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Title Page

Title: Association of periodontal disease with COPD risk and clinical events: a systematic review and meta-analysis

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ABSTRACT

Objectives Studies have suggested contradictory results of the relationship between chronic obstructive pulmonary disease (COPD) and periodontal disease (PD). The aim of this study was to determine the association of PD with COPD risk and its clinical events.

Methods We systematically searched PubMed, EMBASE and CENTRAL from inception to 10 August 2022, to identify relevant articles. Odds ratio (OR) with 95% confident interval (CI) was pooled in a random-effect model with inverse variance method. We also performed stratified and subgroup analyses.

Results In total, 22 observational studies with 51704 participants were included in the meta-analysis. Pooled analysis of 18 studies suggested that PD was weakly associated with risk of COPD (OR 1.20; 95% CI 1.09 to 1.32; I^2=79%) after adjusting for smoking status. In stratified and subgroup analyses, with more strict adjustment for smoking, PD no longer related to COPD risk, when adjusting for smoking intensity (OR 1.14; 95% CI 0.86 to 1.51), smokers only (OR 1.46; 95% CI 0.92 to 2.31) and for never smokers (OR 0.93; 95% CI 0.72 to 1.21). Pooled analysis of 4 studies indicated that PD did not

increase risk of COPD-related exacerbation or mortality (OR 1.18; 95% CI 0.71 to 1.97; I^2=36%).

Conclusions PD confers no risk for COPD and COPD-related events, with adjustment for confounding by smoking. Further investigations focusing on never smokers are warranted.

STRENGTHS AND LIMITATIONS OF THIS STUDY

1. This is the largest systematic review and meta-analysis on association between chronic obstructive pulmonary disease (COPD) and periodontal disease (PD) collecting data over 20 years.
2. This study firstly synthesized research evidence regarding correlation of PD with COPD-related exacerbation or mortality.
3. Compared with previous reports, the present study was conducted with more strict adjustment for confounding by smoking, which was the most important confounder in the COPD-PD relationship.
4. Our study provided limited evidence on the outcome of COPD-related events because of limited data.
5. Clinical heterogeneity and publication bias compromised the evidence strength of the study, although subgroup and stratified analyses were performed.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death, resulting in enormous economic burden.[1] Commonly, COPD coexists with other disorders, also called comorbidities, which play key roles in COPD progression and prognosis.[2 3] Understanding COPD-comorbidities relationship has been a momentous prerequisite for optimizing disease prevention and management strategies.[2 3]

Given ageing and widespread use of inhaled corticosteroids in COPD, periodontal disease (PD) has been a common comorbidity of COPD.[4] It is a chronic inflammatory condition of tissues surrounding and supporting the teeth, including gingiva, bone and ligament,[5] with the prevalence estimates over 10% around the world and especially prevalent in elderly individuals.[6] To date, diagnosis and assessment of PD are mostly based on periodontal measurements including clinical attachment level (CAL), probing pocket depth (PPD) and alveolar bone loss (ABL).[5] They are primary clinical manifestations of PD, reflecting the extent of periodontal tissue destruction.[5]

Based on the nature of inflammation,[5 7] mounting evidence has shed light on the association between PD and development of COPD.[8 9] Currently three points are proposed. First, they share the same risk factors, such as age, gender, smoking and socioeconomic status.[2 10] Second, they have similar pathogenetic mechanisms. Both diseases are characterized by host susceptibility to environmental factors, immune overreaction, oxidative stress and production of pro-inflammatory cytokines.[7 8] Most importantly, neutrophilic inflammation plays a key role in both diseases.[8 11] Third, oral bacteria released from the dental plaque in PD could trigger progression and acute

exacerbation (AE) of COPD.[12 13]

Meanwhile, epidemiological evidence has indicated that PD increased risk of COPD[11 14 15] and COPD-related events.[13 16] Scannapieco *et al* revealed a 4.5-fold increased risk of developing COPD in patients with PD, compared to those without.[14] A dose-response relationship was further implied between PD severity and lung function.[15] Among patients with both diseases, COPD-related AE and mortality also significantly linked with periodontal status.[13 16] Periodontal therapy, such as scaling and root planing treatment, could ameliorate lung function and decrease frequency of AE in COPD with chronic periodontitis.[17 18] However, there were some other studies revealing opposite results, resulting in a long-standing controversy.[19-21] It is worth noting that, parameters used to determine PD were apparently variable across studies, which also failed to adequately control confounders, especially smoking, the most important confounder in the COPD-PD relationship. Therefore, to provide the latest and most convincing evidence, we systematically reviewed current available literature to investigate association of PD with risk of COPD and COPD-related events. Subgroup and stratified analyses were also conducted to further decrease confounding effect of smoking.

Methods

This systematic review and meta-analysis was conducted and reported in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.[22]

Search strategy and selection criteria

We searched PubMed, EMBASE and CENTRAL for records evaluating association between COPD and PD, from inception to 10 August 2022. The search strategy was described in online supplemental table S1. The language was restricted to English, for the purpose of rapid review.[23] Studies meeting the following criteria were included: (1) adult participants; (2) original studies with randomized controlled trial (RCT), cohort, case-control or cross-sectional study designs; (3) presenting clear diagnostic or assessment criteria for COPD and PD; (4) evaluating association between PD and risk of COPD, or risk of COPD-related AE and mortality, with statistical adjustment for smoking.

According to the inclusion criteria, two independent investigators (MY and XL) performed systematical search, screened titles and abstracts of all retrieved studies to exclude duplicate or irrelevant records. For articles requiring further assessment, full-text reviews were carried out and references of retrieved articles and relevant reviews were also manually checked to identify additional eligible studies. Disagreements were resolved by discussion between the two reviewers or with the help of the third investigator (RP).

Data extraction and quality assessment

Two investigators (MY and RP) independently extracted data from selected studies

using a standardized Excel (Microsoft Corporation) file. The following information was extracted: author, year of publication, country, study design, number of subjects (COPD and non-COPD), demographic characteristics of participants, periodontal variables applied to assess PD, diagnostic criteria for COPD, definition of COPD-related AE and mortality, adjusted odds ratio (OR), relative risk (RR) or hazard ratio (HR) for risk of COPD, AE and mortality in relation to PD, as well as adjustment for confounders. The primary outcome was risk of COPD. Secondary outcome was risk of COPD-related adverse events, including AE and mortality. Quality of studies was independently evaluated using the Newcastle-Ottawa Scale[24] by two investigators (MY and XL). A score of ≥6 was considered a low risk while < 6 a high risk of bias. Both case-control and cohort studies had a maximum score of 9. Cross-sectional study was regarded as case-control study when performing quality assessment. Discrepancies regarding data extraction and quality assessment were resolved through discussion and consensus.

Data analysis

The final pooled estimate was expressed as OR with 95% confident interval (CI). Considering CAL, ABL and PPD have been regarded as the primary variables for assessing PD,[25 26] where more than one adjusted estimate was shown in the paper, we preferentially used the estimate regarding CAL, ABL or PPD, or the estimate being better adjusted for tobacco smoking (never smokers ＞ adjusting for smoking intensity (duration and dose) ＞ adjusting for smoking status), where available. For case-control

and cross-sectional studies, we estimated the OR whereas for cohort studies we estimated the RR or HR. The random-effect model with inverse variance method were applied due to potential heterogeneity resulting from methodological differences. Heterogeneity across studies was identified with the I^2 statistic. I^2 statistic $>50\%$ indicated significant heterogeneity.

To explore heterogeneity, subgroup analyses were conducted based on study design (case-control, cross-sectional and cohort studies), geographical location (Asia, North America, Europe), assessment of PD (CAL, ABL and PPD), definition of COPD (Global Initiative for Chronic Obstructive Lung Diseases, GOLD and non-GOLD criteria) and adjustment for smoking intensity, defined as dose and duration of smoking. To better control the confounding effect of smoking, stratified analyses were also performed in smokers and never smokers respectively.

To test the robustness of study findings, we performed sensitivity analysis on studies with relatively large sample size ($\geqslant 500$ participants), which tended to be more representative of the general population and with smaller bias in the overall estimates in meta-analyses.[27] Additionally, influence of a single study on the overall pooled estimate was tested by omitting one study in each turn. Publication bias was visually assessed using a funnel plot and quantitatively evaluated by the Egger's tests. $p<0.05$ was considered statistically significant. Evaluation of publication bias, subgroup and stratified analyses were performed only for the risk of COPD due to small number of studies for the other outcome. All statistical analyses were performed using Stata version

16 (StataCorp) and Review manager version 5.4 (Cochrane Collaboration).

Patient and public involvement

No patient involved.

RESULTS

Study selection and characteristics

A total of 30165 records were identified from the initial database search. 13662 records were removed for duplicates, and 16227 records were excluded after titles and abstracts screening because of irrelevant content and animal studies. The remaining 276 full-text articles were identified for eligibility, of which 252 were excluded for reasons including duplicates (6 studies), reviews (183 studies), insufficient information (9 studies) and ineligible designs and outcomes (54 studies). Finally, 24 studies[14-16 19-21 28-45] were included in the review. The selection process is shown in **figure 1**.

The characteristics of included 24 studies were shown in online supplemental table S2. The number of participants was 53049 and COPD was more than 21.7%. The mean age of patients with COPD was between 41.4 and 83.1 years while the control subjects was between 42.2 and 80.3 years. These studies were published between 1998 and 2021. The sample size ranged from 117 to 13792. Among included studies, 11 were case-control studies[15 19 28 29 32-34 37 39 42 44] and 10 were cross-sectional studies,[14 20 30 31 35 36 40 41 43 45] only 3 with a cohort study design.[16 21 38] Additionally, 13 studies were conducted in

Asia,[15 16 19 28 33 35 36 38-40 42-44] while 6 in the North America,[14 20 21 28-30] 4 in Europe[31 34 37 41] and one in Africa.[45]

All included articles performed multivariable analyses, in which risk of COPD, or risk of COPD-related events (AE or mortality), was identified as the dependent variable and PD as the independent variable. Control for smoking included stratification (smokers and never smokers) or covariance adjustment in multivariable models (the degree of control: never smokers ＞ adjusting for smoking intensity (duration and dose) ＞ adjusting for smoking status).

The adjustment for confounders of included studies was detailedly presented in online supplemental table S3. 16 articles reported the adjusted ORs and 4 reported adjusted RRs, 2 reporting HRs. One study provided the F value of the one-way analysis of variance for regression analysis[32] while the other one only provided relevant exponential of coefficient for constant, called as Exp (B).[39] Definition of COPD comprised the GOLD criteria, FEV1 ＜65% of predicted volume, having a history of chronic bronchitis and / or emphysema, self-reported and others. Periodontal parameters used for PD assessment were CAL, ABL, PPD, gingival bleeding (GB), bleeding index (BI), plaque index (PLI) and oral health index (OHI).

Assessment of bias

Based on the Newcastle-Ottawa Scale, quality assessment for the 24 studies is shown in online supplemental table S4. Among them, 20 studies[15 19-21 28-30 32-44] were rated as high

quality with a total score of ⩾6 whereas 4 studies[14 16 31 45] as a score of <6, indicating a high risk of bias. The main reasons for lower scores were selection bias (representativeness of sample population), especially for control groups and comparability of cases and control subjects.

Primary outcome

In 20 studies investigating correlation between PD and risk of COPD, only 6[15 19 20 29 33 36] conducted stratified analyses regarding smoking status, which unanimously suggested PD was not associated with risk of COPD in never smokers. In the remaining 14 studies with relatively inadequate adjustment for smoking, 13 studies[14 28 30-32 34 35 37 38 40-43] revealed PD was significantly correlated with COPD risk in smokers and never smokers combined, the OR value ranging from 1.02 to 10.00. Furthermore, 18 studies[14 15 19 20 28-31 33-38 40-43] providing adjusted OR or RR were included in the quantitative analysis, which demonstrated that after adjusting for smoking status, PD increased risk of COPD, but only by a ratio of 1.20 (95% CI 1.09 to 1.32; p=0.0002; I^2=79%) (**figure 2**). Further exclusion of any single study did not materially alter the overall pooled OR, with a range from 1.17 (95% CI 1.06-1.28) to 1.28 (95% CI 1.12-1.46). Sensitivity analysis limited to studies with larger sample size (⩾500)[15 19 20 28-30 35-38 40 41 43] revealed similar results (OR 1.24; 95% CI 1.08 to 1.43; p=0.003; I^2=82%) (online supplemental figure S1). However, significant publication bias was noted by visual inspections of the funnel plot (online supplemental figure S2) and the Egger' s test for small study effects (bias

coefficient 1.49; 95% CI 0.44 to 2.55; p=0.008).

Subgroup analyses indicated that assessment of PD (p=0.02), study design (p=0.05) and diagnosis of COPD (p=0.05) were the potential main causes of heterogeneity (**table 1**). Moreover, there were several findings in subgroup analyses. First, comparing to studies adjusting for smoking status, pooled analyses on those controlling for smoking intensity did not show apparent correlation on PD and COPD risk (OR 1.14; 95% CI 0.86 to 1.51; p=0.38; 10 studies[15 19 20 29-31 33 34 36 38]), similar to those applying a GOLD criterion (OR 1.10; 95% CI 1.00 to 1.22; p=0.06; 12 studies[15 19 20 31 33-36 38 41-43]). Second, with regard to assessment of PD (CAL, ABL and PPD), only those using the parameter of ABL presented results with statistical significance (OR 1.98; 95% CI 1.32 to 2.97; p=0.001; 6 studies[15 28 29 31 33 41]). Third, in the three locations (Asia, North America and Europe), obvious impact of PD on COPD risk was only found in studies of Europe (OR 2.05; 95% CI 1.07 to 3.95; p=0.03; 4 studies[31 34 37 41]).

Table 1 Subgroup analyses regarding risk of COPD

Subgroups	No. Articles	No. Participants /Cases	OR value (95% CI)	P value	I^2, %
Adjusted for smoking intensity[a]					
Yes	10	27,246 / 3,556	1.14 (0.86-1.51)	0.38	67
No	8	22,158 / 5,478	1.29 (1.13-1.48)	**0.0002**	75
Assessment of PD					

CAL	8	24,600 / 3,058	1.04 (0.96-1.14)	0.33	75
ABL	6	4,629 / 1,530	1.98 (1.32-2.97)	**0.001**	56
PPD	8	19,189 / 3,519	1.16 (0.89-1.51)	0.27	63
Geographical location					
Asia	9	18,831 / 3,606	1.07 (0.99-1.17)	0.08	65
North America	5	24,033 / 2,420	1.37 (0.93-2.01)	0.11	63
Europe	4	6,540 / 3,008	2.05 (1.07-3.95)	**0.03**	71
Assessment of COPD					
GOLD	12	19,879 / 3,774	1.10 (1.00-1.22)	0.06	71
Non-GOLD	6	29,525 / 5,260	1.35 (1.14-1.61)	**0.0007**	46
Study design					
Case-control	8	9,911 / 4,472	1.12 (1.01-1.24)	**0.03**	86
Cross-sectional	9	38,593 / 4,540	1.34 (1.08-1.66)	**0.007**	45
Cohort	1	878 / 22	3.51 (1.15-10.74)	**0.03**	-

[a]Duration and dose of smoking.

ABL, alveolar bone loss; CAL, clinical attachment level; CI, confident interval; GOLD, Global Initiative for Chronic Obstructive Lung Disease; OR, odds ratio; PD, periodontal disease; PPD, probing pocket depth.

Bold: subgroups with positive results.

Stratified analyses regarding smoking status revealed that PD did not increase the risk of COPD whether in smokers (OR 1.46; 95% CI 0.92 to 2.31; p=0.11; 7 studies[15 19 20 29 31 33 36]) or never smokers (OR 0.93; 95% CI 0.72 to 1.21; p=0.58; 6 studies[15 19 20 29 33 36]) (**figure 3**).

Secondary outcome

Only four studies evaluated risk of COPD-related AE or mortality, with adjusting for smoking.[16 21 44 45] Definition of AE was acute deterioration in clinical presentations according to the recommendation in GOLD guideline.[21 44 45] These studies applied more than one parameter to assess PD, in which the parameters of CAL, ABL and PPD unanimously showed no association with risk of AE or mortality. Pooled analysis showed that after adjusting for smoking status, PD was also not linked with COPD-related AE or mortality (OR 1.18; 95% CI 0.71 to 1.97; p=0.52; I^2=36%) (**figure 4**).

DISCUSSION

This systematic review and meta-analysis identified 24 observational studies to investigate association of PD on risk of COPD and COPD-related events. The results indicated after adjusting for smoking status, a 1.20-fold increase in the odds of COPD was observed in patients with PD, but with more strict control for smoking intensity, PD no longer correlated with COPD risk, which was verified in the subgroup and stratified analyses. Meanwhile, PD was also not increase risk of COPD-related events (AE or mortality) when controlling for smoking.

To the best of our knowledge, this is the first and largest meta-analysis investigating association of PD with COPD risk and its clinical events, with adequately controlling the confounding effect of smoking. Also, in quantitative analysis, nearly all included

articles were adjusted for age, except the study by Scannapieco *et al*.[14] In prior evidence, PD was suggested significantly increasing risk of COPD and COPD-related events. However, the majority of studies has obvious flaws, such as only applying univariate analyses, not controlling confounding effect of smoking, and using parameters with relatively low specificity to determine PD.[13 25 45] To define periodontal disease as accurately as possible, we preferentially extracted results concerning the parameter of CAL, ABL or PPD rather than PLI, OHI or remaining teeth. CAL, ABL and PPD are clinical measurements reflecting the destruction of periodontal tissues, also the basis for PD diagnosis.[25] Meanwhile, compared with previous meta-analyses, we enrolled more studies, applied more rigorous screening criteria and most importantly, revealed opposite results. In meta-analyses with incomplete adjustment for smoking, OR value for COPD risk in relation to PD ranged from 1.64 to 2.08.[46-48] However, our findings were similar to studies conducted in never smokers,[15 19 20 29 33 36] showing PD conferred no risk for COPD. Additionally, pooled results regarding parameters of CAL, ABL and PPD revealed that PD also did not increase risk of COPD-related AE or mortality. These demonstrate that previously reported correlation between PD and COPD may be results of flawed study design, confounding by smoking and even other factors, such as age and living condition.

