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Associations between osteoporosis and risk of periodontitis: A pooled analysis of observational studies

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Abstract

Background: Periodontitis and osteoporosis are most popular among aging population and both conditions might be linked, even though, this suggestion still until now debated.

Objectives: A meta-analysis on previous investigations has been used to evaluate the correlation between periodontitis and osteoporosis to determine whether osteoporosis is a local indicator of bone loss, or whether it is depending on or related to periodontitis causes.

Methods: The literature database, including but not excluding, The Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL, and Science Citation Index Expanded, was searched in this work during Feb, 2020. We conducted the investigations contain cohort studies, cross-sectional studies, as well as case–control studies with relative risk (RR) or odds ratio (OR) and 95% confidence intervals (CIs). Subgroup and Sensitivity analysis were also applied to identify heterogeneity sources.

Results: 23 observational studies with 12 cohorts, 7 cross-sectional and 4 case–control studies, were included, together with 2,157,037 participants. Osteoporosis patients were more exposed to periodontitis (OR, 1.96; 95% CI, 1.50–2.54). Subgroup analyses showed that the higher risk of osteoporosis in periodontitis patients exists in both cross-sectional studies (OR, 2.17; 95% CI, 1.80–2.61) and case–control studies (OR 2.63; 95% CI, 1.69–4.09), and marginally in cohort studies (OR, 1.70; 95% CI, 1.16–2.49).

Conclusion: Review analyses have shown that osteoporosis is closely related to the increased risk of periodontitis in the future. Dental specialists better to understand the potential association between periodontitis and osteoporosis.

KEYWORDS

meta-analysis, observational studies, osteoporosis, periodontitis

1 | INTRODUCTION

Periodontitis is an infectious-inflammatory disease affecting the periodontal tissues which could cause pain, tooth mobility, gingival bleeding, alveolar bone destruction, and periodontal attachment loss that might result in tooth loss (Pihlstrom, Michalowicz, & Johnson, 2005). Periodontitis usually caused by bacterial accumulation on the teeth outer surface, which causes an imbalance between bacterial invasion and host protection (Passos et al., 2013). Periodontitis is a well-known dental problem, and its incidence and severity of public health problems become worse with age. It is found that the periodontitis is affected by gender, genetics, smoking habits, lifestyle, inflammation, and osteoporosis (Gera, 2002).

Osteoporosis is described by bone tissues microarchitectural deterioration and low bone mineral density (BMD). Symptoms lead to bone fragility, which consequentially increase fracture risks (Penoni et al., 2016). Risk factors of periodontal diseases are found including age, lifestyle (smoking, alcohol consumption), low body mass index (BMI), and menopause (Wactawski-Wende et al., 1996). The obvious feature of both diseases is bone loss, and it is highly conceivable that periodontal destruction could be significantly influenced by systemic bone loss. Many previous studies have revealed a positive relationship between systemic osteoporosis and periodontitis (Al Habashneh et al., 2010; Choi et al., 2017; Mongkornkarn et al., 2019; Richa, Puranik, & Shrivastava, 2017), while others disagree (Marjanovic et al., 2013; Sultan & Rao, 2011). Despite the fact many works have been done investigating the relationship between periodontitis and osteoporosis, no clear effect has yet been found, even supposing the current available evidences.

Currently, no identified meta-analysis has been reported to clearly confirm that osteoporosis would definitely cause periodontitis. Different from the usually relatively small sample size of individual studies, a meta-analysis can provide more reliable evidence because the method involves a systematic aggregation of existing studies (Moher, Liberati, Tetzlaff, & Altman, 2009). Herein, this study employed a meta-analysis on numbers of previous investigations with the purpose to evaluate the correlations between periodontitis and osteoporosis. The main goal is to determine whether osteoporosis is a local indicator of bone loss, or whether it is depending on or related to periodontitis causes. Finally, we got the conclusion on that whether osteoporosis depends on its own cause, or if it is a local manifestation caused by a systemic bone loss.

2 | METHODS

2.1 | Research methodology

We conducted and reported this systematic review in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (Liberati et al., 2009) and the Cochrane Handbook for Interventional Reviews (Higgins et al., 2019). We have tried to search the literature database, including Cochrane Library, PubMed, MEDLINE, CINAHL, EMBASE databases, and Science Citation Index Expanded, to identify relevant investigations up to February 2020. "Periodontitis," "alveolar bone loss," "periodontal pocket," "periodontal disease," "bone loss," "bone mineral density," "Osteoporosis," as well as "clinical attachment loss" as shown in Table S1 were used as keywords in search engines. The selected studies were mainly limited to those conducted only on human beings and the articles should be published in English or in Chinese. Furthermore, we also manually checked selected studies to screen out other studies.

2.2 | Selection and eligibility criteria

Consider analyzing eligible studies if the following criteria are met: (a) It should include case–control studies, cross-sectional studies, as well as studies on cohort; (b) Periodontitis definition should be based on two sets of principles: clinical criteria which are based on periodontal charting, including attachment loss (CAL), clinical probing depth (PD), detecting blood, plaque index, gingival index and radiological criteria that can assess mandible or maxillary loss, (Martínez-Maestre, González-Cejudo, Machuca, Torrejón, & Castelo-Branco, 2010); (c) Osteoporosis defined by the World Health Organization (WHO) that young people have a BMD score of 2.5 or a T-score below the average value (Kanis, 1994); (d) Reporting RRs and ORs with 95% CIs; and 5. The sample size includes over 100 topics. Once the separate reports are published for the same population, consider the longest follow-up studies and/or the most recent studies.

