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SYSTEMIC DISEASES (N BUDUNELI, SECTION EDITOR)

An Update on the Association Between Periodontitis and Obstructive Sleep Apnea

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Abstract

Purpose of Review The aim of this systematic review and meta-analysis was to update evidence answering four questions: (1) Is there an association between periodontitis and obstructive sleep apnea (OSA)? (2) Is there evidence of causality? (3) Is there a dose-response relationship between the two conditions? (4) Is there evidence on efficacy of periodontitis interventions on the occurrence and/or severity of OSA or vice versa?

Recent Findings Thirteen studies were included in the qualitative analysis, and nine of them were included in the quantitative analysis. Seven studies were case-control and six were cross-sectional. All studies assessed the association between periodontitis and OSA, five studies evaluated the dose-response relation, and one examined the efficacy of periodontal interventions on OSA occurrence. There is a significant positive association between periodontitis and OSA (adjusted OR = 1.66, 95% CI,1.28, 2.17; $P = 0.0002$). Evidence on a dose-response gradient was conflicting. Evidence was insufficient and non-existent for efficacy of interventions and causality, respectively.

Summary There is mounting evidence that supports an association between periodontitis and OSA. However, future studies are warranted to determine does-response relation, causality, and reversibility.

Keywords Periodontal disease · Sleep apnea · Systematic review · Adult

Introduction

Periodontitis is a severe inflammatory disease that occurs as a result of the host's immune response to bacteria. Over time, this inflammatory state results in the destruction of alveolar bone and the loss of connective tissue, eventually leading to tooth loss [1]. The host's immune response through neutrophils, monocytes, B cells, and T cells recognizes bacteria and foreign entities in the periodontium. This results in the secretion of inflammatory mediators such as cytokines (tumor necrosis factor-a; TNF-a) and more specifically interleukins (IL-6, IL-33, IL-1B) [1]. IL-6 and IL-1B are common cytokines

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found in periodontal sites and are known to strongly induce bone resorption and connective tissue destruction [2]. They also induce proteolytic enzymes, osteoclasts, metalloproteinase enzymes (MMP), and other factors that aid in the destruction of the supporting structures of the teeth [3].

When inflammatory mediators (IL-6, IL-33, IL-1B TNF-a) are released from immune cells, they travel via the vascular system to the sights of infection. Once in the vascular system, these inflammatory mediators are able to affect other parts of the body [4]. Thus, in addition to their role in the progression of periodontal disease, they are related to other systemic diseases and inflammatory conditions such as rheumatoid arthritis [5], coronary heart disease [3], diabetes [6], and more recently obstructive sleep apnea (OSA) [7].

OSA is a sleep-related breathing disorder characterized by repetitive episodes of upper airway complete or partial obstruction resulting in oxygen desaturation and arousals [8]. The prevalence of OSA with excessive daytime sleepiness in adult men is 6% (range 3–18%) and in adult women 4% (range 1–17%) [9]. Individuals with OSA have higher levels of inflammatory cytokines such as IL-6, IL-1B, and TNF-a [10]. The high levels of cytokines seen in OSA have allowed researchers to connect OSA to other inflammatory conditions including periodontitis [11••, 12].

In 2015, Al-Jewair et al. [13] conducted a meta-analysis to evaluate the relationship between periodontitis and OSA in adults. They concluded that there is a plausible relationship between the two conditions (adjusted odds ratio (AOR) = 1.65, 95% confidence interval (CI),1.11,2.46, $P = 0.01$).

Since 2015, more studies have been published. Thus, the aim of this systematic review and meta-analysis was to update evidence and develop a better understanding on the relationship between periodontitis and OSA.

Methods

This review was registered in the center for Reviews and Dissemination, University of York, UK #CRD42018118043, and it followed the Preferred Reporting Items for Systematic Review and Meta-Analysis protocol guidelines [14].

Inclusion/Exclusion Criteria

Adult female and male subjects (+ 18 years old) were considered for inclusion. An OSA diagnosis was confirmed through polysomnography (PSG), conducted in a sleep laboratory or at home sleep test (HST) and subjective validated questionnaires. A diagnosis of periodontitis following the 2017 classification system of periodontal and peri-implant diseases and conditions [15] or the 1999 Consensus Classification System of Periodontal Disease was considered [16]. Study designs considered were prospective and retrospective longitudinal as well as epidemiological studies published in English on humans. Studies published in languages other than English and those of different study design were excluded.

Data Sources

An electronic search was conducted by a health sciences librarian (ES) between November 25 and 27, 2019, without any date or language restrictions. The following databases were searched using a combination of keyword terms and subject headings to represent sleep apnea and periodontal disease: PubMed, Embase via Elsevier, CINAHL Plus with Full Text via EBSCOhost, and Cochrane Central Register of Controlled Trials via Ovid. The original search was created in PubMed and translated to the other databases. Please see Table S1 for the complete search strategy used in PubMed; all other database searches are available upon request.