As a momentous inducer in inflammation-related pathological processes, tobacco is known to correlate with a variety of systemic disorders.[49] It is also one of the foremost risk factors for both PD and COPD.[5 10] From the epidemiological perspective, tobacco

smoking is a confounder with spuriously inflated effect on the relationship between PD and systemic diseases.[49] To investigate the true association between PD and COPD, it is of great importance to rigorously control the confounding effect of smoking, which means initiating research in never smokers. However, the majority of former studies failed to do that. After a wide search, only six studies focusing on never smokers were found, which unanimously indicated PD was not related with COPD risk. We also observed decreased magnitude of the association as the control for smoking elevated in the quantitative analysis. Therefore, it could be too early to make a certain conclusion on the COPD-PD relationship. Although interventional studies revealed that periodontal treatment reduced the risk of AE, a number of problems existed, including small sample size, limited study quality and unclear history of smoking or medication during the follow-up.[17 18] For example, compared with control subjects, patients in treatment groups may reduce smoking intentionally, which could spuriously enhance the positive effect of periodontal treatment. Consequently, future researches need to take these problems into account.

It is worth noting that, another possibility that smoking acts as an effect modifier in the COPD-PD relationship should not be ignored. Two observational studies performed stratified analyses concerning smoking status and found strong correlation of PD with COPD risk was restricted to smokers.[15 20] However, this was not revealed in the current study, thus more investigations in smokers are required.

Besides, current evidence has demonstrated several issues to be addressed in future

relevant study, comprising inconsistent diagnostic criteria of COPD and PD, the lack of prospective study design and differing adjustments for covariates. These contribute to substantial heterogeneity among studies.[46] [47] The present study indicated the heterogeneity was partly explained by study design, diagnostic criteria of COPD and periodontal indexes used to assess PD. Significant association concerning PD and risk of COPD was only identified in subgroups lacking well designs, applying non-GOLD criteria or utilizing ABL as the measure of PD. For one thing, this demonstrated that, as sources of bias, observational study design and nonstandard diagnostic method for COPD could bring apparent errors, confusing the true relationship of PD with COPD. For another, given undetermined diagnostic criteria for PD, discrepancies between ABL and other indexes cannot fully support the COPD-PD association. Notably, as a radiographic measure, although ABL has been widely considered to reflect cumulative effects of periodontal attachment loss over time by chronic inflammation,[28] it does not only exist in PD. Non-periodontal diseases such as liver disorders, cancer and osteoporosis[50] could also result in ABL. As mentioned previously,[28] the observed correlation between ABL and COPD risk may relate to those non-periodontal diseases. Therefore, this remains to be explored further.

Limitations

Several potential limitations should be taken into consideration when interpreting the present results. First, all included studies are observational, which are highly subject to

selection bias and confounding by indication. Second, substantial heterogeneity was identified in current study, though we conducted subgroup and stratified analyses to partly explain and reduce it. As stated above, several problems leading to heterogeneity need to be addressed in future researches. Third, the number of studies on risk of COPD-related events was limited, thus the result needs to be carefully understood. Limited number of studies in subgroup and stratified analyses suggested more relevant studies with larger sample size are required. Fourth, although confounding effects of age and smoking were controlled by stratified analysis and statistical adjustment, other potential confounders such as gender, living condition and socioeconomic status[10] could also reduce reliability of the results. Fifth, obvious publication bias was noted in relevant meta-analyses,[46 47] including the present study. For the purpose of rapid review,[23] we only included articles in English. There could exist non-English publications and unpublished evidence, despite we searched English-language studies as much as possible. Finally, although smoking status and intensity were considered in subgroup analysis, information regarding tobacco content and chemical composition were not collected. This information is difficult to obtain, especially from self-reported smoking, leaving a residual smoking-related bias. Consequently, it is advisable to explore relationship between COPD and PD in never smokers.

CONCLUSION

In summary, this systematic review and meta-analysis suggested that PD was not

associated with risk of COPD and COPD-related events. Previously reported relationship between COPD and PD may be results of flawed study design and confounding by smoking. However, future well-designed studies are required to validate the present findings.

Abbreviations

ABL: Alveolar bone loss; AE: Acute exacerbation; BI: Bleeding index; CAL: Clinical attachment level; CI: Confident interval; COPD: Chronic obstructive pulmonary disease; GB: Gingival bleeding; GOLD: Global Initiative for Chronic Obstructive Lung Diseases; HR: Hazard ratio; OHI: Oral health index; OR: Odds ratio; PD: Periodontal disease; PLI: Plaque index; PPD: Probing pocket depth; RR: Relative risk.

Contributors LC and LL designed the study. MY and XL screened and selected relevant studies. MY, RP and XL rated the study quality and extracted the data. MY, RP, XL and JP analyzed the data. All authors interpreted the data, and MY, RP, XL, JP drafted the paper. LC and LL critically revised the paper. All authors acknowledged and agreed with the format and content of the paper before submission for publication. LC and LL are the guarantors and responsible for the overall contents of this study.

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Patient consent for publication Not applicable.

Ethics approval Not applicable.

Data availability statement The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Figure legends

Figure 1 PRISMA flow diagram of study selection.

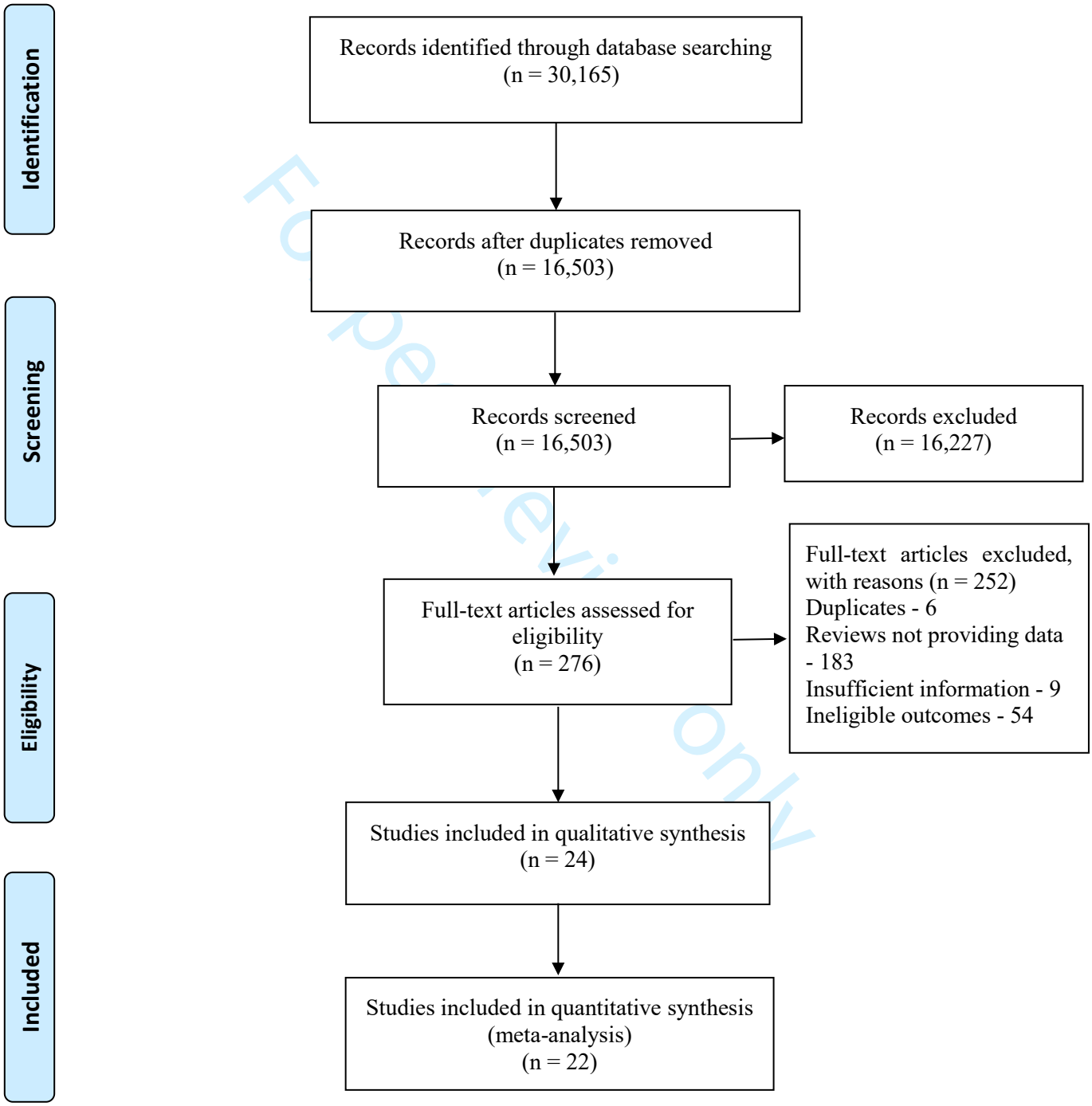
Figure 2 Forest plot of the risk of COPD by periodontal disease, subgroup analysis based

on adjusted by smoking status and intensity versus by smoking status only. Values more than one indicate a higher risk in patients with periodontal disease.

Figure 3 Forest plot of the risk of COPD by periodontal disease. **A** in smokers and **B** in never smokers. Values more than one indicate a higher risk in patients with periodontal disease.

Figure 4 Forest plot of the risk of COPD-related events by periodontal disease. Values more than one indicate a higher risk in patients with periodontal disease.

PRISMA 2009 Flow Diagram



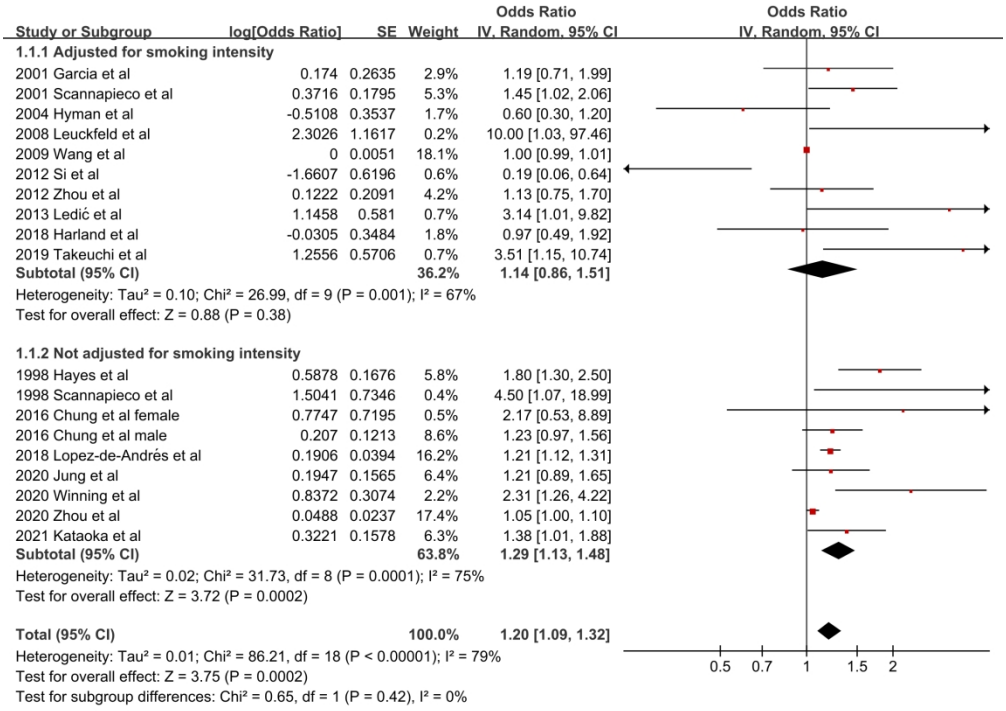


Figure 2 Forest plot of the risk of COPD by periodontal disease, subgroup analysis based on adjusted by smoking status and intensity versus by smoking status only. Values more than one indicate a higher risk in patients with periodontal disease.

536x384mm (118 x 118 DPI)

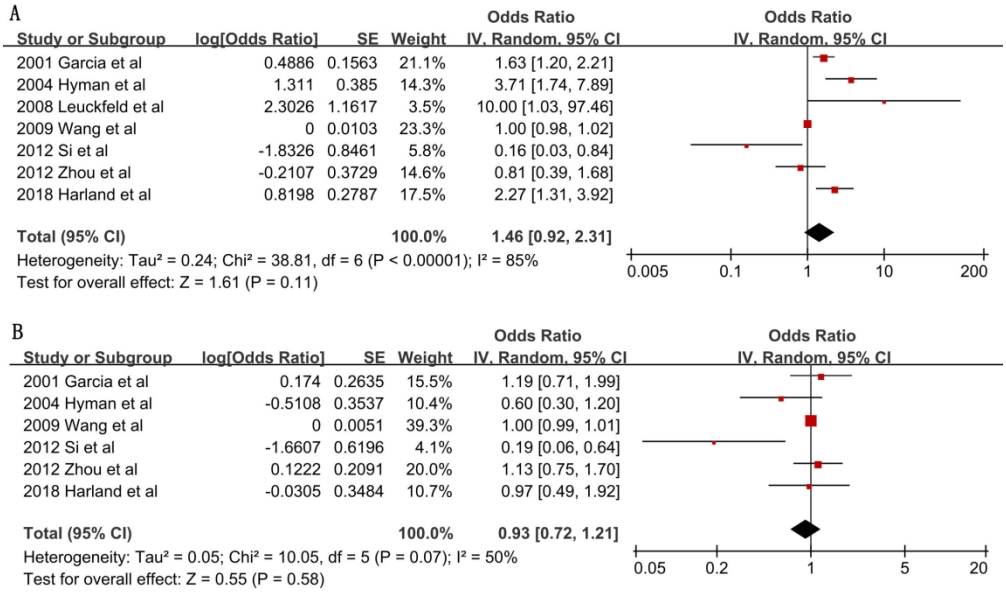


Figure 3 Forest plot of the risk of COPD by periodontal disease. A in smokers and B in never smokers. Values more than one indicate a higher risk in patients with periodontal disease.

192x118mm (300 x 300 DPI)

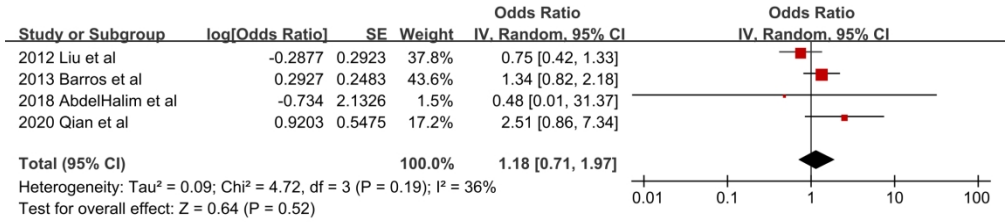


Figure 4 Forest plot of the risk of COPD-related events by periodontal disease. Values more than one indicate a higher risk in patients with periodontal disease.

497x118mm (118 x 118 DPI)

PRISMA 2009 Checklist

Section/topic	Item No	Checklist item	Reported on Page Number/Line Number	Reported on Section/Paragraph
TITLE				
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1 / Line 2	Title page
ABSTRACT				
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2 / Line 27-46	Abstract
INTRODUCTION				
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 3-5 / Line 63-96	Introduction / Paragraph 1-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 5 / Line 96-99	Introduction / Paragraph 4
METHODS				
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Page 5 / Line 102-104	Methods / Paragraph 2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 6 / Line 111-115	Methods / Paragraph 2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 5 / Line 107,108	Methods / Paragraph 2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 5,6 / Line 108,109,119,120	Methods / Paragraph 2 Supplemental table S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 6 / Line 116-122	Methods / Paragraph 3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 6,7 / Line 125,126,137,138	Methods / Paragraph 4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 6 / Line 126-133	Methods / Paragraph 4

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 7 / Line 133-137	Methods / Paragraph 4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 7 / Line 141	Methods / Paragraph 5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 7 / Line 148-151	Methods / Paragraph 5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 8 / Line 162-164	Methods / Paragraph 7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 7,8 / Line 152-162	Methods / Paragraph 6,7
RESULTS				
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 8,9 / Line 174-181	Results / Paragraph 1 Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 9,10 / Line 182-205	Results / Paragraph 2-4 Table S2 and S3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 10 / Line 208-213	Results / Paragraph 5 Table S4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 10,11 / Line 216-221	Results / Paragraph 6 Figure 2 and 4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 11 / Line 221-224 Page 13 / Line 262-264	Results / Paragraph 6,9; Figure 2 and 4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 11 / Line 224-226, 229-231	Results / Paragraph 6 Figure S2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page 11-13 / Line 226-228, 232-243, 252-255	Results / Paragraph 6,7 Table 1, Figure 3 and S1
DISCUSSION				
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 13-17 / Line 267-335	Discussion / Paragraph 1-5
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 17,18 / Line 338-357	Discussion / Paragraph 6
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 18 / Line 360-364	Conclusion / Paragraph 1

FUNDING				
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 19 / Line 380,381	Funding

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Please leave this space alone as it will be supplemented by the editorial office when needed.