2.3 | Data extraction

Following data classification, the 1st and 2nd co-authors were independently tasked with selecting the studies for inclusion and data extraction. Data uncertainties were resolved independently by the 4th co-author. The following information was extracted from the selected publications, such as the details of first author and country, type of studies and the size of the sample, gender, age, adjusted OR/RR values, follow-up duration (in years), diagnostic criteria (osteoporosis and periodontitis), study model and quality, as well as publication year.

2.4 | Quality evaluation

Based on the above results, we further evaluate the cross-sectional study and cohort study quality using the Agency for Healthcare Research and Quality (Owens et al., 2010) combined with The Newcastle–Ottawa Quality Assessment Scale (Stang, 2010), and the Methodological Expectations for Cochrane Intervention Reviews (MECIR) (Higgins et al., 2019). Scores system has been

built, for example, 0–4 is considered as low quality, 5 score to 7 score means moderate quality, high quality means the score should be 8 to 11 (Hu et al., 2015). The study quality increases with higher scores.

2.5 | Statistical analysis

To evaluate statistical variances among the involved investigations, Cochran's Q test and the I^2 metric have been employed for quantification. The I^2 parameter was used to determine OR across studies consistent estimation (Melsen, Bootsma, Rovers, & Bonten, 2014). Statistically significant heterogeneity for the Q statistic was considered in case of p value <.10. During this study, some cut-off points were used for the I^2 statistic as following: <30% (low or no heterogeneity), 30%–75% (medium heterogeneity), and >75% (high heterogeneity) (Chen et al., 2015). With subgroup analysis based on adjusted OR, potential causes and possible associations of heterogeneity are explored. This was according to study design, geographical region, sample size, gender, diagnostic criteria, follow-up period, and methodological quality. Furthermore, funnel plots combined with Egger's linear regression approach, as well as the Begg's rank correlation test were conducted to assess potential publication bias (Begg & Mazumdar, Mazumdar, 1994; Egger, Davey Smith, Schneider, & Minder, 1997). In cases of possible publication bias, a trim and fill algorithm strategy were used to correct the asymmetry of the funnel plot (Duval & Tweedie, 2000). Finally, we further conducted sensitivity analysis by removing a study according to the rules of the meta-analysis with the STATA software. The software version is 12.0 and made by STATA Corporation, TX, USA. It should be noted that the condition with P lower than 0.05 is considered as statistically significant.

3 | RESULTS

3.1 | Literature screening

Figure 1 presents the process description of this study. Briefly, 893 relevant articles were identified in the preliminary literature search. After titles and abstracts were evaluated, 147 studies were selected for more detailed study. Finally, 21 articles from 23 studies (Al Habashneh et al., 2010; Chang et al., 2014; Choi et al., 2017; Gomes-Filho et al., 2007; Huang et al., 2016; Inagaki et al., 2005; Kim et al., 2014; Lin et al., 2015; Marjanovic et al., 2013; Mau et al., 2017; Moedano, Irigoyen, Borges-Yanez, Flores-Sanchez, & Rotter, 2011; Mongkornkarn et al., 2019; Özçaka, Becerik, Biçakci, & Kiyak, 2014; Passos et al., 2010, 2013; Penoni et al., 2016; Renvert, Berglund, Persson, & Persson, 2011; Richa et al., 2017; Shum et al., 2010; Sperr et al., 2018; Taguchi et al., 2005) comprising data from 2,157,037 participants were studied by meta-analysis.

3.2 | Study characteristics

Table 1 shown a list of adjusted covariates and characteristics of each study. Studies analyzed were all published during 1990–2016 and data contained were all collected between 1997 and 2015. The reports included 12 cohort studies (Chang et al., 2014; Choi et al., 2017; Huang et al., 2016; Lin et al., 2015; Mau et al., 2017; Moedano et al., 2011; Özçaka et al., 2014; Renvert et al., 2011; Sperr et al., 2018; Taguchi et al., 2005), 7 cross-sectional studies (Al Habashneh et al., 2010; Inagaki et al., 2005; Kim et al., 2014; Marjanovic et al., 2013; Mau et al., 2017; Penoni et al., 2016; Richa et al., 2017), and 4 case–control studies (Gomes-Filho et al., 2007; Passos et al., 2010, 2013; Shum et al., 2010). Geographically, fourteen