In addition, a gray literature search was performed by the following resources: OpenGrey, ProQuest Theses and Dissertations Global, Clinicaltrials.gov, and the International Association of Dental Research (IADR) Abstract Archives. The search strategies for each resource included a combination of the keywords "sleep apnea" and "periodontal or periodontitis or dental." No date or language restrictions were used with the exception of the IADR Abstract Archive; the archive is only searchable from 2001 to present.

Study Selection, Data Extraction, and Quality Assessment

Studies were screened by two independent reviewers (IA, TAJ) who assessed the titles and abstracts of each article. Disagreements were resolved by consulting a third reviewer (RK). At the full-text stage, the same authors carried out the independent appraisal of each article.

Data were then extracted from each article using a custom data abstraction sheet. The Newcastle-Ottawa Scale (NOS) for the assessment of non-randomized studies was then used to assess the risk of bias in the case-control studies, whereas cross-sectional studies were assessed using an adapted form of the NOS developed by Herzog et al. [17, 18]. The scale evaluates three elements: the selection of the study groups, the comparability of the groups, and the evaluation of exposure or outcome using a Star system with nine being the maximum possible score for case-control and ten for cross-sectional studies. Studies were categorized into low (scored ≥ 8), medium (scored 6–8), and high-risk of bias groups (scored ≤ 5). The overall quality of evidence was then assessed using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach [19].

Statistical Analysis

Meta-analyses on the association between periodontitis and OSA were conducted using Review Manager software (Version 5.3, Cochrane Collaboration, Canada) [20]. The AOR, 95% CI, and *P* values were extracted from each study. Studies were combined using the inverse variance random-effects models method. The effect size was calculated using pooled ORs and their 95% CI and was considered significant if $P < 0.05$. The I^2 statistic was used to evaluate heterogeneity with cut-offs of 25%, 50%, and 75% to represent low, moderate, and high heterogeneity [21]. Sensitivity analyses were performed to assess robustness of results. Assessment of publication bias was considered if at least 10 studies were included.

Results

A total of 452 studies were identified. After removal of duplicates, 328 studies were screened. After exclusion by title and abstract, the full texts of 32 studies were assessed, and 19 of them were excluded for different reasons. A total of 13 studies [7, 11••, 12, 22•, 23–28, 29••, 30, 31] were included in the systematic review, and they represent a total sample size of 43,369 individuals. Of the 13 studies, nine were included in the meta-analysis [11••, 22•, 23–28, 29••] (Table 1, Fig. 1).

Seven studies were case-control [11••, 12, 27, 28, 29••, 30, 31] and the rest were cross-sectional [7, 22•, 23, 24–26]. All studies evaluated the association between periodontitis and OSA [7, 11••, 12, 22•, 23, 24–27, 28, 29••, 30, 31], five [11••, 23, 25–27] assessed the dose-response relation, and one [28] evaluated evidence of reversibility with periodontitis interventions. However, none of the studies evaluated the cause-effect relationship.

OSA was measured using PSG at a sleep clinic or using HST in ten studies [7, 11••, 12, 22•, 23, 25, 26, 28, 30, 31], self-reported questionnaires in two studies [24, 27], and both HST and a questionnaire in one study [29••]. The types of questionnaires utilized in the studies were the STOP [27], STOP-BANG [29••], Berlin [24], and Epworth sleepiness scale [24, 29••]. Periodontitis was measured using clinical and radiographic measures in all studies. Additionally, four studies [11••, 12, 30, 31] evaluated inflammatory biomarkers in gingival crevicular fluid (GCF) and saliva.

Association Between Periodontitis and OSA

All 13 studies evaluated the association between periodontitis and OSA. The prevalence of periodontitis ranged from 32.5 to 96.4% in case-control studies [11••, 27, 28, 29••] and from 17.5 to 85.2% in cross-sectional studies [7, 22•, 23, 24, 26]. The prevalence of OSA diagnosed by PSG or HST ranged from 24.3 to 75% [7, 11••, 12, 22•, 23, 25, 26, 28, 29••, 30, 31], while the prevalence of OSA risk determined through validated questionnaires was 60% and 81.5% in two studies [24, 27]. All studies evaluated periodontal disease as the exposure except for one [27] that considered it as the outcome.

Nine studies found a significant positive relationship between periodontitis and OSA. In three [26–28] of the nine studies, the AORs for periodontitis in OSA diagnosed or high risk for OSA patients were 1.75 (95% CI, 1.68, 1.88; $P < 0.001$), 1.84 (95% CI, 1.18, 2.87), and 4.1 (95% CI, 1.9, 11.4). Sanders et al. [25] found the odds for periodontitis to be 1.6 (95% CI, 1.1, 2.2) in mild OSA and 1.5 (95% CI, 1.0, 2.3) in moderate/severe OSA. Latorre et al. [22•] reported higher odds (OR = 1.37; 95% CI,1.11, 2.68; $P = 0.041$) for periodontitis in mild OSA compared with non-OSA referents. This association was more frequent in women with hypertension or hypertensive cardiomyopathy, whereas periodontitis was associated with severe OSA in men with hypertension or hypertensive cardiomyopathy.