Table S1 Search strategy

Search term
1. (Oral health) OR (periodontal disease) OR (periodontal health) OR (periodontitis) OR (clinical attachment level) OR (alveolar bone loss) OR (probing depth)
2. (Respiratory disease) OR (chronic obstructive pulmonary disease) OR (pulmonary function) OR (airflow limitation)
3. 1 AND 2

Table S2 Characteristics of included studies

Year / Study	Design	Location	No. COPD / Control subjects	Age (COPD / Control subjects)	Assessment of PD	Assessment of COPD
1998 Hayes *et al*[1]	Case-control	United States	261/857	45.1±9.7/42.2±9.1	ABL	FEV1
1998 Scannapieco *et al*[2]	Cross-sectional	United States	77/309	NA	OHI	Self-reported
2001 Garcia *et al*[3]	Case-control	United States	279/833	NA	ABL, PPD	FEV1
2001 Scannapieco *et al*[4]	Cross-sectional	United States	810/12,982	51.2±17.9/43.9±17.7	CAL, GB	Self-reported
2004 Hyman *et al*[5]	Cross-sectional	United States	993/6,632	62.3±14.1/47.4±14.2	CAL	GOLD
2008 Leuckfeld *et al*[6]	Cross-sectional	Norway	130/50	54.9±4.9/47.0±9.8	ABL	GOLD
2009 Deo *et al*[7]	Case-control	India	150/50	41.4±7.5/43.6±5.5	CAL, GB	FEV1 / FVC
2009 Wang *et al*[8]	Case-control	China	306/328	63.9±9.8/63.3±9.0	CAL, PLI	GOLD
2012 Liu *et al*[9]	Case-control	China	183/209*	64.3±10.1/63.6±9.7*	CAL, PPD, BI	GOLD
2012 Si *et al*[10]	Case-control	China	581/438	63.9±9.4/62.8±9.5	CAL, ABL, PPD, PLI, BI	GOLD
2012 Zhou *et al*[11]	Case-control	China	193/181	63.6±10.3/62.1±9.1	CAL, ABL, PPD, PLI, BI	GOLD
2013 Barros *et al*[12]	Cohort	United States	399/1,236[§]	63.9±5.7/66.0±5.1[#]	CAL, PPD	GOLD
2013 Ledić *et al*[13]	Case-control	Croatia	93/43	65.8±9.7/62.1±11.9	CAL	GOLD
2016 Chung *et al*[14]	Cross-sectional	Korea	697/5,181	64.3±0.2/54.6±0.1	PPD, GB	GOLD
2018 AbdelHalim *et al*[15]	Cross-sectional	Egypt	134/116*	56.8±10.4/55.3±9.1*	CAL, PPD, BI, PLI, OHI	GOLD
2018 Harland *et al*[16]	Cross-sectional	Japan	149/1,325	61.3±9.1/54.5±8.7	PPD	GOLD

2018 Lopez-de-Andrés *et al*[17]	Case-control	Spain	2,699/2,699	63±14/61±14	Self-reported	Self-reported
2019 Bomble *et al*[18]	Case-control	India	39/78	NA	CAL, OHI, PPD	GOLD
2019 Takeuchi *et al*[19]	Cohort	Japan	22/878	NA	CAL, PPD	GOLD
2020 Jung *et al*[20]	Cross-sectional	Korea	1,134/6,585	62.6±0.4/53.6±0.2	PPD	FEV1 / FVC
2020 Qian *et al*[21]	Cohort	China	23‡/NA	83.1±4.8/80.3±3.7	ABL	NR
2020 Winning *et al*[22]	Cross-sectional	Sweden	86/740	NA	ABL	GOLD
2020 Zhou *et al*[23]	Case-control	China	60/60	63.1±10.1/60.0±9.4	CAL, PLI	GOLD
2021 Kataoka *et al*[24]	Cross-sectional	Japan	464/249	54.1±9.4/NA	PPD	GOLD

Continuous data are presented as mean ± standard deviation (SD) unless otherwise indicated.

*No. COPD subjects with frequent exacerbation (⩾2 exacerbations in the last year)/Infrequent exacerbation (< 2 exacerbations in the last year).

§No. COPD subjects with events (hospitalization for exacerbation or COPD-related death) in the 5-year follow-up visit/COPD subjects without events in the 5-year follow-up visit.

‡No. COPD-related mortality in a follow-up visit more than 5 years.

ABL, alveolar bone loss; BI, bleeding index; CAL, clinical attachment level; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; GB, gingival bleeding; GOLD, Global Initiative for Chronic Obstructive Lung Disease; NA, not available; OHI, oral health index; PD, periodontal disease; PLI, plaque index; PPD, probing pocket depth.

Table S3 Adjustment for confounders of included studies

Study Author	Covariates in logistic regression multivariable model
Hayes *et al*[1]	Age, smoking, education, height
Scannapieco *et al*[2]	Smoking
Garcia *et al*[3]	Age, height, alcohol, education **(with stratified analysis on smoking)**
Leuckfeld *et al*[6]	Age, female gender, **pack years of smoking**
Deo *et al*[7]	Age, gender and smoking
Liu *et al*[9]	Age, gender, BMI and smoking
Wang *et al*[8]	Age, gender, BMI **(with stratified analysis on smoking)**
Si *et al*[10]	Age, gender, occupation, educational level **(with stratified analysis on smoking)**
Zhou *et al*[11]	Age, gender, smoking, BMI, season **(with stratified analysis on smoking)**
Ledić *et al*[13]	Age, gender, **pack years of smoking**, BMI
Lopez-de-Andrés *et al*[17]	Age, gender, smoking, educational level, DM, obesity
Bomble *et al*[18]	Smoking
Zhou *et al*[23]	Age, gender, smoking, BMI
Kataoka *et al*[24]	Age, smoking
Qian *et al*[21]	Age, sex, education levels, BMI, smoking, drinking, hypertension, DM
Barros *et al*[12]	Age, gender, Race, BMI, education, **pack years of smoking**, hypertension
Scannapieco *et al*[4]	Age, gender, **pack years of smoking**, Race, education, income, dental visits, alcohol, DM
Hyman *et al*[5]	Age, gender, Race, history of hypertension and heart attack, dental visit within 1 year, BMI, family income **(with stratified analysis on smoking)**
Chung *et al*[14]	Age, smoking, family income, education, alcohol, exercise, BMI, tooth brushing frequency, DM, number of natural teeth
Harland *et al*[16]	Age, number of present teeth, BMI, alcohol consumption, occupation,

	hypertension, DM **(with stratified analysis on smoking)**
Takeuchi *et al*[19]	Age, gender, **pack years of smoking**, occupation, DM, BMI, physical activity, alcohol intake, number of present teeth
Jung *et al*[20]	Age, gender, smoking, educational level, household income, alcohol consumption, periodontal status, number of missing teeth, oral health factors
Winning *et al*[22]	Age, gender, smoking, height, BMI, exercise, DM, hypertension, MI, education level, living condition
AbdelHalim *et al*[15]	Age, BMI, low-level of education, **pack years of smoking**, MRC, CAT, hospitalizations, COPD category (C-D), FVC (% predicted), FEV1 (% predicted), FEV1 / FVC (% predicted), MMEF (% predicted), PEF (% predicted), CRP

BMI, body mass index; CAT, chronic obstructive pulmonary disease assessment test; CRP, C-reactive protein; DM, diabetes mellitus; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; MI, myocardial infarction; MMEF, maximum mid-expiratory flow; MRC, Medical Research Council; PEF, peak expiratory flow.
Bold: the covariate of smoking intensity (duration and dose) or stratified analyses on smoking status.

Table S4 Quality assessment based on the Newcastle-Ottawa Scale

(A) Cohort study

Study Author	Selection				Comparability	Outcome			Total score
	Exposed cohort	Nonexposed cohort	Ascertainment of exposure	Outcome of interest		Assessment of outcome	Length of follow-up	Adequacy of follow-up	
Barros *et al*[12]	*	*	*	…	…	*	*	*	6
Takeuchi *et al*[19]	*	*	*	*	…	*	*	*	7
Qian *et al*[21]	…	*	*	…	…	*	*	…	4

(B) Case-control / cross-sectional study

Study Author	Selection				Comparability	Outcome			Total score
	Case definition	Representati-veness of the cases	Control selection	Control definition		Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	
Hayes *et al*[1]	*	…	*	*	*	*	*	*	7
Scamapieco *et al*[2]	…	*	*	*	…	*	*	…	5
Garcia *et al*[3]	*	…	*	*	*	*	*	*	7
Scamapieco *et al*[4]	…	*	*	*	…	*	*	*	6
Hyman *et al*[5]	*	*	*	*	…	*	*	*	7
Leuckfeld *et al*[6]	*	…	…	*	…	*	*	*	5
Deo *et al*[7]	*	*	…	*	*	*	*	*	7
Wang *et al*[8]	*	*	…	*	*	*	*	*	7
Liu *et al*[9]	*	*	…	*	*	*	*	*	7
Si *et al*[10]	*	*	…	*	*	*	*	*	7
Zhou *et al*[11]	*	*	…	*	*	*	*	*	7
Ledis *et al*[13]	*	*	…	*	*	*	*	*	7
Chung *et al*[14]	*	*	*	*	…	*	*	*	7
AbdelHalim *et al*[15]	*	…	…	*	…	*	*	*	5
Harland *et al*[16]	*	*	…	*	…	*	*	*	6
Lopez-de-Andrés *et al*[17]	…	*	*	*	*	…	*	*	6
Bomble *et al*[18]	*	*	…	*	**	*	*	*	8
Jung *et al*[20]	…	*	*	*	…	*	*	*	6
Winning *et al*[22]	*	*	*	*	…	*	*	*	7

Zhou *et al*[23]	*	*	…	…	**	*	*	*	7
Kataoka *et al*[24]	*	*	*	*	…	*	*	*	7

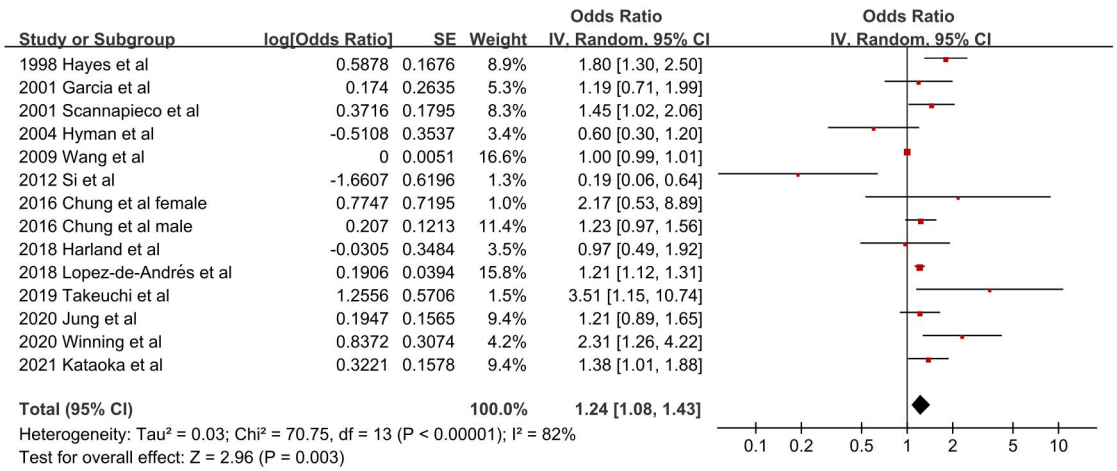


Figure S1 Sensitivity analysis on studies with larger sample size (N ⩾ 500). Values more than one indicate a higher risk of COPD in patients with PD.

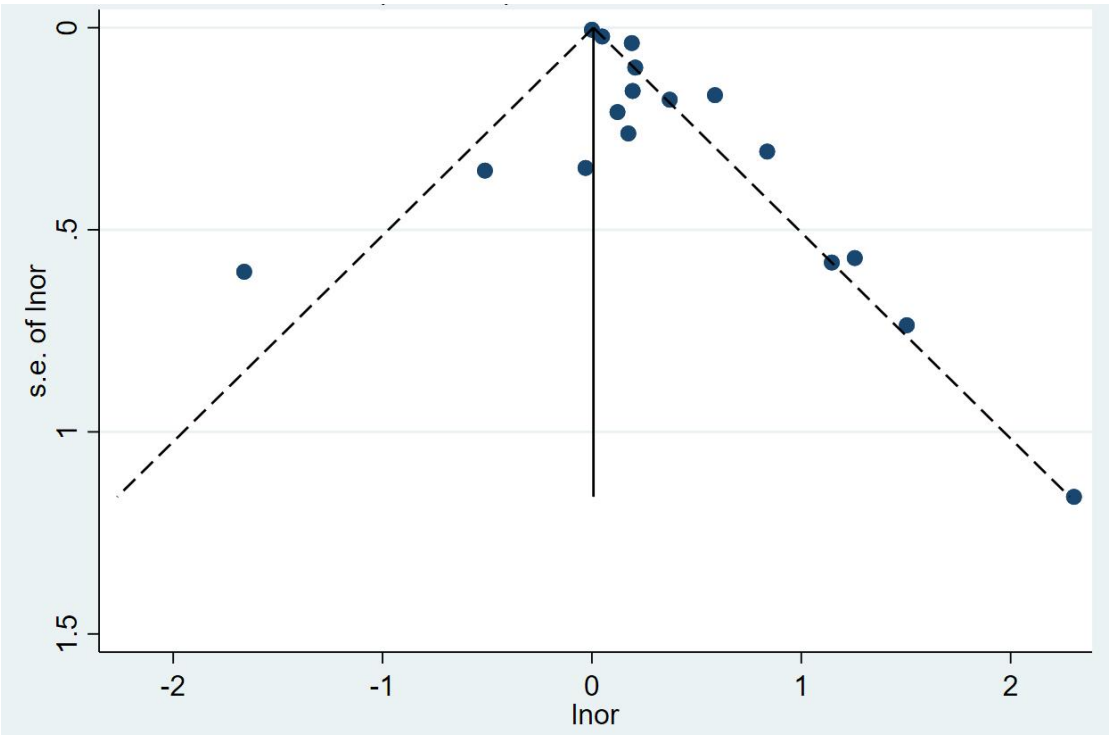


Figure S2 Funnel plot for risk of COPD, with pseudo 95% confidence limits.

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14. Chung JH, Hwang HJ, Kim SH, *et al.* Associations Between Periodontitis and Chronic Obstructive Pulmonary Disease: The 2010 to 2012 Korean National Health and Nutrition Examination Survey. *J Periodontol* 2016;87:864-71.

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The association between chronic obstructive pulmonary disease and periodontal disease: a systematic review and meta-analysis

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Title Page

Title: The association between chronic obstructive pulmonary disease and periodontal disease: a systematic review and meta-analysis

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The association between chronic obstructive pulmonary disease and periodontal disease: a systematic review and meta-analysis

ABSTRACT

Objectives Studies have suggested contradictory results on the relationship between chronic obstructive pulmonary disease (COPD) and periodontal disease (PD). The aim of this study was to determine whether PD increased the risk of COPD and COPD-related clinical events.

Design Systematic review and meta-analysis.

Data sources PubMed, EMBASE and CENTRAL were searched from inception to 22 February 2023.

Eligibility criteria for studies We included trials and observational studies evaluating association of PD with the risk of COPD or COPD-related events (exacerbation and mortality), with statistical adjustment for smoking.

Data extraction and synthesis Two investigators independently extracted data from selected studies using a standardized Excel file. Quality of studies was evaluated using the Newcastle-Ottawa Scale. Odds ratio (OR) with 95% confident interval (CI) was pooled in a random-effect model with inverse variance method.

Results 22 observational studies with 51704 participants were included. Pooled analysis of 18 studies suggested that PD was weakly associated with the risk of COPD (OR 1.20, 95% CI 1.09 to 1.32). However, in stratified and subgroup analyses, with strict adjustment for smoking, PD no longer related to the risk of COPD (adjusting for smoking intensity: OR 1.14, 95% CI 0.86 to 1.51; smokers only: OR 1.46, 95% CI 0.92 to 2.31; never smokers only: OR 0.93, 95% CI 0.72 to 1.21). Moreover, PD did not increase the risk of COPD-related exacerbation or mortality (OR 1.18, 95% CI 0.71 to 1.97) in the pooled result of four studies.

Conclusions This study demonstrates PD confers no risk for COPD and COPD-related events when strictly adjusted by smoking. Large-scale prospective cohort studies with control of potential confounding factors are warranted to validate the present findings.

STRENGTHS AND LIMITATIONS OF THIS STUDY

1. This is the largest systematic review and meta-analysis on association between chronic obstructive pulmonary disease (COPD) and periodontal disease (PD) collecting data over 20 years.
2. This is the first meta-analysis investigating whether PD increases the risk of COPD-related events (exacerbation or mortality).
3. Compared with previous reports, this study was conducted with more strict adjustment for confounding by smoking, which was the most important confounder in the COPD-PD relationship.

4. Our study provided limited evidence on the outcome of COPD-related events because of limited data.
5. Clinical heterogeneity and publication bias compromised the evidence strength of this study, although subgroup and stratified analyses were performed.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death, resulting in enormous economic burden.[1] Commonly, COPD coexists with a variety of disorders, called comorbidities, which play significant roles in the progression and prognosis of COPD.[2 3] Understanding the COPD-comorbidities relationship has been a momentous prerequisite for optimizing disease prevention and management strategies.[2 3]

Given ageing and widespread use of inhaled corticosteroids in COPD, periodontal disease (PD) has been a common comorbidity of COPD.[4] It is a chronic inflammatory condition of tissues surrounding and supporting the teeth, including gingiva, bone and ligament,[5] with the prevalence estimates over 10% around the world and especially prevalent in elderly individuals.[6] To date, diagnosis and assessment of PD are mostly based on periodontal measurements including clinical attachment level (CAL), probing pocket depth (PPD) and alveolar bone loss (ABL).[5] They are primary clinical manifestations of PD, reflecting the extent of periodontal tissue destruction.[5]

Based on the nature of inflammation,[5 7] mounting evidence has shed light on the

association between PD and development of COPD.[8 9] Currently three points are proposed. First, they share the same risk factors, such as age, gender, smoking and socioeconomic status.[2 10] Second, they have similar pathogenetic mechanisms. Both diseases are characterized by host susceptibility to environmental factors, immune overreaction, oxidative stress and production of pro-inflammatory cytokines.[7 8] Most importantly, neutrophilic inflammation plays a key role in both diseases.[8 11] Third, oral bacteria released from the dental plaque in PD could trigger progression and acute exacerbation (AE) of COPD.[12 13]

Meanwhile, epidemiological evidence has indicated that PD increases risk of COPD[11 14 15] and COPD-related events.[13 16] Scannapieco *et al* revealed a 4.5-fold increased risk of COPD in patients with PD, compared with those without.[14] A dose-response relationship was further implied between PD severity and lung function.[15] Among patients with both diseases, COPD-related AE and mortality also significantly linked with periodontal status.[13 16] Periodontal therapy, such as scaling and root planing treatment, may ameliorate lung function and decrease frequency of AE in COPD with chronic periodontitis.[17 18] However, there were some other studies revealing opposite results, resulting in a long-standing controversy.[19-21] It is worth noting that, parameters used to determine PD apparently varied across studies, and these studies also failed to adequately control for confounders, especially smoking, the most important confounder for the COPD-PD relationship. Therefore, to provide the latest and most convincing evidence, we systematically reviewed current available literature to investigate whether

PD increases the risk of COPD. The secondary objective was to evaluate the association between PD and the risk of COPD-related events. Subgroup and stratified analyses were also conducted to adjust for the confounding by smoking.