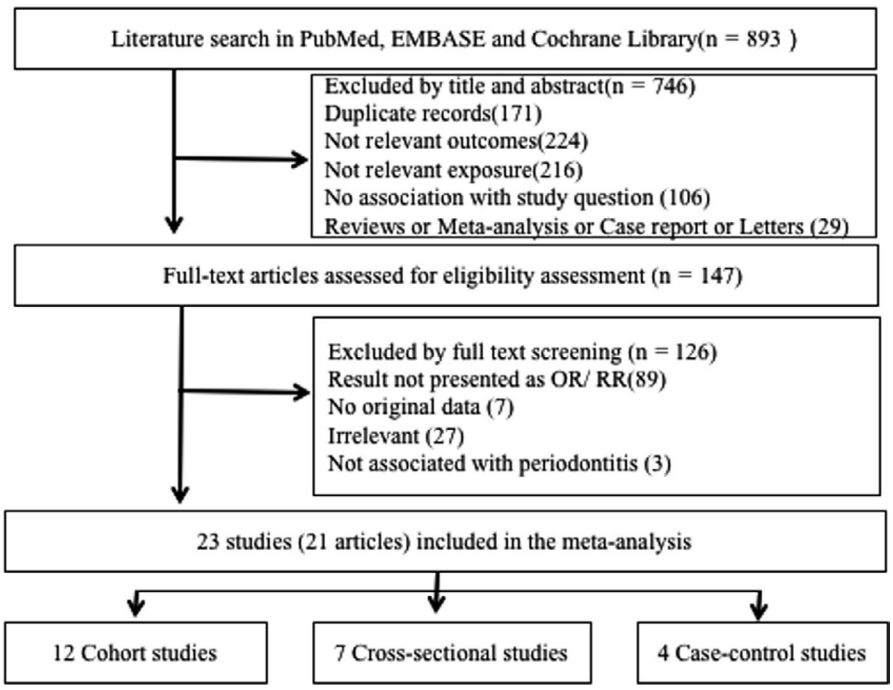


FIGURE 1 Flowchart demonstrating the process from the identification of eligible studies to the final inclusion

TABLE 1 The characteristics of the studies in included in the analysis

Author	Year	Country	Study design	Sample size (case/control)	Male/Female
Sperr et al. (2018)	2018	Austria	a nationwide population-based cohort study	1,199 patients with Periodontitis	558 males; 641 females,
Choi et al. (2017)	2017	Korea	a nationwide population-based cohort study	13,464 participants	8,884males; 4,580 females
Choi et al. (2017)	2017	Korea	a nationwide population-based cohort study	13,464 participants	8,884males; 4,580 females
Mau et al. (2017)	2017	China (Taiwan)	population-based cohort study	29,463 patients with Periodontitis	16,114male 13,349 Female
Huang et al. (2016)	2016	China (Taiwan)	population-based cohort study	85,583 (35,127 Osteoporosis patients and 50,498 controls	21,994male 63,588 female
Lin et al. (2015)	2015	China (Taiwan)	population-based cohort study	2,000,000	927,189male 951,212 female
Lin et al. (2015)	2015	China (Taiwan)	population-based cohort study	2,000,000	927,189male 951,212 female
Chang et al. (2014)	2014	China (Taiwan)	population-based cohort study	10,102(2,527Osteoporosis 7,575 Non-Osteoporosis)	2,626 males 7,476 females,
Özçaka et al. (2014)	2014	Turkey	population-based cohort study	201 older subjects	130male 71female
Renvert et al. (2011)	2011	Sweden	population-based cohort study	778 subjects	365male 412female
Moedano et al. (2011)	2011	Mexico	population-based cohort study	166	19male
147female	69.1 ± 6.7(60–80)	NS	BMD at lumbar spine by DXA	CAL	1.82(1.04–3.18)
Taguchi et al. (2005)	2005	Japan	population-based cohort study	253	postmenopausal women
Mongkornkarn et al. (2019)	2019	Thailand	cross-sectional study	3,282	2,393male 889female
Richa et al. (2017)	2017	India	cross-sectional comparative study	600(300 osteoporotic and 300 non-osteoporotic)	postmenopausal women
Penoni et al. (2016)	2016	Brazil	cross-sectional study	134(48 normal BMD and 86 Osteoporosis)	postmenopausal women

