR 2.096; 95%CI [1.677, 2.621]; $Z = 6.496$ $P < 0.05$; $I^2 = 49\%$, $P = 0.047$).

The meta-analysis also found elevated periodontal parameters in patients with OSA compared to healthy individuals, including PD (Fig. 3A; SMD = 0.681, 95% CI: 0.062–1.301, $Z = 2.61$, $P = 0.031$; $I^2 = 94.9\%$, $P = 0.000$), and CAL (Fig. 3B; SMD = 0.694, 95% CI: 0.167–1.22, $Z = 2.58$, $P = 0.01$; $I^2 = 92.4\%$, $P = 0.000$). However a significant differences in BOP, PI, and GI were not observed (Fig. 4A:

BOP: SMD = 0.202, 95% CI: − 0.197 to 0.602, $Z = 0.99$, $P = 0.320$; $I^2 = 86.6\%$, $P = 0.000$; Fig. 4B: PI: SMD = 0.108, 95% CI: − 0.176 to 0.392, $Z = 0.75$, $P = 0.456$; $I^2 = 70.4\%$, $P = 0.002$; Fig. 4C: GI: SMD = 0.178, 95% CI: − 0.177 to 0.532, $Z = 0.98$, $P = 0.326$; $I^2 = 80.6\%$, $P = 0.000$).

Meta-regression was applied to identify the source of heterogeneities, and the diagnostic standard of OSA and the type of study design were considered as covariates. The result showed that the diagnostic standard of OSA explained 82% of the heterogeneity in the results of BOP. Therefore, we conducted a subgroup analysis according to the diagnostic standard. In the studies which employed polysomnography for the diagnostic of OSA, we found BOP was significantly increased in patients with OSA compared with healthy individuals, and the heterogeneity was decreased (Fig. 5: SMD = 0.357, 95% CI: 0.079–0.635, $Z = 2.52$, $P = 0.012$; $I^2 = 64.3\%\%$, $P = 0.006$);