METHODS

This systematic review and meta-analysis was conducted and reported in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.[22]

Search strategy and selection criteria

We searched PubMed, EMBASE and CENTRAL for records evaluating association between COPD and PD, from inception to 22 February 2023. The search strategy was described in online supplemental table S1. The language was restricted to English, for the purpose of rapid review.[23] Studies meeting the following criteria were included: (1) adult participants (≥18 years); (2) original studies with randomized controlled trial (RCT), cohort, case-control or cross-sectional study designs; (3) presenting clear diagnostic or assessment criteria for COPD and PD; (4) evaluating association between PD and the risk of COPD, or risk of COPD-related events (AE and mortality), with statistical adjustment for smoking, and providing the adjusted odds ratio (OR), relative risk (RR) or hazard ratio (HR) for the risk of COPD, AE and mortality in relation to PD.

According to the inclusion criteria, two independent investigators (MY and XL)

performed systematical search, screened titles and abstracts of all retrieved studies to exclude duplicate or irrelevant records. For articles requiring further assessment, full-text reviews were carried out and references of retrieved articles and relevant reviews were also manually checked to identify additional eligible studies. Disagreements were resolved by discussion between the two reviewers or with the help of the third investigator (RP).

Data extraction and quality assessment

Two investigators (MY and RP) independently extracted data from selected studies using a standardized Excel (Microsoft Corporation) file. The following information was extracted: author, year of publication, country, study design, number of subjects (COPD and non-COPD), demographic characteristics of participants, periodontal variables applied to assess PD, diagnostic criteria for COPD, definition of COPD-related AE and mortality, adjusted OR, RR or HR for the risk of COPD, AE and mortality in relation to PD, as well as adjustment for confounders. The primary outcome was the risk of COPD. Secondary outcome was the risk of COPD-related adverse events, including AE and mortality. Quality of studies was independently evaluated using the Newcastle-Ottawa Scale[24] by two investigators (MY and XL). A score of ≥6 was considered a low risk while < 6 a high risk of bias. Both case-control and cohort studies had a maximum score of 9. Cross-sectional study was regarded as case-control study when performing quality assessment. Discrepancies regarding data extraction and quality assessment were

resolved through discussion and consensus.

Data analysis

The final pooled estimate was expressed as OR with 95% confident interval (CI). Considering CAL, ABL and PPD have been regarded as the primary parameters for PD,[25 26] where more than one adjusted estimate was shown in the paper, we preferentially used the estimate regarding these parameters (CAL > ABL > PPD), or the estimate being better adjusted for tobacco smoking (never smokers > adjusting for smoking intensity [duration and dose] > adjusting for smoking status), or the estimate regarding more severe PD, where available. For case-control and cross-sectional studies, we estimated the OR whereas for cohort studies we estimated the RR or HR. The random-effect model with inverse variance method were applied due to potential heterogeneity resulting from methodological differences. Heterogeneity across studies was identified with the I^2 statistic. I^2 statistic >50% indicated significant heterogeneity.

To explore heterogeneity, subgroup analyses were conducted based on study design (case-control, cross-sectional and cohort studies), geographical location (Asia, North America, Europe), assessment of PD (CAL, ABL and PPD), definition of COPD (Global Initiative for Chronic Obstructive Lung Diseases, GOLD and non-GOLD criteria) and adjustment for smoking intensity (dose and duration of smoking). To better control the confounding effect of smoking, stratified analyses were performed in smokers and never smokers respectively.

To test the robustness of study findings, we performed sensitivity analysis on studies with relatively large sample size (≥500 participants), which tended to be more representative of the general population and with smaller bias in the overall estimates in meta-analyses.[27] Additionally, influence of a single study on the overall pooled estimate was tested by omitting one study in each turn. Publication bias was visually assessed using a funnel plot and quantitatively evaluated by the Egger's tests. P <0.05 was considered statistically significant. All statistical analyses were performed using Stata version 16 (StataCorp) and Review manager version 5.4 (Cochrane Collaboration).

Patient and public involvement

No patient involved.

RESULTS

Study selection and characteristics

A total of 30165 records were identified from the initial database search. 13662 records were removed for duplicates, and 16227 records were excluded after titles and abstracts screening because of irrelevant content and animal studies. The remaining 276 full-text articles were identified for eligibility, of which 254 were excluded for reasons including duplicates (six studies), reviews (183 studies), insufficient information (nine studies) and ineligible designs and outcomes (56 studies). Finally, 22 studies[14-16 19-21 28-43] were included in the review. The selection process is shown in **figure 1**.

The characteristics of included 22 studies were shown in **table 1**. The number of participants was 51704 and there were 9973 (18.9%) patients with COPD. The mean age of patients with COPD was between 45.1 and 83.1 years while the control subjects was between 42.2 and 80.3 years. These studies were published between 1998 and 2021. The sample size ranged from 120 to 13792. Nine studies were case-control studies[15 19 28 29 32 33 36 40 42] and 10 studies were cross-sectional studies,[14 20 30 31 34 35 38 39 41 43] only three studies with a cohort study design.[16 21 37] Additionally, 11 studies were conducted in Asia,[15 16 19 32 34 35 37 38 40-42] while six studies in the North America,[14 20 21 28-30] four studies in Europe[31 33 36 39] and one study in Africa.[43]

Table 1 Characteristics of included studies

Year / Study	Design	Location	No. COPD / Control subjects	Age (COPD / Control subjects)	Assessment of PD	Assessment of COPD
1998 Hayes *et al*[28]	Case-control	United States	261/857	45.1±9.7/42.2±9.1	ABL	FEV_1
1998 Scannapieco *et al*[14]	Cross-sectional	United States	77/309	NA	OHI	Self-reported
2001 Garcia *et al*[29]	Case-control	United States	279/833	NA	ABL, PPD	FEV_1
2001 Scannapieco *et al*[30]	Cross-sectional	United States	810/12,982	51.2±17.9/43.9±17.7	CAL, GB	Self-reported
2004 Hyman *et al*[20]	Cross-sectional	United States	993/6,632	62.3±14.1/47.4±14.2	CAL	GOLD
2008 Leuckfeld *et al*[31]	Cross-sectional	Norway	130/50	54.9±4.9/47.0±9.8	ABL	GOLD
2009 Wang *et al*[19]	Case-control	China	306/328	63.9±9.8/63.3±9.0	CAL, PLI	GOLD
2012 Liu *et al*[42]	Case-control	China	183/209*	64.3±10.1/63.6±9.7	CAL, PPD, BI	GOLD

2012 Si *et al*[15]	Case-control	China	581/438	63.9±9.4/62.8±9.5	CAL, ABL, PPD, PLI, BI	GOLD
2012 Zhou *et al*[32]	Case-control	China	193/181	63.6±10.3/62.1±9.1	CAL, ABL, PPD, PLI, BI	GOLD
2013 Barros *et al*[21]	Cohort	United States	399/1,236§	63.9±5.7/66.0±5.1	CAL, PPD	GOLD
2013 Ledić *et al*[33]	Case-control	Croatia	93/43	65.8±9.7/62.1±11.9	CAL	GOLD
2016 Chung *et al*[34]	Cross-sectional	Korea	697/5,181	64.3±0.2/54.6±0.1	PPD, GB	GOLD
2018 AbdelHalim *et al*[43]	Cross-sectional	Egypt	134/116*	56.8±10.4/55.3±9.1	CAL, PPD, BI, PLI, OHI	GOLD
2018 Harland *et al*[35]	Cross-sectional	Japan	149/1,325	61.3±9.1/54.5±8.7	PPD	GOLD
2018 Lopez-de-Andrés *et al*[36]	Case-control	Spain	2,699/2,699	63±14/61±14	Self-reported	Self-reported
2019 Takeuchi *et al*[37]	Cohort	Japan	22/878	NA	CAL, PPD	GOLD
2020 Jung *et al*[38]	Cross-sectional	Korea	1,134/6,585	62.6±0.4/53.6±0.2	PPD	FEV_1 / FVC
2020 Qian *et al*[16]	Cohort	China	23‡/NA	83.1±4.8/80.3±3.7	ABL	NR
2020 Winning *et al*[39]	Cross-sectional	Sweden	86/740	NA	ABL	GOLD
2020 Zhou *et al*[40]	Case-control	China	60/60	63.1±10.1/60.0±9.4	CAL, PLI	GOLD
2021 Kataoka *et al*[41]	Cross-sectional	Japan	464/249	54.1±9.4/NA	PPD	GOLD

Continuous data are presented as mean ± standard deviation (SD) unless otherwise indicated.

*No. COPD subjects with frequent exacerbation (≥2 exacerbations in the last year)/Infrequent exacerbation (< 2 exacerbations in the last year).

§No. COPD subjects with events (hospitalization for exacerbation or COPD-related death) in the 5-year follow-up visit/COPD subjects without events in the 5-year follow-up visit.

‡No. COPD-related mortality in a follow-up visit more than 5 years.

ABL, alveolar bone loss; BI, bleeding index; CAL, clinical attachment level; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GB, gingival bleeding; GOLD, Global Initiative for Chronic Obstructive Lung

Disease; NA, not available; OHI, oral health index; PD, periodontal disease; PLI, plaque index; PPD, probing pocket depth.

All included articles performed multivariable analyses, in which the risk of COPD, or risk of COPD-related events (AE or mortality), was identified as the dependent variable and PD as the independent variable. Controlling for confounding by smoking included stratification (smokers and never smokers) or covariance adjustment in multivariable models (the degree of control: never smokers > adjusting for smoking intensity [duration and dose] > adjusting for smoking status).

The adjustment for confounders of included studies was detailedly presented in online supplemental table S2. 16 articles reported the adjusted ORs and 4 reported adjusted RRs, two studies reporting HRs. Definition of COPD comprised the GOLD criteria,[2] FEV_1 <65% of predicted volume, having a history of chronic bronchitis and / or emphysema, self-reported and others. Periodontal parameters used for PD assessment were CAL, ABL, PPD, gingival bleeding (GB), bleeding index (BI), plaque index (PLI) and oral health index (OHI).

Assessment of bias

Based on the Newcastle-Ottawa Scale, quality assessment for the 22 studies was shown in online supplemental table S3. Among them, 18 studies[15 19-21 28-30 32-42] were rated as high quality with a total score of ≥6 whereas four studies[14 16 31 43] as a score of <6, indicating a high risk of bias. The main reasons for lower scores were selection bias (representativeness of sample population), especially for control groups and

comparability of cases and control subjects.

Primary outcome

18 studies[14 15 19 20 28-41] provided data for the risk of COPD in relation to PD. Quantitative analysis demonstrated that after adjusting for smoking status, PD increased the risk of COPD, but only by a ratio of 1.20 (95% CI 1.09 to 1.32, p=0.0002, I^2=79%) (**figure 2**). Further exclusion of any single study did not materially alter the overall pooled OR, with a range from 1.17 (95% CI 1.06-1.28) to 1.28 (95% CI 1.12-1.46). Sensitivity analysis limited to studies with larger sample size (≥500)[15 19 20 28-30 34-39 41] revealed similar results (OR 1.24, 95% CI 1.08 to 1.43, p=0.003, I^2=82%) (online supplemental figure S1). However, significant publication bias was noted by visual inspections of the funnel plot (online supplemental figure S2) and the Egger' s test for small study effects (bias coefficient 1.49, 95% CI 0.44 to 2.55, p=0.008).

Subgroup analyses indicated that assessment parameters of PD (p=0.02), study design (p=0.05) and diagnosis of COPD (p=0.05) were the potential main causes of heterogeneity (**table 2**). Moreover, there were several findings in subgroup analyses. First, after further controlling for smoking intensity, PD did not increase the risk of COPD (OR 1.14, 95% CI 0.86 to 1.51, p=0.38, 10 studies[15 19 20 29-33 35 37]), similar to the subgroup applying a GOLD criterion (OR 1.10, 95% CI 1.00 to 1.22, p=0.06, 12 studies[15 19 20 31-35 37 39-41]). Second, among the parameters of CAL, ABL and PPD, only subgroup using the parameter of ABL showed a significant association between PD and

the risk of COPD (OR 1.98, 95% CI 1.32 to 2.97, p=0.001, six studies[15 28 29 31 32 39]). Third, in the three geographical locations (Asia, North America and Europe), only the subgroup of Europe indicated that PD increased the risk of COPD (OR 2.05, 95% CI 1.07 to 3.95, p=0.03, four studies[31 33 36 39]).

Table 2 Subgroup analyses regarding the risk of COPD

Subgroups	No. Studies	No. Participants /Cases	OR value (95% CI)	P value	I^2, %
Adjusted for smoking intensity[a]					
Yes	10	27,246 / 3,556	1.14 (0.86-1.51)	0.38	67
No	8	22,158 / 5,478	1.29 (1.13-1.48)	**0.0002**	75
Assessment of PD					
CAL	8	24,600 / 3,058	1.04 (0.96-1.14)	0.33	75
ABL	6	4,629 / 1,530	1.98 (1.32-2.97)	**0.001**	56
PPD	8	19,189 / 3,519	1.16 (0.89-1.51)	0.27	63
Geographical location					
Asia	9	18,831 / 3,606	1.07 (0.99-1.17)	0.08	65
North America	5	24,033 / 2,420	1.37 (0.93-2.01)	0.11	63
Europe	4	6,540 / 3,008	2.05 (1.07-3.95)	**0.03**	71
Assessment of COPD					
GOLD	12	19,879 / 3,774	1.10 (1.00-1.22)	0.06	71

Non-GOLD	6	29,525 / 5,260	1.35 (1.14-1.61)	**0.0007**	46
Study design					
Case-control	8	9,911 / 4,472	1.12 (1.01-1.24)	**0.03**	86
Cross-sectional	9	38,593 / 4,540	1.34 (1.08-1.66)	**0.007**	45
Cohort	1	878 / 22	3.51 (1.15-10.74)	**0.03**	-

[a]Duration and dose of smoking.

ABL, alveolar bone loss; CAL, clinical attachment level; CI, confident interval; GOLD, Global Initiative for Chronic Obstructive Lung Disease; OR, odds ratio; PD, periodontal disease; PPD, probing pocket depth.

Bold: subgroups with positive results.

Stratified analyses regarding smoking status revealed that PD did not increase the risk of COPD whether in smokers (OR 1.46, 95% CI 0.92 to 2.31, p=0.11, seven studies[15 19 20 29 31 32 35]) or never smokers (OR 0.93, 95% CI 0.72 to 1.21, p=0.58, six studies[15 19 20 29 32 35]) (**figure 3**).

Secondary outcome

Only four studies evaluated the risk of COPD-related AE or mortality.[16 21 42 43] Definition of AE was acute deterioration in clinical presentations according to the recommendation in GOLD guideline.[21 42 43] Pooled analysis showed that after adjusting for smoking status, PD did not increase the risk of COPD-related AE or mortality (OR 1.18, 95% CI 0.71 to 1.97, p=0.52, I^2=36%) (**figure 4**).

DISCUSSION

This systematic review and meta-analysis identified 22 observational studies to investigate the association between COPD and PD. The results indicated that, after strictly adjusting for confounding by smoking, PD did not increase the risk of COPD, as well as the risk of COPD-related AE or mortality. Moreover, these findings were consistent across the subgroup and stratified analyses.

To the best of our knowledge, this is the first and largest meta-analysis investigating the association of PD with the risk of COPD and its clinical events, with adequately controlling the confounding effect of smoking. Besides, nearly all included articles were adjusted for age, except the study by Scannapieco *et al*.[14] Prior publications have suggested that PD significantly increased the risk of COPD and COPD-related events. However, the majority of studies have non-negligible flaws, such as only performing univariate analyses, not controlling the confounding by smoking, and using parameters with relatively low specificity for determining PD.[13 25 43] In the present study, to define PD as accurately as possible, we preferentially extracted data concerning the parameters of CAL, ABL and PPD rather than PLI, OHI or remaining teeth. CAL, ABL and PPD are clinical measurements reflecting the destruction of periodontal tissues and momentous parameters for diagnosis of PD.[25 44] Meanwhile, compared with previous meta-analyses, we enrolled more studies, applied more rigorous screening criteria and most importantly, revealed opposite results. In the meta-analyses with incomplete adjustment for smoking, OR value for the risk of COPD ranged from 1.28 to 2.08.[45-48] However, our findings were similar to studies conducted in never smokers,[15 19 20 29 32 35]

which showed that PD conferred no risk for COPD. Additionally, pooled analyses regarding parameters of CAL, ABL and PPD revealed that PD also did not increase the risk of COPD-related AE or mortality. These findings demonstrate that previously reported correlation between PD and COPD may be results of flawed study design, confounding by smoking and even other factors, such as age and living condition.

As a momentous inducer for inflammation-related pathological processes, tobacco is known to correlate with a variety of systemic disorders.[49] It is also one of the foremost risk factors for both COPD and PD.[5 10] From the epidemiological perspective, tobacco smoking is a confounder with spuriously inflated effect on the relationship between PD and systemic diseases.[49] To investigate the true association between PD and COPD, it is of great importance to rigorously control the confounding effect of smoking, which means initiating research in never smokers. However, the majority of former studies failed to do that. After a wide search, only six studies focusing on never smokers were found, which unanimously indicated PD was not related with the risk of COPD. We also observed a decreased intensity of the association between both diseases with the increase of control for smoking. Therefore, it could be too early to make a certain conclusion on the COPD-PD relationship. Although interventional studies revealed that periodontal treatment reduced the risk of AE, a number of problems existed, including small sample size, limited study quality and unclear history of smoking or medication during the follow-up.[17 18] For example, compared with control subjects, patients in treatment groups may reduce smoking intentionally, which could spuriously enhance the positive effect

of periodontal treatment. Consequently, future researches need to take these problems into account.