Age/median age(range)	Follow-up (years)	Diagnostic criteria		OR (95% CI)	Adjustment for covariates	Quality
		Osteoporosis	Periodontitis			
49 (14 to 83)	January 2006 to April 2009	bone densitometry	CAL	0.44 (0.28–0.70)	sex, age, education, smoking, alcohol consumption, and BMI	high
≥30	2002 to 2013	bone densitometry	NS	Male 1.39 (0.85–2.29)	NS	low
≥30	2002 to 2013	diagnostic code M80–M82	Diagnostic code ICD-10, K05.3-K05.6	Female 1.22 (1.01–1.48)	NS	low
≥40	2002 to 2008	diagnostic codeICD-9CM, 733.0 by DXA)	diagnosis codes ICD-9-CM, 5,234	2.08 (1.08–4.03)	age, sex, diabetes mellitus, hypertension, coronary artery disease, stroke, hyperlipidemia, chronic kidney disease	low
61.7	2000 and 2010	diagnosis code (ICD-9-CM 733.0, V13.51, and V82.81)	NS	6.02 (4.65–7.81)	age, sex, and comorbidities	low
	2005 and 2010	diagnostic code ICD-9-CM ,733.0. CD	PD	male 2.37 (0.88–6.39)	age, income, and geographical region	high
	2005 and 2010	diagnostic code ICD-9-CM ,733.0. CD	PD	Female 1.96 (1.17–3.26)	age, income, and geographical region.	high
70.16 (50–100)	2003–2005	diagnostic code (ICD-9-CM: 733.0 to 733.90)	probing sulcus, and radiographs	1.14 (1.05–1.24)	Urbanization level, monthly income, geographic region, hypertension, hyperlipidemia	high
M:62.65 ± 5.31F:62.23 ± 4.86	March 2008 and May 2009	bone densitometry	PI	2.05 (1.11–3.78)	age, sex, smoking	high
73.9 ± 9.4 (59– 96)	September 2001 and April 2004	bone density assessment by PIXI	panoramic radiograph	1.80 (1.10–3.30)	NS	low
sex, socio-economic status and dental plaque	high					
56.6 ± 7.7	1997 and 2003	BMD at the lumbar spine and the femoral neck by DXA	periodontal symptoms	2.01 (1.15–3.50)	age and height	high
30–82	2012–2014	BMD at femoral neck, total hip and lumbar spine by DXA	CAL	3.97 (1.20–13.19)	sex, age, plaque score, diabetes, BMI, smoking, alcohol consumption, income, education and menopause.	high
45–65	October 2012 and March 2013.	BMD at heel by an ultrasonometer based on QUS	CAL	2.52 (1.43–4.44)	the other variables presented.	low
69.84 ± 3.90	December 2013 and January 2015	BMD at lumbar spine, femoral neck, and total femur by DXA	PD and CAL	2.49 (1.14–5.43)	NS	low

(Continues)

Author	Year	Country	Study design	Sample size (case/control)	Male/Female
Kim et al. (2014)	2014	Korean	cross-sectional study	9,977 subjects	4,446male 5,531female
Marjanovic et al. (2013)	2013	UK	cross-sectional study	380	women
Al Habashneh et al. (2010)	2010	Jordan	cross-sectional study	400	postmenopausal women
Inagaki et al. (2005)	2005	Japan	cross-sectional study	356(171 premenopausal 185 postmenopausal)	women
Passos et al. (2013)	2013	Brazil	case–control study	521(cases :94 postmenopausal women control: 427 comparisons)	women
Passos et al. (2010)	2010	Brazil	case–control study	139(case: 48 postmenopausal women and control:91	women
Shum et al. (2010)	2010	China	case–control study	200	male
Gomes-Filho et al. (2007)	2007	Brazil	case–control study	139(case:48 Periodontitis control:91 without Periodontitis)	postmenopausal women

Abbreviations: BMI, body mass index; CAL, clinical attachment loss; CXD, computerized X-ray densitometry; DXA, dual-energy X-ray absorptiometry; NS, not specified; OR, odd rat; PD, pocket depth; PI, plaque index; PIXI, ultrasonography calcaneus T-scores; QUS, quantitative ultrasound technique.

studies were conducted in Asia (Al Habashneh et al., 2010; Chang et al., 2014; Choi et al., 2017; Huang et al., 2016; Inagaki et al., 2005; Kim et al., 2014; Lin et al., 2015; Mau et al., 2017; Mongkornkarn et al., 2019; Richa et al., 2017; Shum et al., 2010; Taguchi et al., 2005) while five in the Americas (Gomes-Filho et al., 2007; Moedano et al., 2011; Passos et al., 2010, 2013; Penoni et al., 2016) and three in Europe (Marjanovic et al., 2013; Özçaka et al., 2014; Renvert et al., 2011; Sperr et al., 2018). Among all, reported participants ages ranged from 14 to 100 years old. Except three, other studies were reported with adjusted OR, for potential confounders. Osteoporosis in all studies had been confirmed by bone mineral density. The parameters such as plaque index (PI), gingival bleeding index, clinical attachment loss (CAL), and pocket depth (PD) of periodontitis were included. The selected studies quality was quite high with no significant limitations as shown in Table S2 in the Supplemental Information.

3.3 | Meta-analysis

Figure 2 exhibited the adjusted ORs from 23 reports. Generally, after excluding smoking, age, and sex factors, osteoporosis revealed an obvious relationship with periodontitis (OR, 1.96; 95% CI, 1.50–2.54). The results indicate that patients who suffer from osteoporosis are significantly exposed to increased risk of periodontitis.

A random effects model combining OR values was used in some statistical heterogeneities studies ($Q = 222.69$, $p < .001$, $I2 = 90.1\%$). Figure 3 shows some revealed minor publication bias were funnel plot, Begg's test with P equal 0.139 and Egger's test with $P <$ lower than .05. Therefore, the pruning and filling methods were used to re-evaluate the aggregated risk estimates, that is, "no pruning; data unchanged" results, by eliminating each study once and performing a sensitivity analysis to reveal the influence of previous investigations on the combined OR. Through deleting a single report in turn,