Of the remaining four studies, two case-control studies [12, 31] compared inflammatory biomarkers between cases with mild/moderate OSA and severe OSA and non-OSA controls. They found significant changes in the composition of microbes in plaque ($P < 0.01$), significant higher levels of serum and salivary IL-6 ($P < 0.05$), and salivary IL-33 ($P < 0.05$) in the cases compared with controls. Salivary apelin was significantly higher in the severe OSA group over controls. Clinical attachment loss (CAL) and pocket depth (PD) were significantly correlated with incidence and duration of apnea ($P < 0.05$) as well as with OSA severity indicators (AHI, ODI, SpO_2, sleep time (min and %) with $SpO_2 < 90\%$); $P < 0.01$ for CAL and $P < 0.05$ for PD. Gunaratnam et al. [7] found that CAL was significantly correlated with one of OSA indicators (total sleep time; $P < 0.05$), and Gamsiz-Isik et al. [11••] concluded that all periodontal clinical parameters ($P < 0.001$), serum hs-CRP ($P < 0.05$), and GCF IL-1β ($P < 0.05$) concentrations were significantly higher in patients with OSA than in the controls.

On the contrary, three studies [23, 24, 30] found no significant association between periodontitis and OSA, and one [28••] concluded that subjects with symptomatic mild OSA (OR = 0.13, 95% CI, 0.01, 1.53) or moderate/severe OSA (OR = 0.13, 95% CI, 0.01, 1.29) were less likely to have moderate/severe chronic periodontitis than subjects with asymptomatic mild or no OSA.

Quantitative synthesis included nine studies [11••, 22•, 23, 24–28, 29••] that utilized multivariate logistic regression to study the relationship between periodontitis and OSA while controlling for some known confounders. In one study [26], OSA was indicated by a cut-off AHI ≥ 5. Only the AORs for this category were included. In another study, [23] the logistic regression model for moderate/severe periodontitis and OSA used

Table 1 Included studies on the association between periodontitis and OSA

Authors (year), country	Study design	Population	Periodontitis assessment	OSA assessment	Research question investigated*	Authors' conclusions
Latorre et al, (2018), Columbia	Cross-sectional	– $N = 199$ subjects	– CAL, PPD, and gingival margin measurements	Polysomnography at sleep clinic, interpreted according to AASM criteria	1	– There is a significant association between periodontitis and mild OSA, and this association was more frequent in women with hypertension or hypertensive cardiomyopathy
		– F/M ratio = 107/92 – Mean ages = 49.9 years – Age range = 30–85 years				– Periodontitis was associated with severe OSA in men with hypertension or hypertensive cardiomyopathy
Gamsiz-Isik et al (2017), Turkey	Case-control	– $N = 163$ subjects	– PI, GI, BOP, PPD, CAL	Polysomnography	1,3	– OSA is associated with higher periodontal indices and local inflammatory parameters such as IL-1B
		– Cases = 83 with OSA – Controls = 80 non-OSA – F/M ratio = 41/122 – Mean age = 45.58 ± 9.12 years Age range = 30–68 years	– GCF, IL-1B, TNF-alpha, hs-CRP, and serum hs-CRP			– The prevalence of severe periodontitis was higher in moderate-severe OSA patients.
Kornegay (2016), USA	Case-control	– $N = 37$ subjects – F/M ratio = 26/11 – Age groups = 44–59 years. = 12 subjects, 60–60 years. = 14 subjects, 70 years. ≤ = 11 subjects – Age range = 40–75 years	– CAL, BOP, PD, REC, mobility, and furcation involvement Salivary IL-6, IL-33, IL-IB, MMP-8, Oncostatin, and CRP	– Two-night at home sleep apnea test, STOP Questionnaire, STOP-Bang Questionnaire, and the Epworth sleepiness Sscale	1	– There is no association between CP and sleep disordered breathing based on standard of care periodontal measurements and home sleep test estimates of AHI
Nizam et al (2016), Turkey	Case-control	– Cases = 17 with mild/moderate OSA	– PI, BOP, PPD, CAL	Polysomnography	1	– OSA appeared to alter the tested bacteria in plaque and correlates to the increasing periodontal disease severity
		– Cases = 22 with severe OSA – Controls = 13 without OSA – F/M ratio = 20/32 – Age range = 21–64 years	– Salivary, serum concentrations of IL-6, TNF-alpha, osteoprotegerin, soluble receptor activator of nuclear factor-kappa B ligand (sRANKL), and apelin – Bacterial counts			– In patients with OSA, the increase in salivary apelin and IL-6 may have an effect on or be due to the periodontal disease