It is worth noting that, another possibility that smoking acts as an effect modifier in the COPD-PD relationship should not be ignored. Two observational studies performing stratified analyses concerning smoking status found that the strong correlation of PD with the risk of COPD was restricted to smokers.[15 20] However, this was not revealed in the present study, thus more investigations in smokers and never smokers respectively are required.

Besides, current evidence has demonstrated several issues to be addressed in future study, comprising inconsistent diagnostic criteria of COPD and PD, the lack of prospective study design and differing adjustments for covariates. These contribute to substantial heterogeneity among studies.[45 46] The present study indicated the heterogeneity was partly explained by study design, diagnostic criteria of COPD and periodontal indexes used to assess PD. Significant association concerning PD and risk of COPD was only identified in subgroups lacking well designs, applying non-GOLD criteria or utilizing ABL as the measure of PD. For one thing, this demonstrated that, as sources of bias, observational study design and nonstandard diagnostic method for COPD could induce apparent deviations, confusing the true relationship between COPD and PD. For another, given undetermined diagnostic criteria for PD, discrepancies between ABL and other indexes cannot fully support the COPD-PD association. Notably, as a radiographic measure, although ABL has been widely considered to reflect

cumulative effects of periodontal attachment loss over time by chronic inflammation,[28] it does not only exist in PD. Non-periodontal diseases such as liver disorders, cancer and osteoporosis[50] could also result in ABL. As mentioned previously,[28] the observed correlation between ABL and risk of COPD may relate to those non-periodontal diseases.

Limitations

Several potential limitations should be taken into consideration when interpreting the present results. First, all included studies are observational, which are highly subject to selection bias and confounding by indication. Second, substantial heterogeneity was identified in current study, though we conducted subgroup and stratified analyses to partly explain and reduce it. As stated above, several problems leading to heterogeneity need to be addressed in future researches. Third, the number of studies on risk of COPD-related events was limited, thus the result needs to be carefully understood. Limited number of studies in subgroup and stratified analyses suggested more relevant studies with larger sample size are required. Fourth, although confounding effects of age and smoking were controlled by stratified analysis and statistical adjustment, other potential confounders such as gender, living condition and socioeconomic status[10] could also reduce reliability of the results. Fifth, obvious publication bias was noted in relevant meta-analyses,[45 46] including the present study. For the purpose of rapid review,[23] we only included articles in English. There could exist non-English publications and unpublished evidence, although we searched English-language studies as much as

possible. Finally, although smoking status and intensity were considered in subgroup analysis, information regarding tobacco content and chemical composition were not collected. This information is difficult to obtain, especially from self-reported smoking, leaving a residual smoking-related bias. Consequently, it is advisable to explore relationship between COPD and PD in never smokers.

CONCLUSION

In summary, this systematic review and meta-analysis suggests that PD is not associated with the risk of COPD and COPD-related events after strict adjustment for smoking, although the positive relationship between COPD and PD was previously reported. Large-scale prospective cohort studies with control of potential confounding factors are warranted to validate the present findings.

Abbreviations

ABL: Alveolar bone loss; AE: Acute exacerbation; BI: Bleeding index; CAL: Clinical attachment level; CI: Confident interval; COPD: Chronic obstructive pulmonary disease; GB: Gingival bleeding; GOLD: Global Initiative for Chronic Obstructive Lung Diseases; HR: Hazard ratio; OHI: Oral health index; OR: Odds ratio; PD: Periodontal disease; PLI: Plaque index; PPD: Probing pocket depth; RR: Relative risk.

Contributors LC and LL designed the study. MY and XL screened and selected relevant

studies. MY, RP and XL rated the study quality and extracted the data. MY, RP, XL and JP analyzed the data. All authors interpreted the data, and MY, RP, XL, JP drafted the paper. LC and LL critically revised the paper. All authors acknowledged and agreed with the format and content of the paper before submission for publication. LC and LL are the guarantors and responsible for the overall contents of this study.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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Figure legends

Figure 1 PRISMA flow diagram of study selection.

Figure 2 Forest plot of the risk of COPD by periodontal disease, subgroup analysis based on adjusted by smoking status and intensity versus by smoking status only. Values more than one indicate a higher risk in patients with periodontal disease.

Figure 3 Forest plot of the risk of COPD by periodontal disease. **A** in smokers and **B** in never smokers. Values more than one indicate a higher risk in patients with periodontal disease.

Figure 4 Forest plot of the risk of COPD-related events by periodontal disease. Values more than one indicate a higher risk in patients with periodontal disease.

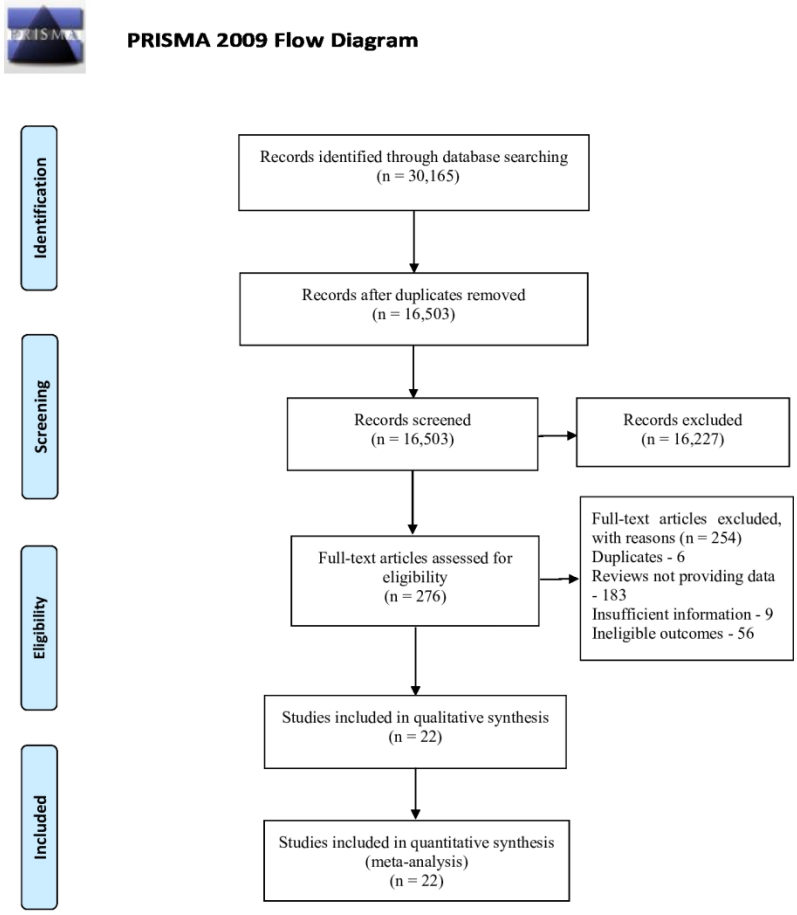

Figure 1 PRISMA flow diagram of study selection.

215x279mm (200 x 200 DPI)

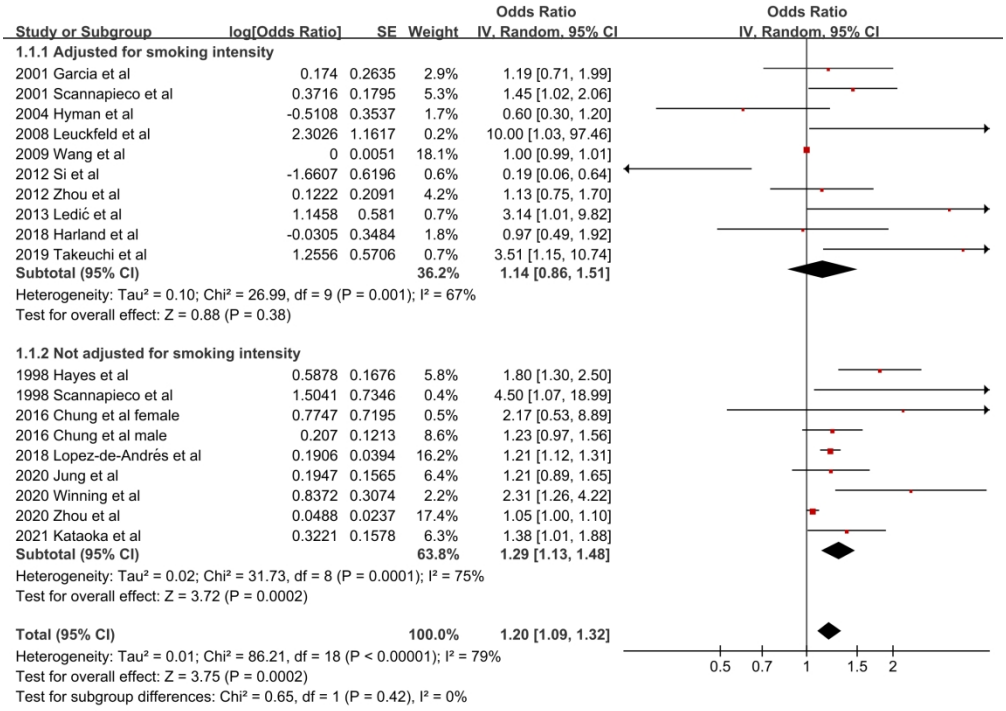

Figure 2 Forest plot of the risk of COPD by periodontal disease, subgroup analysis based on adjusted by smoking status and intensity versus by smoking status only. Values more than one indicate a higher risk in patients with periodontal disease.

536x384mm (118 x 118 DPI)

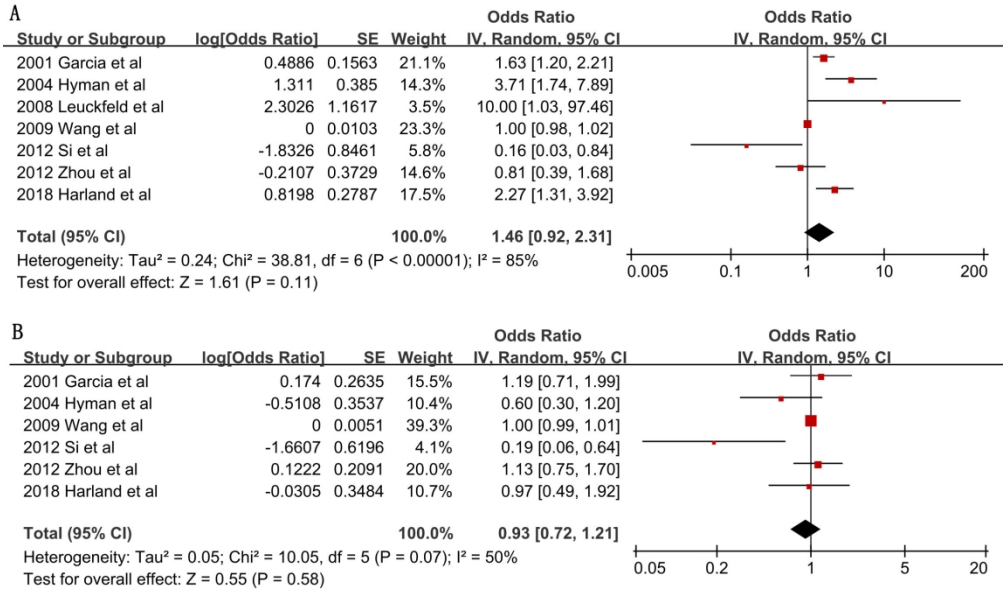

Figure 3 Forest plot of the risk of COPD by periodontal disease. A in smokers and B in never smokers. Values more than one indicate a higher risk in patients with periodontal disease.

192x118mm (300 x 300 DPI)

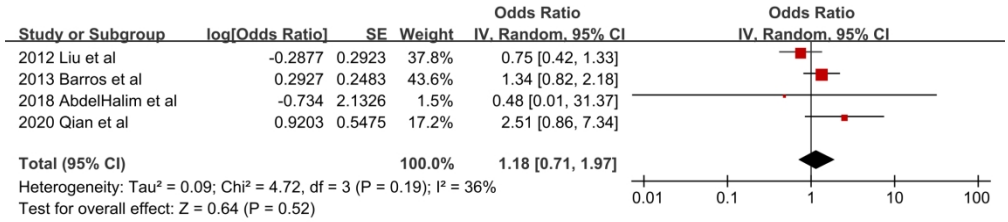

Figure 4 Forest plot of the risk of COPD-related events by periodontal disease. Values more than one indicate a higher risk in patients with periodontal disease.

497x118mm (118 x 118 DPI)

Table S1 Search strategy

Search term
1. (Oral health) OR (periodontal disease) OR (periodontal health) OR (periodontitis) OR (clinical attachment level) OR (alveolar bone loss) OR (probing depth)
2. (Respiratory disease) OR (chronic obstructive pulmonary disease) OR (pulmonary function) OR (airflow limitation)
3. 1 AND 2

Table S2 Adjustment for confounders of included studies

Study Author	Covariates in logistic regression multivariable model
Hayes *et al*[1]	Age, smoking, education, height
Scannapieco *et al*[2]	Smoking
Garcia *et al*[3]	Age, height, alcohol, education **(with stratified analysis on smoking)**
Leuckfeld *et al*[4]	Age, female gender, **pack years of smoking**
Liu *et al*[5]	Age, gender, BMI and smoking
Wang *et al*[6]	Age, gender, BMI **(with stratified analysis on smoking)**
Si *et al*[7]	Age, gender, occupation, educational level **(with stratified analysis on smoking)**
Zhou *et al*[8]	Age, gender, smoking, BMI, season **(with stratified analysis on smoking)**
Ledić *et al*[9]	Age, gender, **pack years of smoking**, BMI
Lopez-de-Andrés *et al*[10]	Age, gender, smoking, educational level, DM, obesity
Zhou *et al*[11]	Age, gender, smoking, BMI
Kataoka *et al*[12]	Age, smoking
Qian *et al*[13]	Age, sex, education levels, BMI, smoking, drinking, hypertension, DM
Barros *et al*[14]	Age, gender, Race, BMI, education, **pack years of smoking**, hypertension
Scannapieco *et al*[15]	Age, gender, **pack years of smoking**, Race, education, income, dental visits, alcohol, DM
Hyman *et al*[16]	Age, gender, Race, history of hypertension and heart attack, dental visit within 1 year, BMI, family income **(with stratified analysis on smoking)**
Chung *et al*[17]	Age, smoking, family income, education, alcohol, exercise, BMI, tooth brushing frequency, DM, number of natural teeth
Harland *et al*[18]	Age, number of present teeth, BMI, alcohol consumption, occupation, hypertension, DM **(with stratified analysis on smoking)**
Takeuchi *et al*[19]	Age, gender, **pack years of smoking**, occupation, DM, BMI, physical

	activity, alcohol intake, number of present teeth
Jung *et al*[20]	Age, gender, smoking, educational level, household income, alcohol consumption, periodontal status, number of missing teeth, oral health factors
Winning *et al*[21]	Age, gender, smoking, height, BMI, exercise, DM, hypertension, MI, education level, living condition
AbdelHalim *et al*[22]	Age, BMI, low-level of education, **pack years of smoking**, MRC, CAT, hospitalizations, COPD category (C-D), FVC (% predicted), FEV1 (% predicted), FEV1 / FVC (% predicted), MMEF (% predicted), PEF (% predicted), CRP

BMI, body mass index; CAT, chronic obstructive pulmonary disease assessment test; CRP, C-reactive protein; DM, diabetes mellitus; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; MI, myocardial infarction; MMEF, maximum mid-expiratory flow; MRC, Medical Research Council; PEF, peak expiratory flow.

Bold: the covariate of smoking intensity (duration and dose) or stratified analyses on smoking status.

Table S3 Quality assessment based on the Newcastle-Ottawa Scale

(A) Cohort study

Study Author	Selection				Comparability	Outcome			Total score
	Exposed cohort	Nonexposed cohort	Ascertainment of exposure	Outcome of interest		Assessment of outcome	Length of follow-up	Adequacy of follow-up	
Barros *et al*[14]	*	*	*	…	…	*	*	*	6
Takeuchi *et al*[19]	*	*	*	*	…	*	*	*	7
Qian *et al*[13]	…	*	*	…	…	*	*	…	4

(B) Case-control / cross-sectional study

Study Author	Selection				Comparability	Outcome			Total score
	Case definition	Representati--veness of the cases	Control selection	Control definition		Ascertainment of exposure	Same method of ascertainment for cases and controls	Non--response rate	
Hayes *et al*[1]	*	…	*	*	*	*	*	*	7
Scannapieco *et al*[2]	…	*	*	*	…	*	*	…	5
Garcia *et al*[3]	*	…	*	*	*	*	*	*	7
Scannapieco *et al*[15]	…	*	*	*	…	*	*	*	6
Hyman *et al*[16]	*	*	*	*	…	*	*	*	7
Leuckfeld *et al*[4]	*	…	…	*	…	*	*	*	5
Wang *et al*[6]	*	*	…	*	*	*	*	*	7
Liu *et al*[5]	*	*	…	*	*	*	*	*	7
Si *et al*[7]	*	*	…	*	*	*	*	*	7
Zhou *et al*[8]	*	*	…	*	*	*	*	*	7
Ledić *et al*[9]	*	*	…	*	*	*	*	*	7
Chung *et al*[17]	*	*	*	*	…	*	*	*	7
AbdelHalim *et al*[22]	*	…	…	*	…	*	*	*	5
Harland *et al*[18]	*	*	…	*	…	*	*	*	6
Lopez-de-Andrés *et al*[10]	…	*	*	*	*	…	*	*	6
Jung *et al*[20]	…	*	*	*	…	*	*	*	6
Winning *et al*[21]	*	*	*	*	…	*	*	*	7
Zhou *et al*[11]	*	*	…	…	**	*	*	*	7
Kataoka *et al*[12]	*	*	*	*	…	*	*	*	7

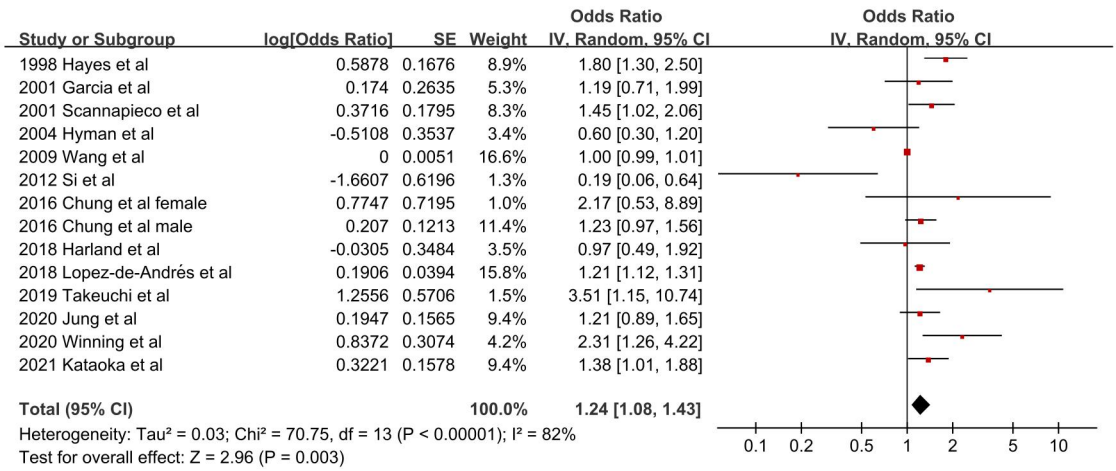

Figure S1 Sensitivity analysis on studies with larger sample size (N ≥500). Values more than one indicate a higher risk of COPD in patients with PD.