Age/median age(range)	Follow-up (years)	Diagnostic criteria		OR (95% CI)	Adjustment for covariates	Quality
		Osteoporosis	Periodontitis			
≥40 years	2008, 2009, and 2010,	BMD at the lumbar vertebrae and the left femur by DXA	PD	2.26 (1.83–2.78)	age, sex, sociodemographic variables (household income, educational level, smoking, and high-risk drinking), and medical status variables (diabetes mellitus, BMI, and limitation of physical activity	high
45–65 years	March 2008 and June 2010	BMD at lumbar spine and proximal femur by DXA	PD	1.17 (0.67–2.05)	age, smoking, hormone replacement therapy, alcohol	high
62.5 ± 6.4(50–75)	June 2008 and February 2009	BMD at lumbar spine,femoral neck and trochanter by DXA	PD and CAL	2.45 (1.38–4.34)	age, years of education, income,	high
premenopausal (37.9 ± 8.0) postmenopausal (63.3 ± 7.7)	May 1998 and 1999	BMD at right second metacarpal by CXD	PD	2.00 (1.10–3.70)	age and menopausal status	high
60.8 ± 7.4 (50–80)	June 2008 and September 2011	bone mineral density	CAL	2.24 (1.24–4.06)	age, smoking habit, last visit to dentist, and family income	high
>50	June and November 2006	bone mineral density	PD and CAL	3.75 (1.22–11.49)	smoking habit and age	high
71.9 ± 3.3(69–78)	May 2005 and July 2006	BMD at the hip, spine (lumbar vertebrae 1 through 4) by DXA	CAL	5.30 (0.10–10.05)	smoking and BM	high
>50	June and November 2006	BMD	PD and CAL	2.71 (1.12–6.55)	smoking habit and age	high

the combined OR and 95% CI did not show any significant changes (Figure 4). This shows that the proposed results are reproducible and reasonable.

3.4 | Subgroup analysis

To inspect the studies reproducibility based on several factors, we further conduct subgroup analyses deeply. Patients with periodontitis exists in both cross-sectional studies with OR of 2.17 and 95% CI ranging from 1.80 to 2.61, and case–control studies with OR of 2.63 and 95% CI ranging from 1.69 to 4.09, and have higher risk, and slightly in cohort studies (OR, 1.70; 95% CI, 1.16–2.49). When we stratified subjects by sex, we found that female with osteoporosis (OR, 2.24; 95% CI, 1.52–3.30) are exposed to a higher risk of developing periodontitis, compared to male (OR, 1.61; 95% CI, 1.04–2.50) as shown in Table 2. All in all, the results from subgroup analysis showed that patients with osteoporosis are at high risk for periodontitis.

4 | DISCUSSION

Our results indicate an obvious association between osteoporosis and periodontitis, which is consistent with previous investigations. Since Groen et al. (Groen, Menczel, & Shapiro, 1968) first reported the relationship between chronic destructive periodontal disease and presenile osteoporosis, several investigators have referred to a correlation between periodontal disease progression and low BMD in postmenopausal women. Previously, Wowern, Klausen, and Kollerup (1994) have found that the disease stages are different between osteoporosis patients and a control group