Table 1 (continued)

Authors (year), country	Study design	Population	Periodontitis assessment	OSA assessment	Research question investigated*	Authors' conclusions
Sales-Peres et al, (2016), Brazil	Cross-sectional	– $N = 108$ subjects – F/M ratio = 85/23 – Age range = 30–60 years	PD, CAL, gingival bleeding index, BOP, and the presence of calculus	Berlin questionnaire and Epworth sleepiness scale	1	– There is no association between periodontal disease and OSAS risk in class III obese patients
Nizam et al, (2015), Turkey	Case-control	– $N = 50$ subjects	– Plaque index, PD, CAL, and BOP	Polysomnography	1	– There is no pathophysiological link between the severity of OSAS and clinical periodontal status via neutrophil products and MMPs
		– F/M ratio = 20/30 – Age range = 21–64 years	– Salivary and serum concentrations of MMP-8, proMMP-2, MMP-9, TIMP-1, MPO, and NE			– The clinical periodontal parameters were highest in the severe OSAS group but these differences were not statistically different (there was no statistical significant differences in clinical periodontal parameters and the study groups)
Sanders et al (2015), USA	Cross-sectional	– $N = 12{,}469$ subjects	PPD with and without BOP, gingival recession, CAL	Single night home sleep test	1,3	– The prevalence of severe periodontitis was more common at mild levels of SDB severity, and this relationship was strongest in the youngest age group of 18–34 years
		– F/M = 7473/4996				– There is an independent association between severe periodontitis and SDB
		– Age range = 18–74 yrs – 1783 subjects had 0 AHI – 7039 subjects had 0.1–4.9 AHI – 2298 subjects had 5–14.9 AHI – 1349 subjects had ≥ 15.0 AHI				– Blood levels of hs-CRP did not explain the relationship
Loke et al (2014), USA	Cross-sectional	– $N = 100$ subjects – F/M gender ratio = 9/91 – Age range = 28–79 years – Mean ages = 52.6 years	PPD, CAL, REC, BOP, % of sites with plaque, % of sites with PD ≥ 5 mm, % of sites with CAL ≥ 3 mm	Polysomnography	1,3	OSA was not significantly associated with the prevalence of moderate to severe periodontitis and all periodontal parameters, except for % plaque

Table 1 (continued)

Authors (year), country	Study design	Population	Periodontitis assessment	OSA assessment	Research question investigated*	Authors' conclusions
Nizam et al (2014), Turkey	Case-control	– Cases = 17 with mild/moderate OSA – Cases = 22 with severe OSA – Controls = 13 with primary snoring and AHI < 5 – F/M ratio = 20/32 – Age range = 21–64 years	– CAL, PI, PPD, BOP, number of teeth present – Salivary cytokines (IL-Iβ, IL-6, IL-21, IL-33, and PTX3)	Polysomnography	1	OSA may have an increasing effect on salivary IL-6 and IL-33 levels independent of OSA severity
Ahmad et al, (2013), USA	Case-control	– *N* = 154 subjects – F/M ratio = 93/61 – Mean ages = 61 years	– Plaque index, gingival index, CAL, mobility, furcation involvement, bleeding index, PPD, gingival recession, and bone loss	STOP Questionnaire	1,3	– A significant association was seen between a risk for OSA and moderate or severe periodontitis – Patients with a high risk of OSA had a 4.1 times greater odds of moderate or severe periodontitis compared to low risk patients
Keller et al (2013), Taiwan	Population based Case-control	– Cases = 7321 with OSA – Controls = 21,963 without OSA – F/M ratio = 11,052/18,232 Mean ages = 47.6 ± 15.4 years	– PPD ≥ 3 mm, inspection of color and shape of gingival tissue, BOP, tooth mobility – Radiographic ABL	Polysomnography	1,4	– There was an association between OSA and a prior diagnosis of chronic periodontitis
Seo et al (2013), Korea	Cross-sectional	– *N* = 687 subjects – F/M ratio = 227/460 – Mean age = 55.85 ± 6.63 years – Age range = 47–77 years	– CAL, PPD, BOP, REC, PI, GI	Polysomnography at home or at the sleep laboratory	1,3,4	– There is a significant association between OSA and periodontal disease – OSA was positively associated with periodontitis, probing pocket depth, and CAL in a dose–response manner
Gunaratnam et al (2009), Australia	Cross-sectional	– *N* = 66 subjects – F/M ratio = 12/54 – Mean ages = 54.9 ± 12.8 years – Median ages = 57 years	– CAL, PPD, BOP, REC, PI	Polysomnography	1	– The prevalence of periodontitis in OSA patients was higher than in non-OSA subjects