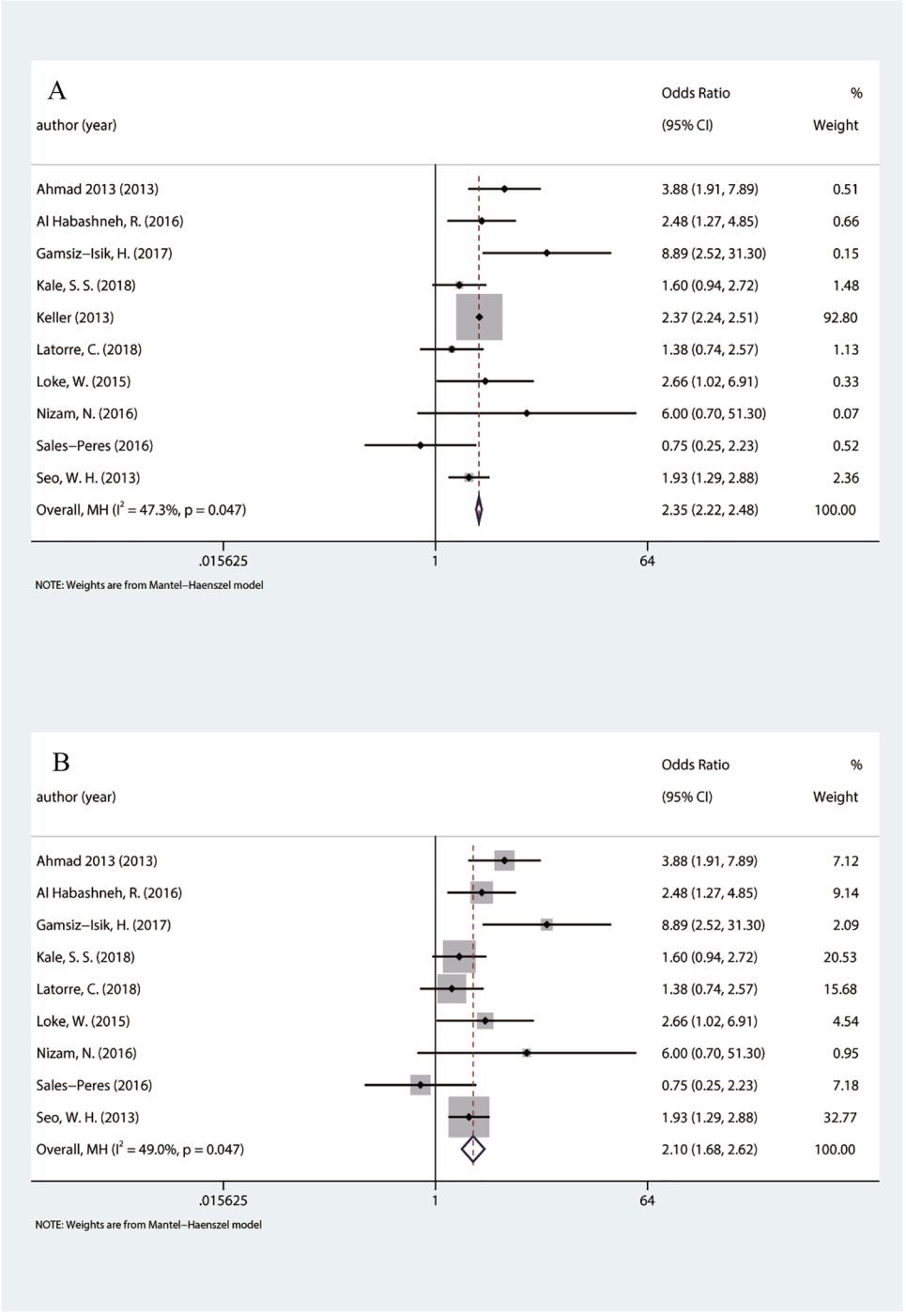

Fig. 2 Forest plots for the influence of OSA on the prevalence of periodontitis

Discussion

In 2015 and 2020, Thikriat et al. published the first meta-analysis and an update investigating the relationship between OSA and periodontitis providing initial evidence to a plausible association between the two diseases [15, 25]. In recent years, several pertinent observational studies were published. The present study increased the number of included studies ($n = 13$), and the periodontal parameters such as PD, CAL, BOP, PI, and GI were first evaluated by meta-analysis to clarify the interaction between OSA and periodontitis. The present finding suggest that OSA may be associated with an increased prevalence of periodontitis and impaired periodontal status.

In accordance with the previous meta-analysis [15], the present results also demonstrated a positive association between OSA and periodontitis. In the present study, the number of the included studies was increased for the statistical analysis ($n = 11$), and as the amount of evidence increased, statistical heterogeneity decreased ($I^2 = 41.5\%$, $P = 0.072$).