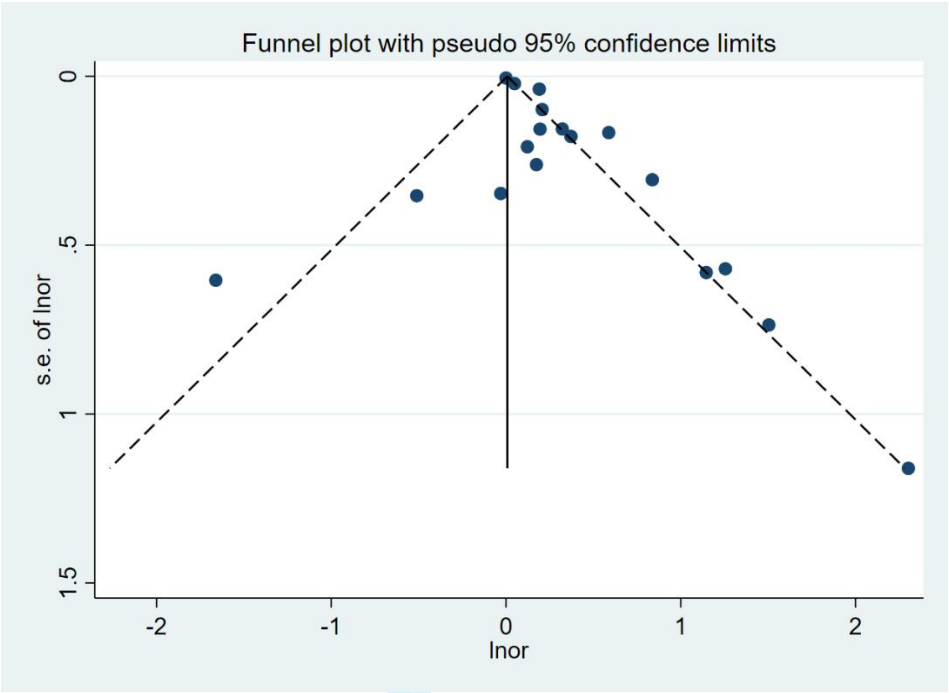

Figure S2 Funnel plot for the risk of COPD, with pseudo 95% confidence limits.

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PRISMA 2009 Checklist

Section/topic	Item No	Checklist item	Reported on Page Number/Line Number	Reported on Section/Paragraph
TITLE				
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1 / Line 2,3	Title page
ABSTRACT				
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2,3 / Line 28-52	Abstract
INTRODUCTION				
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 4,5 / Line 69-103	Introduction / Paragraph 1-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 5 / Line 103-107	Introduction / Paragraph 4
METHODS				
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Page 5,6 / Line 110-112	Methods / Paragraph 1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 6 / Line 118-124	Methods / Paragraph 2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 6 / Line 115,116	Methods / Paragraph 2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 6 / Line 116-118	Methods / Paragraph 2 Supplemental table S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 6 / Line 125-131	Methods / Paragraph 3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 7 / Line 134,135	Methods / Paragraph 4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 7 / Line 135-140	Methods / Paragraph 4

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 7 / Line 142-147	Methods / Paragraph 4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 7 / Line 150	Methods / Paragraph 5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 8 / Line 156-160	Methods / Paragraph 5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 8 / Line 171-173	Methods / Paragraph 7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 8 / Line 161-171	Methods / Paragraph 6,7
RESULTS				
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 9 / Line 181-188	Results / Paragraph 1; Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 9-12 / Line 189-223	Results / Paragraph 2-4; Table 1 and S2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 12 / Line 225-231	Results / Paragraph 5; Table S3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 12,13 / Line 234-243	Results / Paragraph 6; Figure 2 and 4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 12 / Line 234-236 Page 15 / Line 272-274	Results / Paragraph 6,8; Figure 2 and 4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 12,13 / Line 237-238; 241-243	Results / Paragraph 6; Figure S2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page 12 / Line 238-240; Page 13,14 / Line 244-267	Results / Paragraph 6-8; Table 2, Figure 2,3 and S1
DISCUSSION				
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 15-18 / Line 277-343	Discussion / Paragraph 1-5
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 18 / Line 346-365	Discussion / Paragraph 6
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 19 / Line 368-372	Conclusion / Paragraph 1

FUNDING				
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 20 / Line 388,389	Funding

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The association between chronic obstructive pulmonary disease and periodontal disease: a systematic review and meta-analysis

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Title Page

Title: The association between chronic obstructive pulmonary disease and periodontal disease: a systematic review and meta-analysis

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The association between chronic obstructive pulmonary disease and periodontal disease: a systematic review and meta-analysis

ABSTRACT

Objectives Studies have suggested contradictory results on the relationship between chronic obstructive pulmonary disease (COPD) and periodontal disease (PD). The aim of this study was to determine whether PD increased the risk of COPD and COPD-related clinical events.

Design Systematic review and meta-analysis.

Data sources PubMed, EMBASE and CENTRAL were searched from inception to 22 February 2023.

Eligibility criteria for studies We included trials and observational studies evaluating association of PD with the risk of COPD or COPD-related events (exacerbation and mortality), with statistical adjustment for smoking.

Data extraction and synthesis Two investigators independently extracted data from selected studies using a standardized Excel file. Quality of studies was evaluated using the Newcastle-Ottawa Scale. Odds ratio (OR) with 95% confident interval (CI) was pooled in a random-effect model with inverse variance method.

Results 22 observational studies with 51704 participants were included. Pooled analysis

of 18 studies suggested that PD was weakly associated with the risk of COPD (OR 1.20, 95% CI 1.09 to 1.32). However, in stratified and subgroup analyses, with strict adjustment for smoking, PD no longer related to the risk of COPD (adjusting for smoking intensity: OR 1.14, 95% CI 0.86 to 1.51; smokers only: OR 1.46, 95% CI 0.92 to 2.31; never smokers only: OR 0.93, 95% CI 0.72 to 1.21). Moreover, PD did not increase the risk of COPD-related exacerbation or mortality (OR 1.18, 95% CI 0.71 to 1.97) in the pooled result of four studies.

Conclusions This study demonstrates PD confers no risk for COPD and COPD-related events when strictly adjusted by smoking. Large-scale prospective cohort studies with control of potential confounding factors are warranted to validate the present findings.

STRENGTHS AND LIMITATIONS OF THIS STUDY

1. This is the largest systematic review and meta-analysis on association between chronic obstructive pulmonary disease (COPD) and periodontal disease (PD) collecting data over 20 years.
2. This is the first meta-analysis investigating whether PD increases the risk of COPD-related events (exacerbation or mortality).
3. Compared with previous reports, this study was conducted with more strict adjustment for confounding by smoking, which was the most important confounder in the COPD-PD relationship.
4. Our study provided limited evidence on the outcome of COPD-related events

because of limited data.

5. Clinical heterogeneity and publication bias compromised the evidence strength of this study, although subgroup and stratified analyses were performed.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death, resulting in enormous economic burden.[1] Commonly, COPD coexists with a variety of disorders, called comorbidities, which play significant roles in the progression and prognosis of COPD.[2 3] Understanding the COPD-comorbidities relationship has been a momentous prerequisite for optimizing disease prevention and management strategies.[2 3]

Given ageing and widespread use of inhaled corticosteroids in COPD, periodontal disease (PD) has been a common comorbidity of COPD.[4] It is a chronic inflammatory condition of tissues surrounding and supporting the teeth, including gingiva, bone and ligament,[5] with the prevalence estimates over 10% around the world and especially prevalent in elderly individuals.[6] To date, diagnosis and assessment of PD are mostly based on periodontal measurements including clinical attachment level (CAL), probing pocket depth (PPD) and alveolar bone loss (ABL).[5] They are primary clinical manifestations of PD, reflecting the extent of periodontal tissue destruction.[5]

Based on the nature of inflammation,[5 7] mounting evidence has shed light on the association between PD and development of COPD.[8 9] Currently three points are

proposed. First, they share the same risk factors, such as age, gender, smoking and socioeconomic status.[2 10] Second, they have similar pathogenetic mechanisms. Both diseases are characterized by host susceptibility to environmental factors, immune overreaction, oxidative stress and production of pro-inflammatory cytokines.[7 8] Most importantly, neutrophilic inflammation plays a key role in both diseases.[8 11] Third, oral bacteria released from the dental plaque in PD could trigger progression and acute exacerbation (AE) of COPD.[12 13]

Meanwhile, epidemiological evidence has indicated that PD increases risk of COPD[11 14 15] and COPD-related events.[13 16] Scannapieco *et al* revealed a 4.5-fold increased risk of COPD in patients with PD, compared with those without.[14] A dose-response relationship was further implied between PD severity and lung function.[15] Among patients with both diseases, COPD-related AE and mortality also significantly linked with periodontal status.[13 16] Periodontal therapy, such as scaling and root planing treatment, may ameliorate lung function and decrease frequency of AE in COPD with chronic periodontitis.[17 18] However, there were some other studies revealing opposite results, resulting in a long-standing controversy.[19-21] It is worth noting that, parameters used to determine PD apparently varied across studies, and these studies also failed to adequately control for confounders, especially smoking, the most important confounder for the COPD-PD relationship. Therefore, to provide the latest and most convincing evidence, we systematically reviewed current available literature to investigate whether PD increases the risk of COPD. The secondary objective was to evaluate the association

between PD and the risk of COPD-related events. Subgroup and stratified analyses were also conducted to adjust for the confounding by smoking.

METHODS

This systematic review and meta-analysis was conducted and reported in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.[22]

Search strategy and selection criteria

We searched PubMed, EMBASE and CENTRAL for records evaluating association between COPD and PD, from inception to 22 February 2023. The search strategy was described in **online supplemental table 1**. The language was restricted to English, for the purpose of rapid review.[23] Studies meeting the following criteria were included: (1) adult participants (≥18 years); (2) original studies with randomized controlled trial (RCT), cohort, case-control or cross-sectional study designs; (3) presenting clear diagnostic or assessment criteria for COPD and PD; (4) evaluating association between PD and the risk of COPD, or risk of COPD-related events (AE and mortality), with statistical adjustment for smoking, and providing the adjusted odds ratio (OR), relative risk (RR) or hazard ratio (HR) for the risk of COPD, AE and mortality in relation to PD.

According to the inclusion criteria, two independent investigators (MY and XL) performed systematical search, screened titles and abstracts of all retrieved studies to

exclude duplicate or irrelevant records. For articles requiring further assessment, full-text reviews were carried out and references of retrieved articles and relevant reviews were also manually checked to identify additional eligible studies. Disagreements were resolved by discussion between the two reviewers or with the help of the third investigator (RP).

Data extraction and quality assessment

Two investigators (MY and RP) independently extracted data from selected studies using a standardized Excel (Microsoft Corporation) file. The following information was extracted: author, year of publication, country, study design, number of subjects (COPD and non-COPD), demographic characteristics of participants, periodontal variables applied to assess PD, diagnostic criteria for COPD, definition of COPD-related AE and mortality, adjusted OR, RR or HR for the risk of COPD, AE and mortality in relation to PD, as well as adjustment for confounders. The primary outcome was the risk of COPD. Secondary outcome was the risk of COPD-related adverse events, including AE and mortality. Quality of studies was independently evaluated using the Newcastle-Ottawa Scale[24] by two investigators (MY and XL). A score of ≥6 was considered a low risk while < 6 a high risk of bias. Both case-control and cohort studies had a maximum score of 9. Cross-sectional study was regarded as case-control study when performing quality assessment. Discrepancies regarding data extraction and quality assessment were resolved through discussion and consensus.

Data analysis

The final pooled estimate was expressed as OR with 95% confident interval (CI). Considering CAL, ABL and PPD have been regarded as the primary parameters for PD,[25 26] where more than one adjusted estimate was shown in the paper, we preferentially used the estimate regarding these parameters (CAL > ABL > PPD), or the estimate being better adjusted for tobacco smoking (never smokers > adjusting for smoking intensity [duration and dose] > adjusting for smoking status), or the estimate regarding more severe PD, where available. For case-control and cross-sectional studies, we estimated the OR whereas for cohort studies we estimated the RR or HR. The random-effect model with inverse variance method were applied due to potential heterogeneity resulting from methodological differences. Heterogeneity across studies was identified with the I^2 statistic. I^2 statistic >50% indicated significant heterogeneity.

To explore heterogeneity, subgroup analyses were conducted based on study design (case-control, cross-sectional and cohort studies), geographical location (Asia, North America, Europe), assessment of PD (CAL, ABL and PPD), definition of COPD (Global Initiative for Chronic Obstructive Lung Diseases, GOLD and non-GOLD criteria) and adjustment for smoking intensity (dose and duration of smoking). To better control the confounding effect of smoking, stratified analyses were performed in smokers and never smokers respectively.

To test the robustness of study findings, we performed sensitivity analysis on studies

with relatively large sample size (≥500 participants), which tended to be more representative of the general population and with smaller bias in the overall estimates in meta-analyses.[27] Additionally, influence of a single study on the overall pooled estimate was tested by omitting one study in each turn. Publication bias was visually assessed using a funnel plot and quantitatively evaluated by the Egger's tests. P <0.05 was considered statistically significant. All statistical analyses were performed using Stata version 16 (StataCorp) and Review manager version 5.4 (Cochrane Collaboration).

Patient and public involvement

No patients or other individuals are involved in the design, conduct, reporting or dissemination of this research.

RESULTS

Study selection and characteristics

A total of 30165 records were identified from the initial database search. 13662 records were removed for duplicates, and 16227 records were excluded after titles and abstracts screening because of irrelevant content and animal studies. The remaining 276 full-text articles were identified for eligibility, of which 254 were excluded for reasons including duplicates (six studies), reviews (183 studies), insufficient information (nine studies) and ineligible designs and outcomes (56 studies). Finally, 22 studies[14-16 19-21 28-43] were included in the review. The selection process is shown in **figure 1**.

The characteristics of included 22 studies were shown in **table 1**. The number of participants was 51704 and there were 9973 (18.9%) patients with COPD. The mean age of patients with COPD was between 45.1 and 83.1 years while the control subjects was between 42.2 and 80.3 years. These studies were published between 1998 and 2021. The sample size ranged from 120 to 13792. Nine studies were case-control studies[15 19 28 29 32 33 36 40 42] and 10 studies were cross-sectional studies,[14 20 30 31 34 35 38 39 41 43] only three studies with a cohort study design.[16 21 37] Additionally, 11 studies were conducted in Asia,[15 16 19 32 34 35 37 38 40-42] while six studies in the North America,[14 20 21 28-30] four studies in Europe[31 33 36 39] and one study in Africa.[43]

Table 1 Characteristics of included studies

Year / Study	Design	Location	No. COPD / Control subjects	Age (COPD / Control subjects)	Assessment of PD	Assessment of COPD
1998 Hayes *et al*[28]	Case-control	United States	261/857	45.1±9.7/42.2±9.1	ABL	FEV_1
1998 Scannapieco *et al*[14]	Cross-sectional	United States	77/309	NA	OHI	Self-reported
2001 Garcia *et al*[29]	Case-control	United States	279/833	NA	ABL, PPD	FEV_1
2001 Scannapieco *et al*[30]	Cross-sectional	United States	810/12,982	51.2±17.9/43.9±17.7	CAL, GB	Self-reported
2004 Hyman *et al*[20]	Cross-sectional	United States	993/6,632	62.3±14.1/47.4±14.2	CAL	GOLD
2008 Leuckfeld *et al*[31]	Cross-sectional	Norway	130/50	54.9±4.9/47.0±9.8	ABL	GOLD
2009 Wang *et al*[19]	Case-control	China	306/328	63.9±9.8/63.3±9.0	CAL, PLI	GOLD
2012 Liu *et al*[42]	Case-control	China	183/209*	64.3±10.1/63.6±9.7	CAL, PPD, BI	GOLD

2012 Si *et al*[15]	Case-control	China	581/438	63.9±9.4/62.8±9.5	CAL, ABL, PPD, PLI, BI	GOLD
2012 Zhou *et al*[32]	Case-control	China	193/181	63.6±10.3/62.1±9.1	CAL, ABL, PPD, PLI, BI	GOLD
2013 Barros *et al*[21]	Cohort	United States	399/1,236§	63.9±5.7/66.0±5.1	CAL, PPD	GOLD
2013 Ledić *et al*[33]	Case-control	Croatia	93/43	65.8±9.7/62.1±11.9	CAL	GOLD
2016 Chung *et al*[34]	Cross-sectional	Korea	697/5,181	64.3±0.2/54.6±0.1	PPD, GB	GOLD
2018 AbdelHalim *et al*[43]	Cross-sectional	Egypt	134/116*	56.8±10.4/55.3±9.1	CAL, PPD, BI, PLI, OHI	GOLD
2018 Harland *et al*[35]	Cross-sectional	Japan	149/1,325	61.3±9.1/54.5±8.7	PPD	GOLD
2018 Lopez-de-Andrés *et al*[36]	Case-control	Spain	2,699/2,699	63±14/61±14	Self-reported	Self-reported
2019 Takeuchi *et al*[37]	Cohort	Japan	22/878	NA	CAL, PPD	GOLD
2020 Jung *et al*[38]	Cross-sectional	Korea	1,134/6,585	62.6±0.4/53.6±0.2	PPD	FEV_1 / FVC
2020 Qian *et al*[16]	Cohort	China	23‡/NA	83.1±4.8/80.3±3.7	ABL	NR
2020 Winning *et al*[39]	Cross-sectional	Sweden	86/740	NA	ABL	GOLD
2020 Zhou *et al*[40]	Case-control	China	60/60	63.1±10.1/60.0±9.4	CAL, PLI	GOLD
2021 Kataoka *et al*[41]	Cross-sectional	Japan	464/249	54.1±9.4/NA	PPD	GOLD

Continuous data are presented as mean ± standard deviation (SD) unless otherwise indicated.