*Questions investigated by each study: 1 = Is there evidence on the association between OSA and PD?, 2 = Is there evidence on causation?, 3 = Is there a dose-response relationship?, 4 = Is there evidence on efficacy of PD interventions on OSA's occurrence, and/or severity, or vice versa

**ABL, alveolar bone loss; AHI, apnea-hypopnea index; BOP, bleeding on probing; ESS, Epworth sleepiness scale; CP, chronic periodontitis; CLA, clinical attachment loss; F, female; GI, gingival index; M, male; OSA, obstructive sleep apnea; ODI, oxygen desaturation index; PI, plaque index; PPD, periodontal pocket depth; REC, gingival recession, SpO2, lowest nocturnal oxygen saturation; CRP, C-reactive protein; hs-CRR, high-sensitivity C-reactive protein; IL-6, Interleukin-6; IL-33, Interleukin-33; IL-1B, Interleukin-1B; MMP-8, Matrix metalloproteinase-8

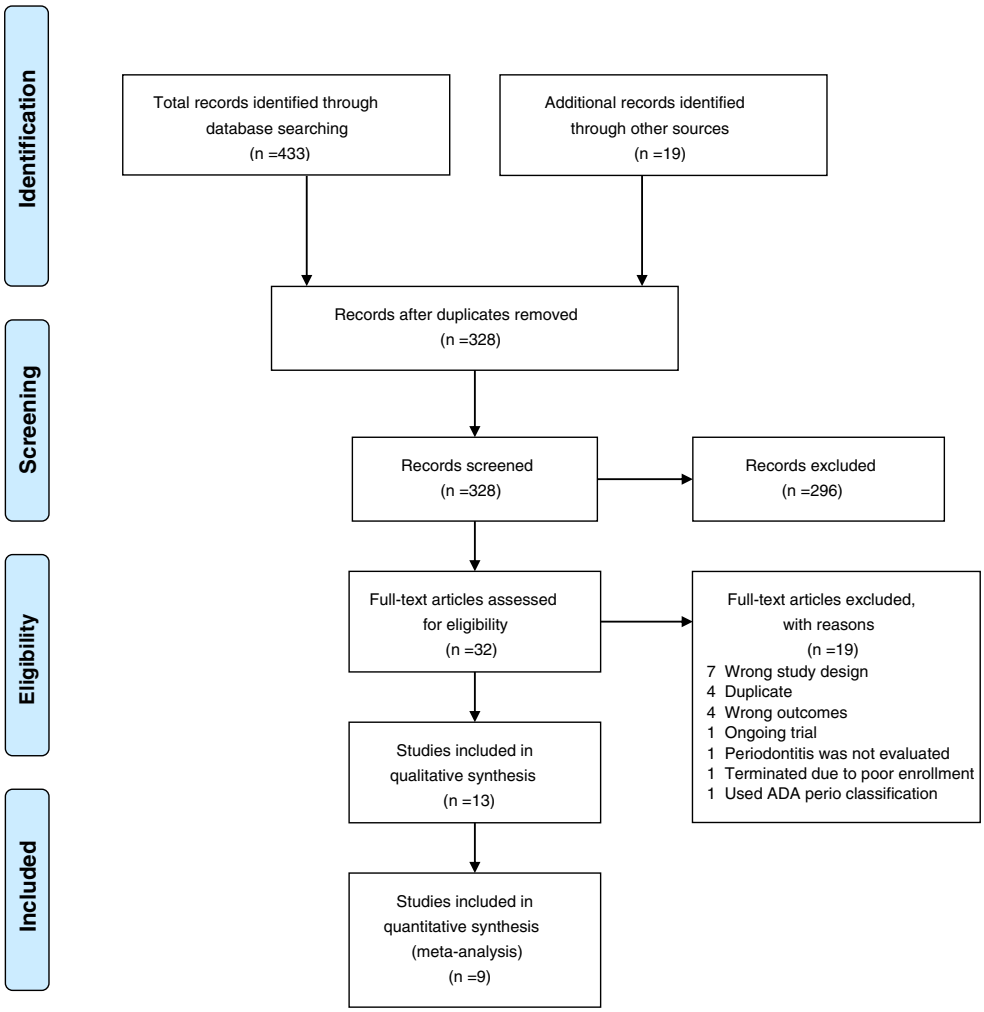

Fig. 1 PRISMA flow diagram

AHI as continuous variable, and AHI absolute values were divided into 10-unit increments.