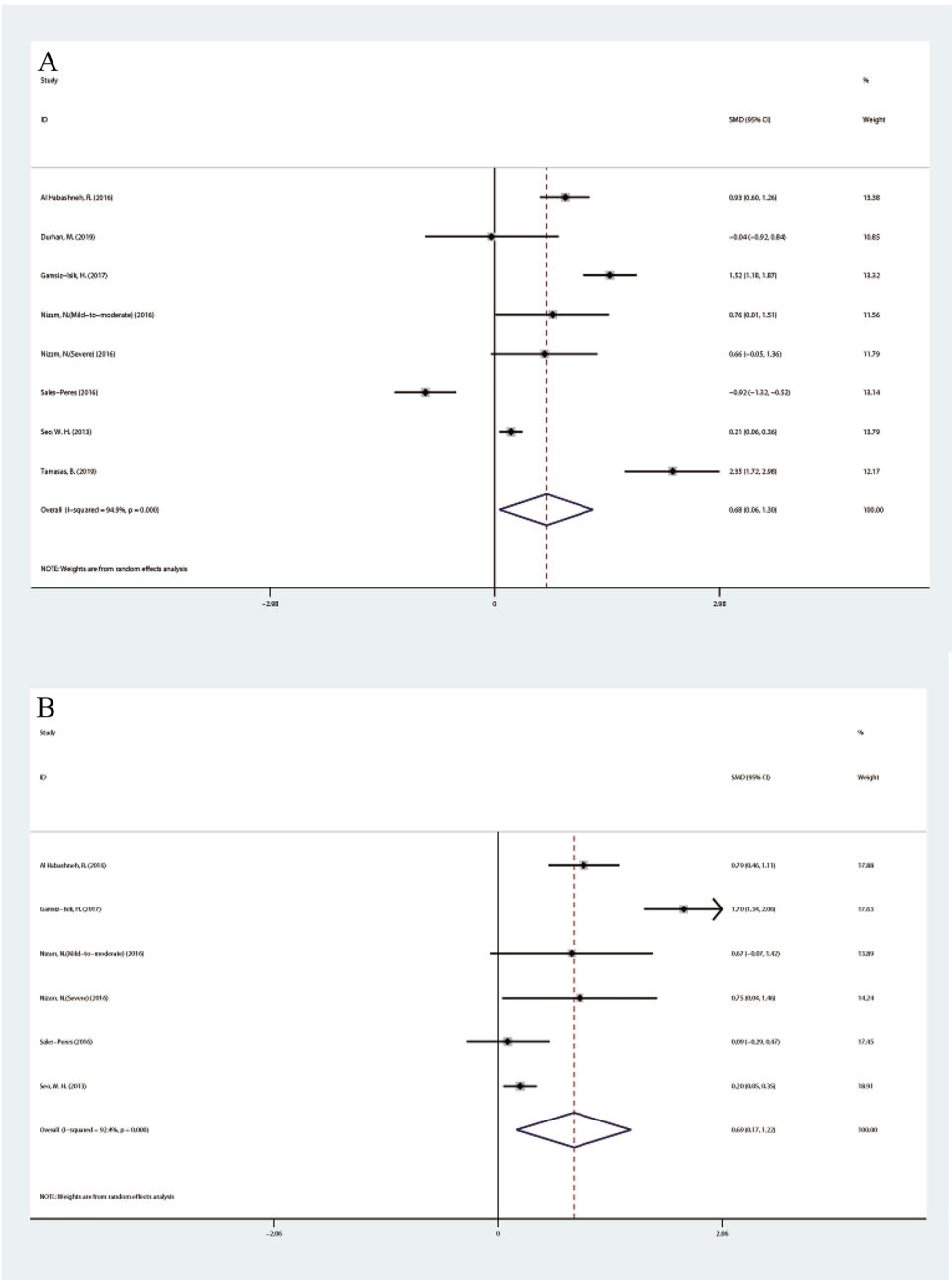

Fig. 3 Forest plots for the influence of OSA on PD and CAL: **A** PD, **B** CAL

It was reported that upper airway anatomy, dilator muscle dysfunction, lung volume, or ventilatory control stability have been associated with the underlying mechanisms of OSA [21]. The primary anthropometric risk factors for OSA included increased BMI, abnormal nasal structure, male gender, and advanced age [26]. Similarly, periodontitis shares risk factors with OSA [27], and both diseases have been reported to be connected with multiple systemic disorders, including diabetes mellitus, hypertension, and coronary artery disease [18].

The pathologic and etiologic plausibility for an association between OSA and periodontitis has been reported by studies [28]. The present study evaluated the differences of the periodontal parameters between patients with and without OSA. Conversely, in a population with periodontitis, it has also been shown that patients with OSA are more common than in subjects without periodontitis, indicating a bidirectional relationship between the two conditions [18].

One of the factors connecting OSA and periodontitis has been sleep bruxism (SB) [29]. The study conducted by M Maluly et al. indicated that having an AHI above 30 is a risk factor for SB [30]. SB also attracted attention as a factor influencing periodontal disease. The development of SB not only influenced periodontal characteristics such as PD and CAL, but also affected periodontal sensation and tooth displacement [31, 32]. Additionally, it has been reported that mouth breathing in OSA reduces the humidity in the oral cavity, thereby preventing the self-cleaning ability of saliva, leading to the bacterial colonization [33]. OSA-related intermittent hypoxemia has also been recognized as a potential factor contributing to the comorbidities [34]. The status of hypoxia has been shown to be related to the apoptosis of periodontal cells during periodontal inflammation [35]. The level of oxygen is important for periodontal tissue functions and homeostasis. If periodontal cells were exposed to the environments with low oxygen tension (1–2% O_2), cell damage could be initiated, and the cell apoptosis process could be initiated [36]. As detected by optical spectroscopy, oxygen desaturation has been observed in inflammatory periodontal sites, compared to healthy sites. The growth of anaerobic microorganisms may be accelerated by the decreased oxygen tension in the periodontal pockets. The altered subgingival bacterial profile may also contribute to the reduced level of oxygen [37, 38]. Additionally, another potential reason for the connections between the two diseases may be the expression of the circadian clock genes, which have been connected to multiple events, including cytokine storm in bacteria inflammation and viral infection [39]. It has been reported that circadian clock genes may be disturbed in patients with OSA [40]. The expression of the circadian clock gene can be observed in periodontal tissues and may contribute to the process of periodontitis [39, 41].