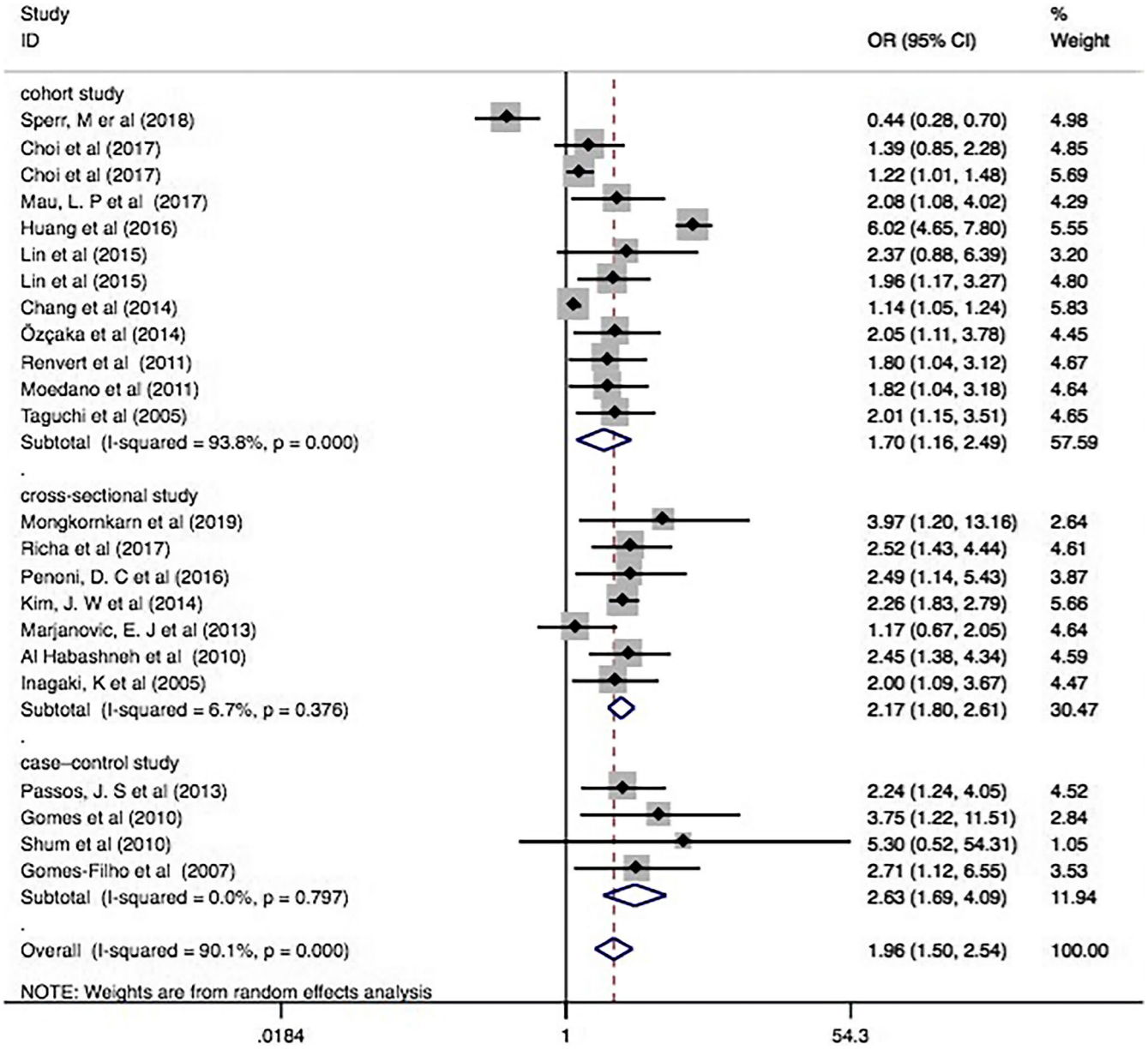


FIGURE 2 Forest plot of osteoporosis and periodontitis in a random effects model meta-analyses by study design. The horizontal lines correspond to the study-specific OR and 95% CI. The areas of the squares reflect the study-specific weights. The diamond represents the pooled results of the OR and 95% CI. OR, odds ratio; CI, confidence interval [Colour figure can be viewed at wileyonlinelibrary.com]

without osteoporosis. Furthermore, relationship between periodontitis, lumbar vertebral BMD, and loss of periodontal adhesion has been reported by Mohammad, Hooper, Vermilyea, Mariotti, and Preshaw (2003). On the other hand, 347 postmenopausal women have been selected by the research group of Takahashi, Yoshihara, Nakamura, and Miyazaki (2012) and it is found that periodontal diseases and truncal BMD have a significant negative correlation. Penoni et al. (2017) have reported a systematic review, in which the postmenopausal women with osteoporosis or osteopenia are shown to exhibit larger possibility to have CAL compared with the control group of women with normal BMD. Finally, it is found that the risk of periodontitis has increased by over twofold in patients with osteoporosis by Al Habashneh et al. (2010), which is consistent with our research. Therefore, osteoporosis is found to increase the possibility of being periodontitis, but the underlying mechanism is still not fully understood.

Based on the above analysis, knowing the relationship between periodontitis and osteoporosis and investigating the underlying causes would be beneficial for health professionals prevent, detection, and earlier treatment (Al Habashneh et al., 2010). The link between osteoporosis and periodontitis is still controversial, and many hypotheses exist. One possible link between osteoporosis and periodontal destruction is systemic and simultaneous alveolar bone resorption. First, systemic bone mineral density decline, taking osteoporosis as an example, also occurs in the alveolar bones of the upper and lower jaws (Takaishi et al., 2005). And the reduction