In four of the nine studies [11••, 22•, 25, 29••], the effect estimates between periodontitis and OSA were reported according to OSA severity. Thus, AORs were analyzed for mild and moderate/severe OSA subgroups independently. Meta-analysis of five studies that assessed the association between periodontitis and OSA and seven other studies in two subgroups revealed a significant association between periodontitis and OSA (pooled AOR = 1.66, 95% CI, 1.28, 2.17; Tau^2 = 0.11; Chi-square = 69.14; df = 11; $P < 0.00001$; $I^2 = 84\%$; test for overall effect, $Z = 3.75$; $P = 0.0002$) (Fig. 2).Sensitivity analysis when excluding two studies [24, 27] with subjective OSA assessment revealed similar results (AOR = 1.60, 95% CI, 1.22, 2.11; $Tau^2 = 0.11$; Chi-square = 65.80; df = 9; $P < 0.00001$; $I^2 = 86\%$; $Z = 3.37$; $P = 0.0007$). Another sensitivity analysis excluding studies with small sample size [11••, 22•, 23, 24, 27, 28] confirmed stability of the results (AOR = 1.77, 95% CI, 1.67, 1.87; $Tau^2 = 0.00$; Chi-square = 1.03; df = 3; $P = 0.79$; $I^2 = 0\%$; $Z = 20.00$; $P < 0.00001$). Analysis of the two subgroups of OSA independently, however, revealed no significant associations. Publication bias was not assessed due to the small number of studies included.

Dose-Response Relationship

The dose-response relationship was examined in five studies [11••, 23, 25–27]. Sanders et al. [25] initially reported a correlation of severe periodontitis with AHI ≥ 15/h (OR = 6.9, 95% CI, 4.8, 10.0). After adjusting for confounders, the relationship remained significant but was attenuated in strength and no longer dose-response. Loke et al. [23] examined a possible dose-response relationship using AHI both as categorical and continuous variable. When comparing the percentage of patients with moderate to severe periodontitis across the four AHI groups normal (AHI < 5/h), mild (≥ 5–15/h), moderate (AHI > 15–30/h), and severe (>30/h), no significant difference was found (Chi-square test, $P = 0.111$). AHI categories were significantly associated with percentage of sites with plaque ($P = 0.037$), but not with bleeding on probing ($P = 0.121$) or CAL ($P = 0.842$). When AHI was expressed as a continuous variable, a negligible correlation between AHI

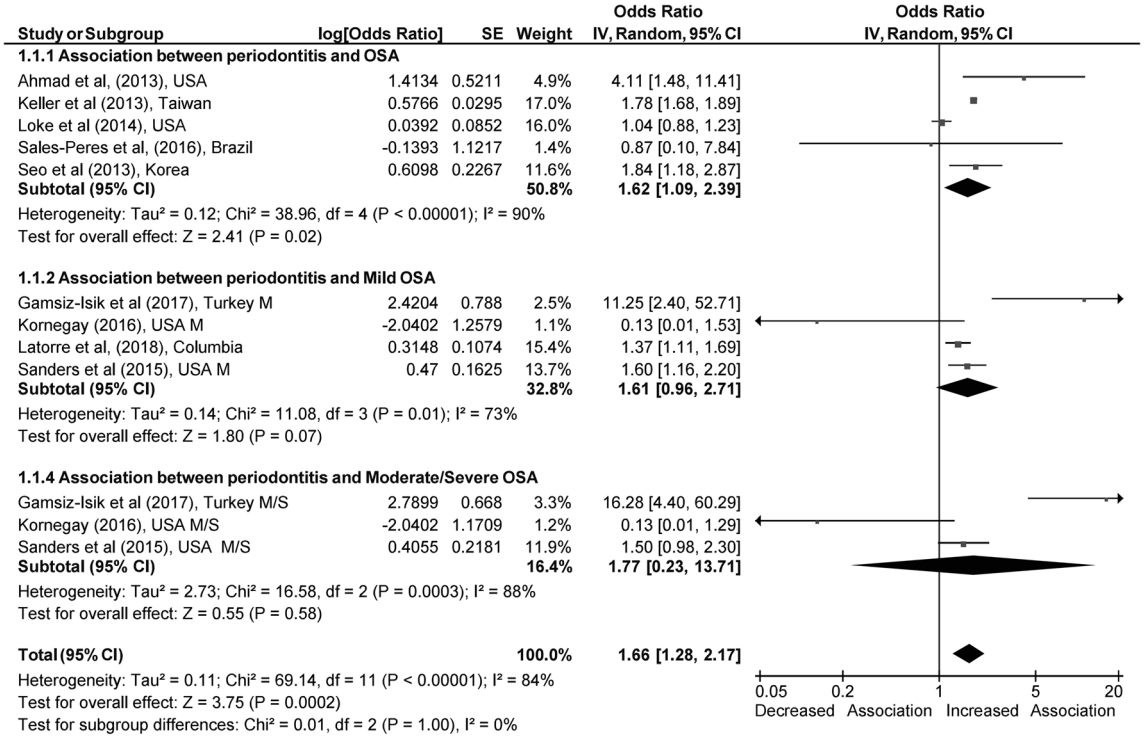

Fig. 2 Forest plot for the meta-analysis of the overall association between periodontitis and OSA and the stratified association by OSA severity