The results of the presented meta-analysis also demonstrated an increase in periodontal parameters in patients with OSA, such as PD and CAL. However, the statistical heterogeneity weakened the evidence of the finding. PD and CAL are both important indexes indicating the level of bone destruction during periodontitis. It can be deduced from the present finding that the tendency of increased alveolar bone destruction may be associated with OSA. However, further data are needed to substantiate this finding.

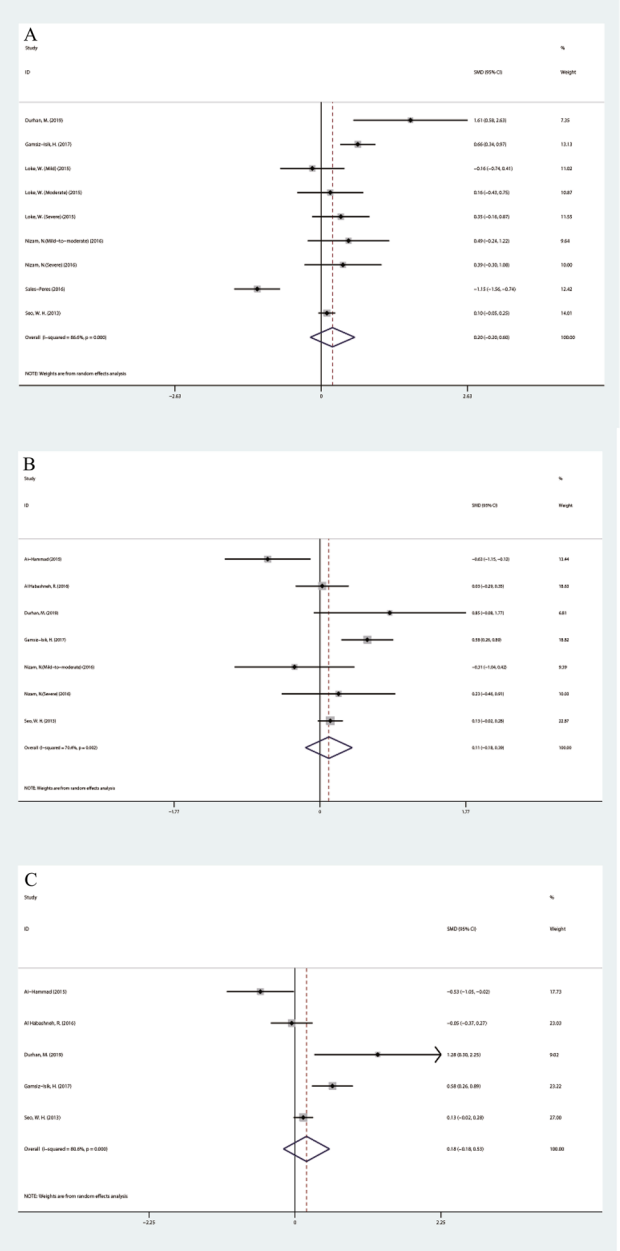

Fig. 4 Forest plots for the influence of OSA on BOP, PI and GI: **A** BOP, **B** PI, **C** GI