*No. COPD subjects with frequent exacerbation (≥2 exacerbations in the last year)/Infrequent exacerbation (< 2 exacerbations in the last year).

§No. COPD subjects with events (hospitalization for exacerbation or COPD-related death) in the 5-year follow-up visit/COPD subjects without events in the 5-year follow-up visit.

‡No. COPD-related mortality in a follow-up visit more than 5 years.

ABL, alveolar bone loss; BI, bleeding index; CAL, clinical attachment level; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GB, gingival bleeding; GOLD, Global Initiative for Chronic Obstructive Lung

Disease; NA, not available; OHI, oral health index; PD, periodontal disease; PLI, plaque index; PPD, probing pocket depth.

All included articles performed multivariable analyses, in which the risk of COPD, or risk of COPD-related events (AE or mortality), was identified as the dependent variable and PD as the independent variable. Controlling for confounding by smoking included stratification (smokers and never smokers) or covariance adjustment in multivariable models (the degree of control: never smokers > adjusting for smoking intensity [duration and dose] > adjusting for smoking status).

The adjustment for confounders of included studies was detailedly presented in **online supplemental table 2**. 16 articles reported the adjusted ORs and 4 reported adjusted RRs, two studies reporting HRs. Definition of COPD comprised the GOLD criteria,[2] FEV_1 <65% of predicted volume, having a history of chronic bronchitis and / or emphysema, self-reported and others. Periodontal parameters used for PD assessment were CAL, ABL, PPD, gingival bleeding (GB), bleeding index (BI), plaque index (PLI) and oral health index (OHI).

Assessment of bias

Based on the Newcastle-Ottawa Scale, quality assessment for the 22 studies was shown in **online supplemental table 3**. Among them, 18 studies[15 19-21 28-30 32-42] were rated as high quality with a total score of ≥6 whereas four studies[14 16 31 43] as a score of <6, indicating a high risk of bias. The main reasons for lower scores were selection bias (representativeness of sample population), especially for control groups and

comparability of cases and control subjects.

Primary outcome

18 studies[14 15 19 20 28-41] provided data for the risk of COPD in relation to PD. Quantitative analysis demonstrated that after adjusting for smoking status, PD increased the risk of COPD, but only by a ratio of 1.20 (95% CI 1.09 to 1.32, p=0.0002, I^2=79%) (**figure 2**). Further exclusion of any single study did not materially alter the overall pooled OR, with a range from 1.17 (95% CI 1.06-1.28) to 1.28 (95% CI 1.12-1.46). Sensitivity analysis limited to studies with larger sample size (≥500)[15 19 20 28-30 34-39 41] revealed similar results (OR 1.24, 95% CI 1.08 to 1.43, p=0.003, I^2=82%) (**online supplemental figure 1**). However, significant publication bias was noted by visual inspections of the funnel plot (**online supplemental figure 2**) and the Egger' s test for small study effects (bias coefficient 1.49, 95% CI 0.44 to 2.55, p=0.008).

Subgroup analyses indicated that assessment parameters of PD (p=0.02), study design (p=0.05) and diagnosis of COPD (p=0.05) were the potential main causes of heterogeneity (**table 2**). Moreover, there were several findings in subgroup analyses. First, after further controlling for smoking intensity, PD did not increase the risk of COPD (OR 1.14, 95% CI 0.86 to 1.51, p=0.38, 10 studies[15 19 20 29-33 35 37]), similar to the subgroup applying a GOLD criterion (OR 1.10, 95% CI 1.00 to 1.22, p=0.06, 12 studies[15 19 20 31-35 37 39-41]). Second, among the parameters of CAL, ABL and PPD, only subgroup using the parameter of ABL showed a significant association between PD and

the risk of COPD (OR 1.98, 95% CI 1.32 to 2.97, p=0.001, six studies[15 28 29 31 32 39]). Third, in the three geographical locations (Asia, North America and Europe), only the subgroup of Europe indicated that PD increased the risk of COPD (OR 2.05, 95% CI 1.07 to 3.95, p=0.03, four studies[31 33 36 39]).

Table 2 Subgroup analyses regarding the risk of COPD

Subgroups	No. Studies	No. Participants /Cases	OR value (95% CI)	P value	I^2, %
Adjusted for smoking intensity[a]					
Yes	10	27,246 / 3,556	1.14 (0.86-1.51)	0.38	67
No	8	22,158 / 5,478	1.29 (1.13-1.48)	**0.0002**	75
Assessment of PD					
CAL	8	24,600 / 3,058	1.04 (0.96-1.14)	0.33	75
ABL	6	4,629 / 1,530	1.98 (1.32-2.97)	**0.001**	56
PPD	8	19,189 / 3,519	1.16 (0.89-1.51)	0.27	63
Geographical location					
Asia	9	18,831 / 3,606	1.07 (0.99-1.17)	0.08	65
North America	5	24,033 / 2,420	1.37 (0.93-2.01)	0.11	63
Europe	4	6,540 / 3,008	2.05 (1.07-3.95)	**0.03**	71
Assessment of COPD					
GOLD	12	19,879 / 3,774	1.10 (1.00-1.22)	0.06	71

Non-GOLD	6	29,525 / 5,260	1.35 (1.14-1.61)	**0.0007**	46
Study design					
Case-control	8	9,911 / 4,472	1.12 (1.01-1.24)	**0.03**	86
Cross-sectional	9	38,593 / 4,540	1.34 (1.08-1.66)	**0.007**	45
Cohort	1	878 / 22	3.51 (1.15-10.74)	**0.03**	-

[a]Duration and dose of smoking.

ABL, alveolar bone loss; CAL, clinical attachment level; CI, confident interval; GOLD, Global Initiative for Chronic Obstructive Lung Disease; OR, odds ratio; PD, periodontal disease; PPD, probing pocket depth.

Bold: subgroups with positive results.

Stratified analyses regarding smoking status revealed that PD did not increase the risk of COPD whether in smokers (OR 1.46, 95% CI 0.92 to 2.31, p=0.11, seven studies[15 19 20 29 31 32 35]) or never smokers (OR 0.93, 95% CI 0.72 to 1.21, p=0.58, six studies[15 19 20 29 32 35]) (**online supplemental figure 3**).

Secondary outcome

Only four studies evaluated the risk of COPD-related AE or mortality.[16 21 42 43] Definition of AE was acute deterioration in clinical presentations according to the recommendation in GOLD guideline.[21 42 43] Pooled analysis showed that after adjusting for smoking status, PD did not increase the risk of COPD-related AE or mortality (OR 1.18, 95% CI 0.71 to 1.97, p=0.52, I^2=36%) (**figure 3**).

DISCUSSION

This systematic review and meta-analysis identified 22 observational studies to investigate the association between COPD and PD. The results indicated that, after strictly adjusting for confounding by smoking, PD did not increase the risk of COPD, as well as the risk of COPD-related AE or mortality. Moreover, these findings were consistent across the subgroup and stratified analyses.

To the best of our knowledge, this is the first and largest meta-analysis investigating the association of PD with the risk of COPD and its clinical events, with adequately controlling the confounding effect of smoking. Besides, nearly all included articles were adjusted for age, except the study by Scannapieco *et al*.[14] Prior publications have suggested that PD significantly increased the risk of COPD and COPD-related events. However, the majority of studies have non-negligible flaws, such as only performing univariate analyses, not controlling the confounding by smoking, and using parameters with relatively low specificity for determining PD.[13 25 43] In the present study, to define PD as accurately as possible, we preferentially extracted data concerning the parameters of CAL, ABL and PPD rather than PLI, OHI or remaining teeth. CAL, ABL and PPD are clinical measurements reflecting the destruction of periodontal tissues and momentous parameters for diagnosis of PD.[25 44] Meanwhile, compared with previous meta-analyses, we enrolled more studies, applied more rigorous screening criteria and most importantly, revealed opposite results. In the meta-analyses with incomplete adjustment for smoking, OR value for the risk of COPD ranged from 1.28 to 2.08.[45-48] However, our findings were similar to studies conducted in never smokers,[15 19 20 29 32 35]

which showed that PD conferred no risk for COPD. Additionally, pooled analyses regarding parameters of CAL, ABL and PPD revealed that PD also did not increase the risk of COPD-related AE or mortality. These findings demonstrate that previously reported correlation between PD and COPD may be results of flawed study design, confounding by smoking and even other factors, such as age and living condition.

As a momentous inducer for inflammation-related pathological processes, tobacco is known to correlate with a variety of systemic disorders.[49] It is also one of the foremost risk factors for both COPD and PD.[5 10] From the epidemiological perspective, tobacco smoking is a confounder with spuriously inflated effect on the relationship between PD and systemic diseases.[49] To investigate the true association between PD and COPD, it is of great importance to rigorously control the confounding effect of smoking, which means initiating research in never smokers. However, the majority of former studies failed to do that. After a wide search, only six studies focusing on never smokers were found, which unanimously indicated PD was not related with the risk of COPD. We also observed a decreased intensity of the association between both diseases with the increase of control for smoking. Therefore, it could be too early to make a certain conclusion on the COPD-PD relationship. Although interventional studies revealed that periodontal treatment reduced the risk of AE, a number of problems existed, including small sample size, limited study quality and unclear history of smoking or medication during the follow-up.[17 18] For example, compared with control subjects, patients in treatment groups may reduce smoking intentionally, which could spuriously enhance the positive effect

of periodontal treatment. Consequently, future researches need to take these problems into account.

It is worth noting that, another possibility that smoking acts as an effect modifier in the COPD-PD relationship should not be ignored. Two observational studies performing stratified analyses concerning smoking status found that the strong correlation of PD with the risk of COPD was restricted to smokers.[15 20] However, this was not revealed in the present study, thus more investigations in smokers and never smokers respectively are required.

Besides, current evidence has demonstrated several issues to be addressed in future study, comprising inconsistent diagnostic criteria of COPD and PD, the lack of prospective study design and differing adjustments for covariates. These contribute to substantial heterogeneity among studies.[45 46] The present study indicated the heterogeneity was partly explained by study design, diagnostic criteria of COPD and periodontal indexes used to assess PD. Significant association concerning PD and risk of COPD was only identified in subgroups lacking well designs, applying non-GOLD criteria or utilizing ABL as the measure of PD. For one thing, this demonstrated that, as sources of bias, observational study design and nonstandard diagnostic method for COPD could induce apparent deviations, confusing the true relationship between COPD and PD. For another, given undetermined diagnostic criteria for PD, discrepancies between ABL and other indexes cannot fully support the COPD-PD association. Notably, as a radiographic measure, although ABL has been widely considered to reflect

cumulative effects of periodontal attachment loss over time by chronic inflammation,[28] it does not only exist in PD. Non-periodontal diseases such as liver disorders, cancer and osteoporosis[50] could also result in ABL. As mentioned previously,[28] the observed correlation between ABL and risk of COPD may relate to those non-periodontal diseases.

Limitations

Several potential limitations should be taken into consideration when interpreting the present results. First, all included studies are observational, which are highly subject to selection bias and confounding by indication. Second, substantial heterogeneity was identified in current study, though we conducted subgroup and stratified analyses to partly explain and reduce it. As stated above, several problems leading to heterogeneity need to be addressed in future researches. Third, the number of studies on risk of COPD-related events was limited, thus the result needs to be carefully understood. Limited number of studies in subgroup and stratified analyses suggested more relevant studies with larger sample size are required. Fourth, although confounding effects of age and smoking were controlled by stratified analysis and statistical adjustment, other potential confounders such as gender, living condition and socioeconomic status[10] could also reduce reliability of the results. Fifth, obvious publication bias was noted in relevant meta-analyses,[45 46] including the present study. For the purpose of rapid review,[23] we only included articles in English. There could exist non-English publications and unpublished evidence, although we searched English-language studies as much as

possible. Finally, although smoking status and intensity were considered in subgroup analysis, information regarding tobacco content and chemical composition were not collected. This information is difficult to obtain, especially from self-reported smoking, leaving a residual smoking-related bias. Consequently, it is advisable to explore relationship between COPD and PD in never smokers.

CONCLUSION

In summary, this systematic review and meta-analysis suggests that PD is not associated with the risk of COPD and COPD-related events after strict adjustment for smoking, although the positive relationship between COPD and PD was previously reported. Large-scale prospective cohort studies with control of potential confounding factors are warranted to validate the present findings.

Abbreviations

ABL: Alveolar bone loss; AE: Acute exacerbation; BI: Bleeding index; CAL: Clinical attachment level; CI: Confident interval; COPD: Chronic obstructive pulmonary disease; GB: Gingival bleeding; GOLD: Global Initiative for Chronic Obstructive Lung Diseases; HR: Hazard ratio; OHI: Oral health index; OR: Odds ratio; PD: Periodontal disease; PLI: Plaque index; PPD: Probing pocket depth; RR: Relative risk.

Contributors LC and LL designed the study. MY and XL screened and selected relevant

studies. MY, RP and XL rated the study quality and extracted the data. MY, RP, XL and JP analyzed the data. All authors interpreted the data, and MY, RP, XL, JP drafted the paper. LC and LL critically revised the paper. All authors acknowledged and agreed with the format and content of the paper before submission for publication. LC and LL are the guarantors and responsible for the overall contents of this study.

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Competing interests None declared.

Patient and public involvement No patients or other individuals are involved in the design, conduct, reporting or dissemination of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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Figure legends

Figure 1 PRISMA flow diagram of study selection.

Figure 2 Forest plot of the risk of COPD by periodontal disease, subgroup analysis based

on adjusted by smoking status and intensity versus by smoking status only. Values more than one indicate a higher risk in patients with periodontal disease.

Figure 3 Forest plot of the risk of COPD-related events by periodontal disease. Values more than one indicate a higher risk in patients with periodontal disease.

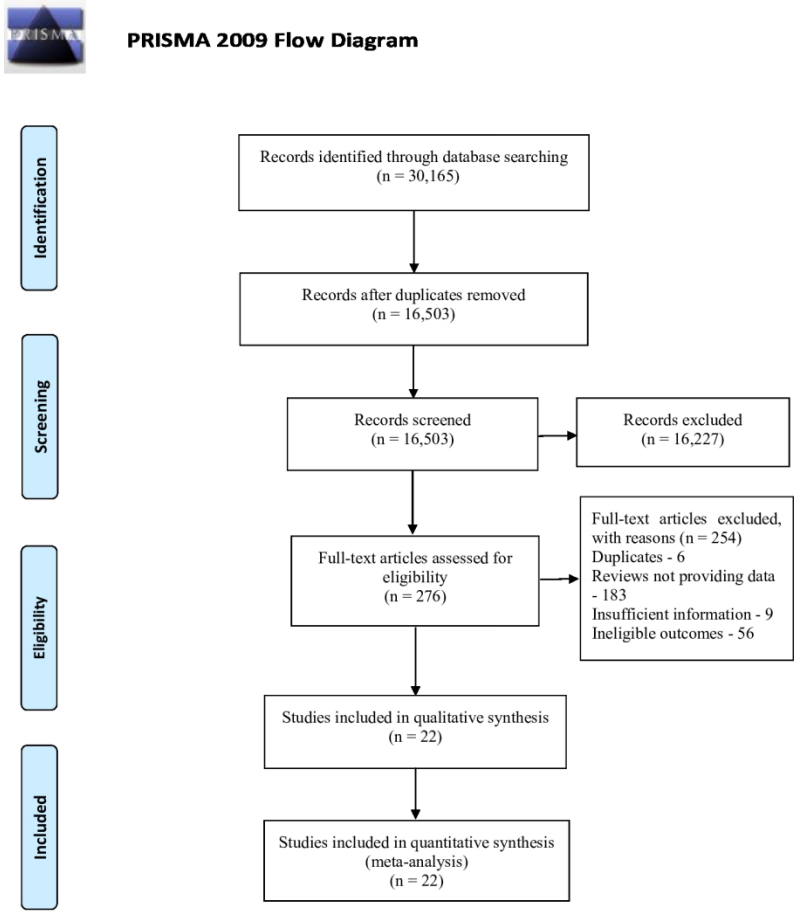

Figure 1 PRISMA flow diagram of study selection.