and periodontal disease severity was observed (rho = 0.191; 95% CI, 0.006, 0.373). Gamsiz-Isik et al. [11••] reported higher prevalence of severe periodontitis in severe-moderate OSA patients (52.2%) than in mild OSA (31.2%), but the difference was not significant. Seo et al. [26] investigated the dose-response relation between OSA severity (AHI categories < 5/h, 5–10/h, ≥ 10/h) and periodontitis. Increased AHI (≥ 10/h) was associated with higher odds of CAL (AOR = 1.97; 95% CI, 1.07, 3.65). In subjects 55 years of age and older, a positive association between high AHI and periodontitis (OR = 2.98, 95% CI, 1.50, 5.91), CAL (OR = 2.89, 95% CI, 1.31, 6.36), and PPD (OR = 5.14, 95% CI, 2.15, 12.25) was also observed. Finally, Ahmad et al. [27] reported an increase in the percentage of moderate/severe periodontitis cases with the increase in the number of affirmative responses on the four-item STOP OSA screening questionnaire. Meta-analysis was not conducted due to variability between the studies.

Evidence on Reversibility

Keller et al. [28] analyzed the odds for OSA among periodontal patients and compared them with the odds for OSA among periodontal patients who underwent gingivectomy or periodontal flap surgery. They stated that the odds for OSA attenuated after periodontal therapy (AOR = 1.36, 95% CI, 1.18, 1.56; $P = 0.002$) and attributed it to a possible reduction in the inflammatory contribution of chronic periodontitis.

Quality Assessment

The mean NOS score for cross-sectional studies was 7.7 (range = 7–10; Table 2). Risk of bias was greater in the non-respondents, and ascertainment of exposure, study design, and confounding factors control domains. The mean NOS score for case-control studies was 4.9 (range = 3–7; Table 3). Risk of bias was detected mainly in representativeness of the cases, definition of controls, study design, confounding factors control, and non-response rate. Risks of bias summary plots are depicted in Fig. 3 a and b. The certainty of evidence on the association between periodontitis and OSA was very low with study inconsistency and serious risk of bias as contributing factors (Table 4).

Discussion

The purpose of this systematic review and meta-analysis was to update evidence concerning the relationship between periodontitis and OSA. Since 2015, multiple studies have been published justifying another evaluation of the relationship between the two conditions.

The association between periodontitis and OSA has been explored in 13 studies. The majority of these were classified as having moderate to low risk of bias, while five had a high risk of bias [12, 28, 29••, 30, 31]. This high risk of bias was attributed to multiple factors, including the lack of calibration of periodontal examiners, the lack of sample size estimation, and

Table 2 Quality assessment of cross-sectional studies using the Newcastle Ottawa Scale (NOS) for non-randomized studies

Authors (year), country	Selection				Comparability	Outcome		Risk of Bias (NOS scale)
	Representativeness of the sample	Sample size	Non-respondents	Ascertainment of the exposure (risk factor):	Subjects in different outcome groups are comparable, based on study design or analysis. Confounding factors controlled	Assessment of outcome	Statistical tests	
Latorre et al. (2018), Columbia	*	-	-	**	-	**	*	Medium (6 stars)
Sales-Peres et al. (2016), Brazil	*	*	-	**	-	**	*	Medium (7 stars)
Sanders et al. (2015), USA	*	*	*	**	**	**	*	Low (10 stars)
Loke et al. (2014), USA	*	*	-	**	-	**	*	Medium (7 stars)
Seo et al. (2013), Korea	*	-	*	**	**	**	*	Low (9 stars)
Gunaratnam et al. (2009), Australia	*	*	-	*	**	**	-	Medium (7 stars)

The NOS scale utilizes a star system with ten being the maximum possible score for cross-sectional studies. The risk of bias was categorized into low (score $\geq$ 8), medium (score 6–8), and high (score $\leq$ 5)

Table 3 Quality assessment of case-control studies using the Newcastle Ottawa Scale (NOS) for non-randomized studies

Authors (year), country	Selection				Comparability	Exposure			Risk of bias (NOS scale)
	Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls on the basis of design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	
Gamsiz-Isik et al. (2017), Turkey	*	*	*	-	**	*	*	-	Medium (7 stars)
Kornegay (2016), USA	*	-	*	-	-	-	*	-	High (3 stars)
Nizam et al. (2016), Turkey	*	-	*	-	-	*	*	-	High (4 stars)
Nizam et al. (2015), Turkey	*	-	*	-	-	*	*	-	High (4 stars)
Nizam et al. (2014), Turkey	*	-	*	-	-	*	*	-	High (4 stars)
Ahmad et al. (2013), USA	*	*	*	-	**	*	*	-	Medium (7 stars)
Keller et al. (2013), Taiwan	-	*	*	-	**	-	*		High (5 stars)

The NOS scale utilizes a star system with nine being the maximum possible score for case-control studies. The risk of bias was categorized into low (score $\geq$ 8), medium (score 6–8), and high (score $\leq$ 5)

Fig. 3 A) Risk of bias within the included studies; B) Weighted summary plot

the absence of control for potential confounders such as obesity and early stage renal disease. Three [12, 30, 31] of the five studies with a high risk of bias were conducted by the same author and were based on the same sample, and thus their results must be interpreted with caution.