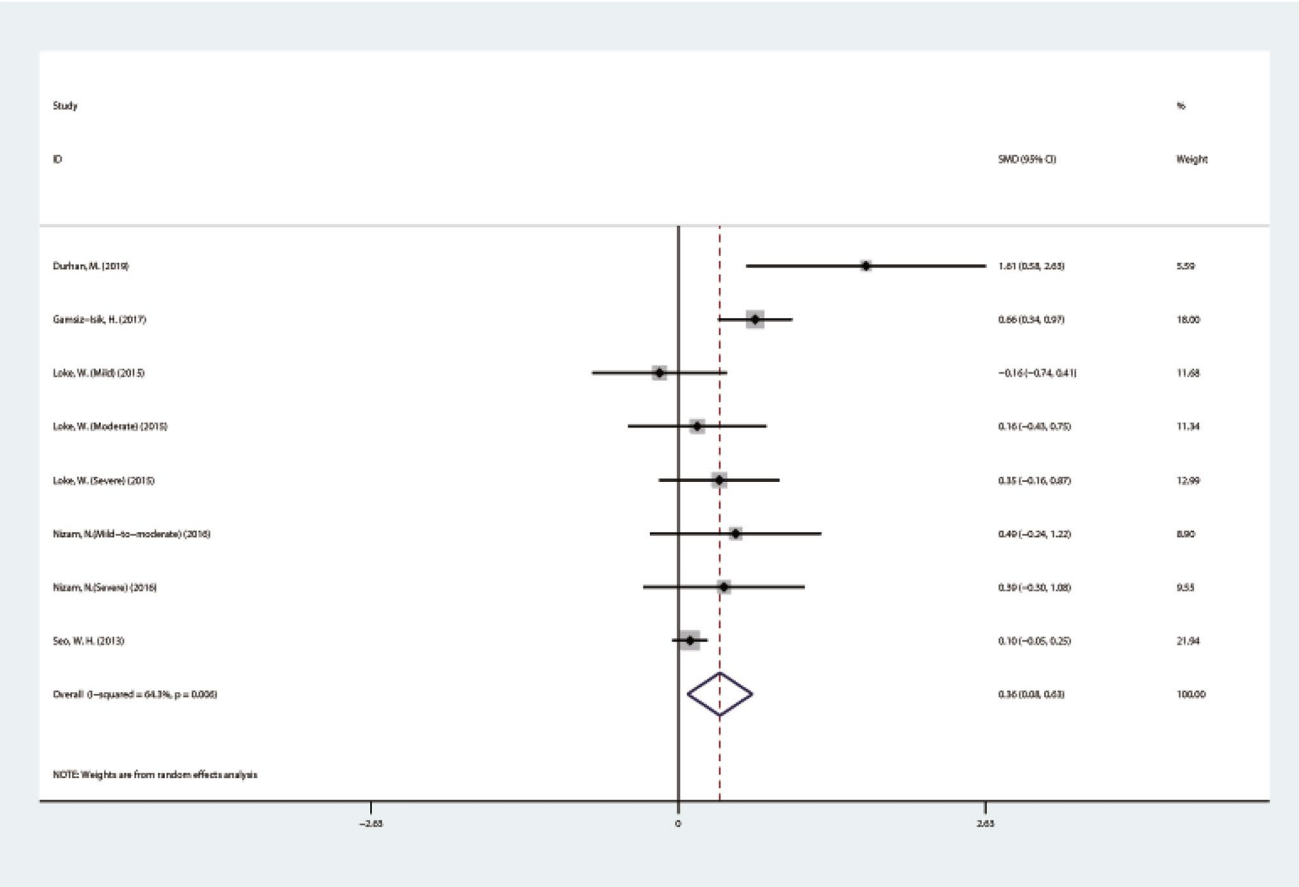

Fig. 5 Forest plots for the influence of OSA on BOP, in the studies employed polysomnography for the diagnostic of OSA

According to the primary statistical results of the present meta-analysis, a significant change was not observed in BOP, PI, and GI. However, meta-regression demonstrated that the diagnostic standard of OSA explained the source of heterogeneity of BOP. The AHI measured by polysomnography is considered to be the gold standard for diagnosing OSA. AHI scores of 515, 15–30, and ≥ 30 events/h indicate mild, moderate, and severe OSA, respectively. And the severity of OSA affects the clinical periodontal symptoms as well as the inflammatory status of saliva [22]. As suggested by the American Academy of Sleep Medicine Clinical Practice Guideline, polysomnography is the first choice to be used for the diagnosis of OSA [42]. When we cumulatively analyzed only the studies that employed polysomnography, we found BOP was significantly increased in OSA and heterogeneity was decreased.

Limitations of the present study include the lack of prospective studies. Most of the studies were cross-sectional, which precludes demonstration of a cause-effect relationship. Additionally, significant heterogeneities were observed in the periodontal indexes, including PD, CAL, PI, and GI. Therefore, these results must be interpreted with caution.

Conclusions

Within the limitations of the evidence, the findings suggest that OSA is associated with an increased prevalence of periodontitis. Further large-scale prospective studies are required to validate these findings.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval For this type of study, ethical approval is not required.

Informed consent This article does not contain any studies with human participants performed by any of the authors.

Conflict of interest The authors declare no competing interests.

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