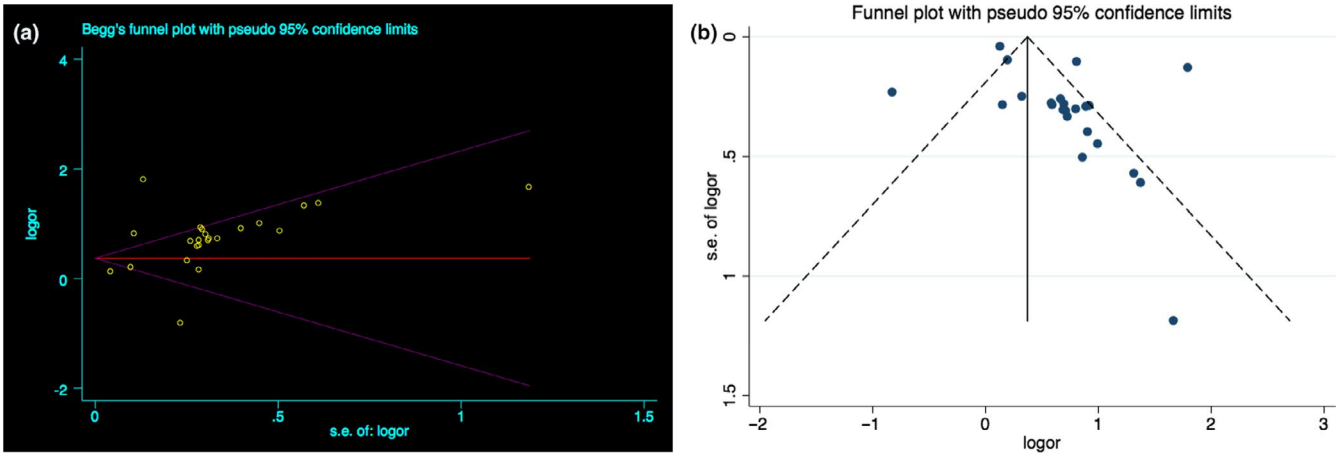
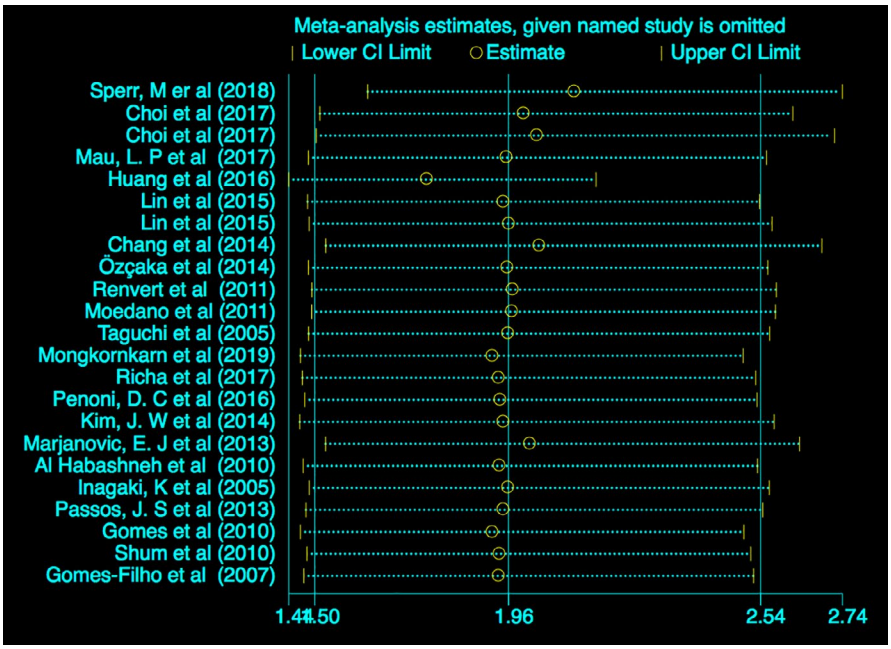


FIGURE 3 Begg's funnel plot of publication bias in the included studies. Each point represents a separate study for the indicated association [Colour figure can be viewed at wileyonlinelibrary.com]

FIGURE 4 Sensitivity analysis of the meta-analysis of the correlation between osteoporosis and periodontitis. The OR and 95% CI were determined by omitting each study from the pool of eligible studies concerning the link between osteoporosis and periodontitis. OR, odds ratio; CI, confidence interval [Colour figure can be viewed at wileyonlinelibrary.com]



of BMD is associated with the effect of oral bacterial flora, which can lead to faster alveolar bone resorption, which can lead to rapid development of periodontal destruction (Estrugo-Devesa, Gómez-Vaquero, & López-López, 2013). On the other hand, the change of local tissue responses can be caused by systemic inflammatory mediators that influence bone remodeling. Cytokines (such as Kappa-B ligand (RANKL), tumor necrosis factor (TNF-α), and interleukin (IL-1β and IL)-known to patients with systemic bone loss and patients with periodontitis- 6) (Lerner, 2006). On the one hand, these cytokines promote the continuous production of osteoclasts by osteoclast progenitor cells, which in turn causes bone loss. On the other hand, it can also impair tissue response to periodontal disease. This increase can stimulate the activity of local osteoclasts, promote clinical loss of adhesion and alveolar bone, and accelerate the development of periodontal disease (Lerner et al., 2006). Generally, one of the possible mechanisms for these two diseases is through the inflammatory pathway. Second, people with genetic factors that are prone to systemic reduction of BMD may be at risk of damaging alveolar bone through the same pathophysiological mechanisms. Finally, daily lifestyles such as smoking and low calcium intake may also increase BMD reduction and the risk of periodontal disease (Hildebolt et al., 1997). Therefore, in summary, we believe that osteoporosis can be listed as one of the risk indicators of periodontitis.

In addition to the above, risk factors that are generally considered to affect BMD due to smoking, diabetes, and hormone levels are also the effects of infection. Some researchers think that periodontitis is an early sign of osteoporosis (Tezal et al., 2000). Considering the biological feasibility of a factor in the occurrence and development of osteoporosis may be periodontitis. It is well known that periodontitis is a chronic inflammatory disease caused by the colonization of bacterial plaque biofilms. Therefore, the

TABLE 2 Results of subgroup analyses included in this meta-analysis

Group	Number of studies	Pooled OR	95% CI	P(heterogeneity)	I^2(%)
All studies	23	1.96	1.50–2.54	0.000	90.1
Diagnostic criteria					
CAL	6	1.83	0.85–3.96	0.000	86.1
PD	7	2.09	1.77–2.45	0.542	0.0
Both	5	2.00	1.21–3.32	0.001	77.6
Study design					
Cohort study	12	1.70	1.16–2.49	0.000	93.8
Cross-sectional study	7	2.17	1.80–2.61	0.376	6.7
Case–control study	4	2.63	1.69–4.09	0.797	0.0
Location					
Asian	14	2.17	1.55–3.05	0.000	93.0
America	5	2.22	1.59–3.09	0.861	0.0
Europe	4	1.16	0.55–2.42	0.000	86.5
Gender					
Male	3	1.61	1.04–2.50	0.381	0.0
Female	13	2.24	1.52–3.30	0.000	88.2
Number participants					
<1,000	13	2.05	1.72–2.45	0.815	0.0
>1,000	10	1.77	1.16–2.69	0.000	95.5
Length of follow-up					
>5 years	7	2.13	1.15–3.51	0.000	93.8
<5 years	15	1.85	1.37–2.48	0.000	84.5
Study quality					
High	16	1.81	1.37–2.39	0.000	83.0
Low and moderate	7	2.19	1.18–4.05	0.000	93.9