While the majority of the studies assessed OSA using PSG, a few [24, 27] assessed the risk for OSA using subjective questionnaires. When these were excluded from the meta-analysis, the association remained statistically significant (AOR = 1.60, 95% CI, 1.22, 2.11, $P = 0.0007$). In one study, both a home sleep test and a questionnaire were utilized [28••]. The sample in this study however was over-represented by women, and thus their results cannot be generalized to other populations.

Meta-analysis of the nine studies [11••, 22•, 23, 24–28, 29••] indicated a significant association between periodontitis

Table 4 GRADE quality assessment

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adult patients with OSA and periodontitis	Adult patients with OSA, but without periodontitis	Relative (95% CI)*	Absolute (95% CI)		
Association												
12[a,b]	Observational studies	Serious [a]	Very serious [b]	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect	3409/43390 (7.9%)	11,449/43390 (26.4%)	OR 1.66 (1.28 to 2.17)	109 more per 1.000 (from 51 more to 174 more)	⊕○○○ Very low	Critical

*CI, confidence interval; OR, odds ratio

[a] Quality assessment based on NOS scale revealed only one study with low risk of bias. The remaining studies were of medium or high risk of bias. Five studies were cross sectionals

[b] The inconsistency was defined by the inverse variance value of I^2, which was 84%

and OSA while controlling for some known confounders. Compared with our findings in 2015 [13], the positive association still stands.

Several potential mechanisms underlying the relationship between periodontitis and OSA have been highlighted in studies included in this review and previous literature. First, chronic mouth breathing associated with OSA leads to the drying of the oral cavity which prevents its self-cleansing action, consequently promoting the progression of periodontitis [32]. Sanders et al. [25] also suggested that extrinsic xerostomia/dry mouth could be one of the potential mechanisms relating periodontitis and OSA. Second, intermittent hypoxia—the hallmark of OSA—increases sympathetic activation and creates ideal conditions for oxidative stress and systemic inflammation cascade [33]. In vitro studies confirm the effect of hypoxia itself in periodontal tissue damage, whereas the reactive oxygen species related to OSA could be assisting in periodontal breakdown [34]. Third, both periodontitis and OSA are associated with systemic inflammation, and this can be seen through high levels of the systemic inflammatory biomarker known as high sensitivity C-reactive protein (hs-CRP). This common biomarker may be a link between these two conditions [11••, 25]. Common risk factors and comorbidities must also be taken into account in order to resolve this controversial association [11••, 22•]. Even with these potential mechanisms, the relationship between periodontitis and OSA is still not fully understood, and further studies are warranted.

Five studies evaluated the dose-response relationship between periodontitis and OSA severity, two of them [25, 26] had a low risk of bias, while the rest had a medium risk of bias [11••, 23, 27]. Some of the limitations that contributed to increased risk of bias included no calibration of examiners was reported [23, 26, 27], periodontal examination was carried out by different operators [27], not all known confounders were accounted for [11••, 23, 26, 27], no sample size estimation [25–27], OSA was subjectively diagnosed [27], and no mention of examiner blindness [11••, 25].

Only two studies [26, 27] found a significant dose-response relation. Ahmad et al. [27] indicated an increase in the percentage of moderate/severe periodontitis cases, with an increase in the number of affirmative responses on the four-item STOP OSA screening questionnaire [35]. It must be noted that although validated for screening a low or high risk of OSA, the STOP questionnaire does not diagnose OSA severity, and thus high scores on a questionnaire may not translate into increased OSA severity. Seo et al. [26] on the other hand, found that an increase in AHI severity (≥ 10/h) was associated with higher odds of CAL. They also suggested that the dose-response relation was modified by an increase in age. The study adjusted for several known confounders including age, BMI, gender, smoking status, alcohol use, habitual snoring, mouth breathing in sleep, and diabetes. Overall, evidence is

still conflicting on the dose-response relation, and future studies using more stringent methodology are warranted.

This review found insufficient evidence of disease reversibility. Future multi-arm clinical trials (periodontal intervention in the presence of OSA vs. periodontal interventions without OSA) are warranted to address this outcome. Hopefully, through a better understanding of this complex relationship, we will be able to take a better stance against periodontitis and OSA in regard to their treatment.

Conclusion

There is growing evidence that supports an association between periodontitis and OSA (AOR = 1.66, 95% CI, 1.28, 2.17). However, future studies are warranted to determine causality, does-response relation, and reversibility of interventions for the occurrence of OSA or vice versa.

Compliance with Ethical Standards

Conflict of Interest The authors report no conflicts of interest related to this study.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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