Abbreviations: CI, confidence interval, CAL, Clinical attachment loss, PD, Pocket depthOR, odds ratio.

host often has an immune response. Locally increased production of cytokines associated with periodontal disease may accelerate systemic bone resorption by regulating host response (Xiao, Li, Pacios, Wang, & Graves, 2016). In addition, these cytokines mentioned above may also be induced by osteoclasts from osteoclast progenitor cells, and therefore are prone to cause bone loss. Therefore, the proinflammatory cytokine IL-6 produced by immune cells may play a key role in this potential mechanism (Aspalli et al., 2014). Generally, in normal bone homeostasis, the production of IL-6 stimulates the activity of osteoclasts, leading to changes in bone resorption. At the same time, some of its effects on BMD can also be adjusted by IL-6. On the other hand, genetic factors that make individuals prone to systemic bone loss may also make them more prone to periodontal damage. Generally, the factors that down-regulate IL-6 gene expression is mainly estrogen and testosterone. Therefore, postmenopausal women have elevated IL-6 levels, even without infection, trauma, or stress. In addition, IL-6 gene expression also changes with individual age. Therefore, both osteoporosis and chronic periodontal disease may be related to age (Ershler & Keller, 2000).

Two major non-modifiable factors causing periodontitis and osteoporosis have been found to be age and gender (Kuo, Polson, & Kang, 2008). Many scientific studies have shown a similar conclusion when women are the object of study, especially postmenopausal women (Lin et al., 2015; Passos et al., 2013; Penoni et al., 2016). Our study also has found that female with osteoporosis (OR, 2.24; 95% CI, 1.52–3.30) faced a higher risk of developing periodontitis, compared to male (OR, 1.61; 95% CI, 1.04–2.50). However, Shum et al. (2010) report that osteoporosis is associated with severe CAL in elderly Chinese men. Based on the assumption that osteoporosis affects only a specific population, this study included only this group of patients. We found that when participants reached the age of 40, the distinction between men and women widened. The reason is that women experience estrogen

deficiency after menopause. Therefore, the main risk factor for osteoporosis in women is menopause, which is related to reducing estrogen (Lin et al., 2015).

In addition, studies show that estrogen tends to reduce the protective effect of bone absorption and inhibit calcium absorption (Recker, Lappe, Davies, & Heaney, 2004). Therefore, one of the mechanisms is that bone remodeling and inflammation-related estrogen deficiency may link osteoporosis to periodontitis (Wang & McCauley, 2016). Due to changes in hormonal secretion, in general, women begin to experience bone loss early in life and then stabilize. On the other hand, due to hormonal changes and their effects on bone remodeling, bone loss will occur later in life (Inagaki et al., 2005). Although research shows that BMD decreases with age. And because sex hormone levels usually drop sharply in postmenopausal women. Therefore, prevention of osteoporosis and the fractures caused by it in women is usually achieved by increasing the total bone mass. In this study, the male participants may be attributed to the small number of studies included in the sub-meta-analysis. Therefore, control of smoking, excessive drinking, insufficient nutrition, low body weight, insufficient exercise, and various drugs and diseases should be taken to prevent bone density loss at all ages, as these factors can lead to osteoporosis (Kim et al., 2014).

Preventing osteoporosis is the most reasonable way to defeat the disease, and early diagnosis is one of the foundations of modern medicine (Richa et al., 2017). Therefore, it is recommended that routine oral and BMD screening be mandatory for postmenopausal women to detect early bone changes and disease conditions, prevent disease early, and hinder disease progression (Wang & McCauley, 2016). Early detection of these conditions could allow patients to be treated more fully before osteoporosis causes debilitating fractures.

5 | CONCLUSION

In summary, we used a meta-analysis to analyze observational studies and the results showed that osteoporosis is an independent risk factor for periodontitis. This finding of this study may affect the clinical understanding of the etiology of periodontitis in this field and may further enrich the knowledge and means of preventing and controlling osteoporosis. Therefore, this study has great research value in the context of clinical practice focusing on oral health, stratifying patients according to osteoporosis risk, and formulating policies to promote oral health. Finally, although this study considered possible mechanisms, further research is needed to explain the specific association between periodontitis and osteoporosis.

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AUTHOR CONTRIBUTIONS

Shuai Xu: Conceptualization; Data curation; Writing-original draft. **Gang Zhang:** Data curation; Methodology. **Jun feng Guo:** Data curation; Supervision. **Yin hui Tan:** Supervision; Writing-review & editing.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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