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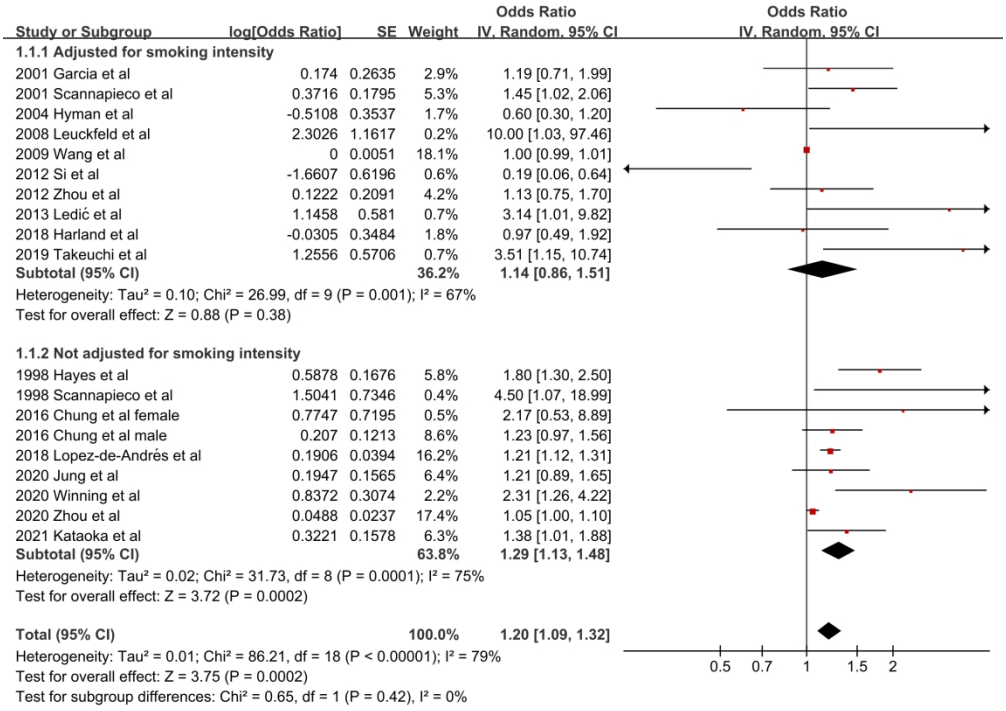

Figure 2 Forest plot of the risk of COPD by periodontal disease, subgroup analysis based on adjusted by smoking status and intensity versus by smoking status only. Values more than one indicate a higher risk in patients with periodontal disease.

536x384mm (118 x 118 DPI)

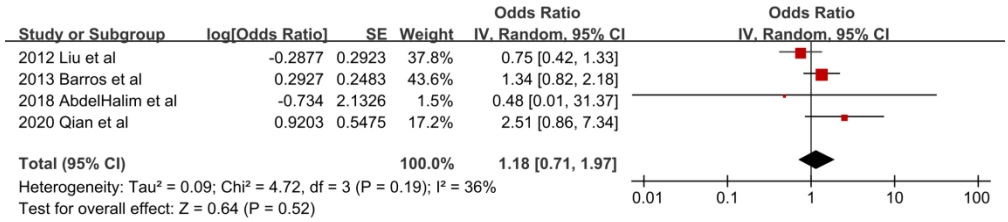

Figure 3 Forest plot of the risk of COPD-related events by periodontal disease. Values more than one indicate a higher risk in patients with periodontal disease.

497x118mm (118 x 118 DPI)

Table 1 Search strategy

Search term
1. (Oral health) OR (periodontal disease) OR (periodontal health) OR (periodontitis) OR (clinical attachment level) OR (alveolar bone loss) OR (probing depth)
2. (Respiratory disease) OR (chronic obstructive pulmonary disease) OR (pulmonary function) OR (airflow limitation)
3. 1 AND 2

Table 2 Adjustment for confounders of included studies

Study Author	Covariates in logistic regression multivariable model
Hayes *et al*[1]	Age, smoking, education, height
Scannapieco *et al*[2]	Smoking
Garcia *et al*[3]	Age, height, alcohol, education **(with stratified analysis on smoking)**
Leuckfeld *et al*[4]	Age, female gender, **pack years of smoking**
Liu *et al*[5]	Age, gender, BMI and smoking
Wang *et al*[6]	Age, gender, BMI **(with stratified analysis on smoking)**
Si *et al*[7]	Age, gender, occupation, educational level **(with stratified analysis on smoking)**
Zhou *et al*[8]	Age, gender, smoking, BMI, season **(with stratified analysis on smoking)**
Ledić *et al*[9]	Age, gender, **pack years of smoking**, BMI
Lopez-de-Andrés *et al*[10]	Age, gender, smoking, educational level, DM, obesity
Zhou *et al*[11]	Age, gender, smoking, BMI
Kataoka *et al*[12]	Age, smoking
Qian *et al*[13]	Age, sex, education levels, BMI, smoking, drinking, hypertension, DM
Barros *et al*[14]	Age, gender, Race, BMI, education, **pack years of smoking**, hypertension
Scannapieco *et al*[15]	Age, gender, **pack years of smoking**, Race, education, income, dental visits, alcohol, DM
Hyman *et al*[16]	Age, gender, Race, history of hypertension and heart attack, dental visit within 1 year, BMI, family income **(with stratified analysis on smoking)**
Chung *et al*[17]	Age, smoking, family income, education, alcohol, exercise, BMI, tooth brushing frequency, DM, number of natural teeth
Harland *et al*[18]	Age, number of present teeth, BMI, alcohol consumption, occupation, hypertension, DM **(with stratified analysis on smoking)**
Takeuchi *et al*[19]	Age, gender, **pack years of smoking**, occupation, DM, BMI, physical

	activity, alcohol intake, number of present teeth
Jung *et al*[20]	Age, gender, smoking, educational level, household income, alcohol consumption, periodontal status, number of missing teeth, oral health factors
Winning *et al*[21]	Age, gender, smoking, height, BMI, exercise, DM, hypertension, MI, education level, living condition
AbdelHalim *et al*[22]	Age, BMI, low-level of education, **pack years of smoking**, MRC, CAT, hospitalizations, COPD category (C-D), FVC (% predicted), FEV1 (% predicted), FEV1 / FVC (% predicted), MMEF (% predicted), PEF (% predicted), CRP

BMI, body mass index; CAT, chronic obstructive pulmonary disease assessment test; CRP, C-reactive protein; DM, diabetes mellitus; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; MI, myocardial infarction; MMEF, maximum mid-expiratory flow; MRC, Medical Research Council; PEF, peak expiratory flow.
Bold: the covariate of smoking intensity (duration and dose) or stratified analyses on smoking status.

Table 3 Quality assessment based on the Newcastle-Ottawa Scale

(A) Cohort study

Study Author	Selection				Comparability	Outcome			Total score
	Exposed cohort	Nonexposed cohort	Ascertainment of exposure	Outcome of interest		Assessment of outcome	Length of follow-up	Adequacy of follow-up	
Barros *et al*[14]	*	*	*	…	…	*	*	*	6
Takeuchi *et al*[19]	*	*	*	*	…	*	*	*	7
Qian *et al*[13]	…	*	*	…	…	*	*	…	4

(B) Case-control / cross-sectional study

Study Author	Selection				Comparability	Outcome			Total score
	Case definition	Representati--veness of the cases	Control selection	Control definition		Ascertainment of exposure	Same method of ascertainment for cases and controls	Non--response rate	
Hayes *et al*[1]	*	…	*	*	*	*	*	*	7
Scannapieco *et al*[2]	…	*	*	*	…	*	*	…	5
Garcia *et al*[3]	*	…	*	*	*	*	*	*	7
Scannapieco *et al*[15]	…	*	*	*	…	*	*	*	6
Hyman *et al*[16]	*	*	*	*	…	*	*	*	7
Heuckfeld *et al*[4]	*	…	…	*	…	*	*	*	5
Wang *et al*[6]	*	*	…	*	*	*	*	*	7
Liu *et al*[5]	*	*	…	*	*	*	*	*	7
Si *et al*[7]	*	*	…	*	*	*	*	*	7
Zhou *et al*[8]	*	*	…	*	*	*	*	*	7
Ledić *et al*[9]	*	*	…	*	*	*	*	*	7
Chung *et al*[17]	*	*	*	*	…	*	*	*	7
AbdelHalim *et al*[22]	*	…	…	*	…	*	*	*	5
Harland *et al*[18]	*	*	…	*	…	*	*	*	6
Lopez-de-Andrés *et al*[10]	…	*	*	*	*	…	*	*	6
Jung *et al*[20]	…	*	*	*	…	*	*	*	6
Winning *et al*[21]	*	*	*	*	…	*	*	*	7
Zhou *et al*[11]	*	*	…	…	**	*	*	*	7
Kataoka *et al*[12]	*	*	*	*	…	*	*	*	7

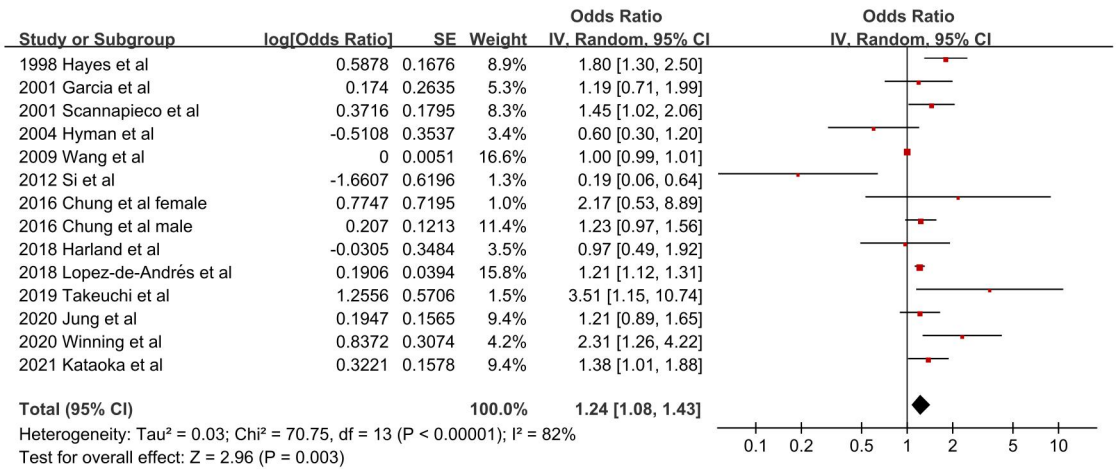

Figure 1 Sensitivity analysis on studies with larger sample size (N ≥500). Values more than one indicate a higher risk of COPD in patients with PD.

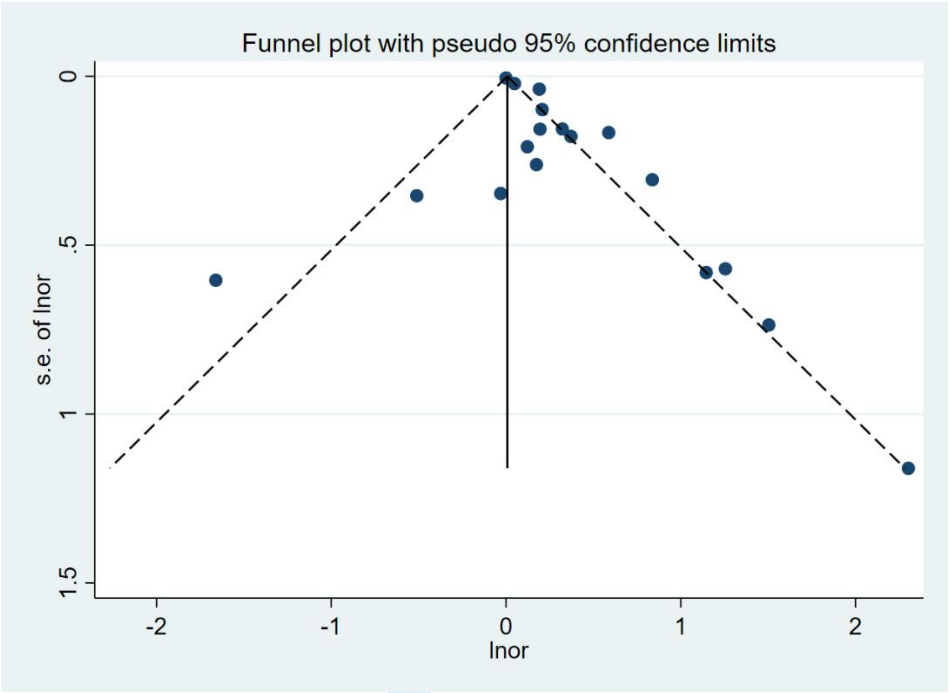

Figure 2 Funnel plot for the risk of COPD, with pseudo 95% confidence limits.

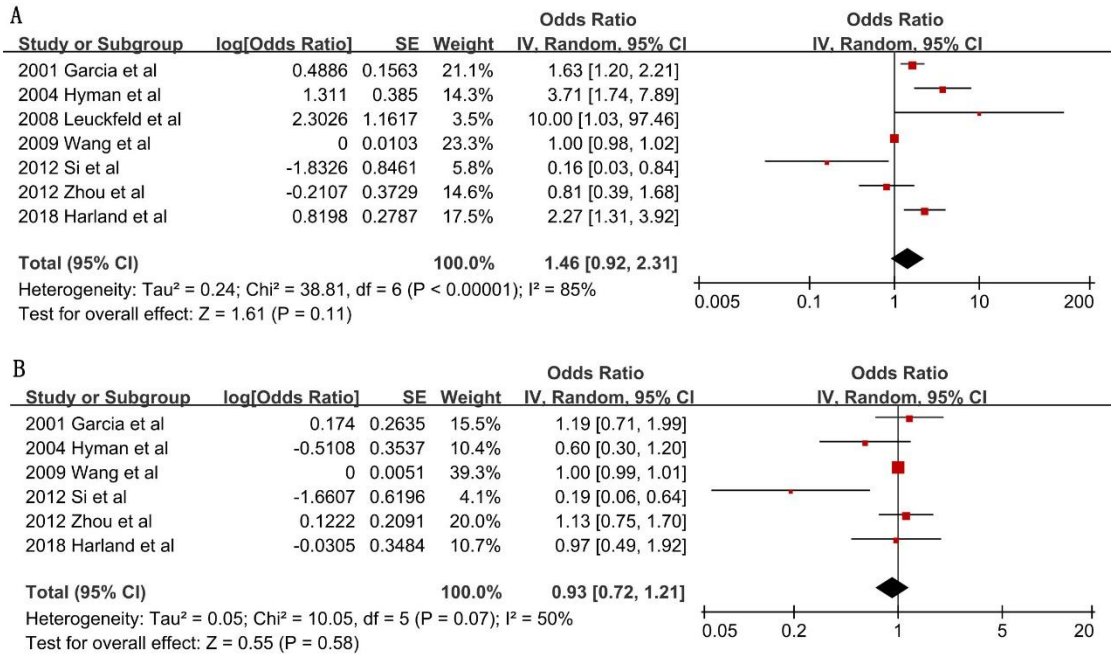

Figure 3 Forest plot of the risk of COPD by periodontal disease. **A** in smokers and **B** in never smokers. Values more than one indicate a higher risk in patients with periodontal disease.

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PRISMA 2009 Checklist

Section/topic	Item No	Checklist item	Reported on Page Number/Line Number	Reported on Section/Paragraph
TITLE				
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1 / Line 2,3	Title page
ABSTRACT				
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2,3 / Line 28-52	Abstract
INTRODUCTION				
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 4,5 / Line 69-103	Introduction / Paragraph 1-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 5 / Line 103-107	Introduction / Paragraph 4
METHODS				
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Page 5,6 / Line 110-112	Methods / Paragraph 1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 6 / Line 118-124	Methods / Paragraph 2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 6 / Line 115,116	Methods / Paragraph 2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 6 / Line 116-118	Methods / Paragraph 2 Supplemental table 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 6 / Line 125-131	Methods / Paragraph 3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 7 / Line 134,135	Methods / Paragraph 4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 7 / Line 135-140	Methods / Paragraph 4

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 7 / Line 142-147	Methods / Paragraph 4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 7 / Line 150	Methods / Paragraph 5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 8 / Line 156-160	Methods / Paragraph 5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 8 / Line 171-173	Methods / Paragraph 7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 8 / Line 161-172	Methods / Paragraph 6,7
RESULTS				
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 9 / Line 182-189	Results / Paragraph 1; Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 9-12 / Line 190-224	Results / Paragraph 2-4; Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 12 / Line 226-232	Results / Paragraph 5; Supplemental table 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 12,13 / Line 234-244	Results / Paragraph 6; Figure 2 and 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 12 / Line 235-237 Page 15 / Line 273-275	Results / Paragraph 6,8; Figure 2 and 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 12,13 / Line 238-239; 242-244	Results / Paragraph 6; Supplemental figure 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page 12 / Line 239-241; Page 13-15 / Line 245-268	Results / Paragraph 6-8; Table 2, Figure 2
DISCUSSION				
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 15-18 / Line 278-344	Discussion / Paragraph 1-5
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 18,19 / Line 346-366	Discussion / Paragraph 6
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 19 / Line 368-373	Conclusion / Paragraph 1

FUNDING				
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 20 / Line 389,390	Funding

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The association between chronic obstructive pulmonary disease and periodontal disease: a systematic review and meta-analysis

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Title Page

Title: The association between chronic obstructive pulmonary disease and periodontal disease: a systematic review and meta-analysis

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The association between chronic obstructive pulmonary disease and periodontal disease: a systematic review and meta-analysis

ABSTRACT

Objectives Studies have suggested contradictory results on the relationship between chronic obstructive pulmonary disease (COPD) and periodontal disease (PD). The aim of this study was to determine whether PD increased the risk of COPD and COPD-related clinical events.

Design Systematic review and meta-analysis.

Data sources PubMed, Ovid EMBASE and Ovid CENTRAL were searched from inception to 22 February 2023.

Eligibility criteria for studies We included trials and observational studies evaluating association of PD with the risk of COPD or COPD-related events (exacerbation and mortality), with statistical adjustment for smoking.

Data extraction and synthesis Two investigators independently extracted data from selected studies using a standardized Excel file. Quality of studies was evaluated using the Newcastle-Ottawa Scale. Odds ratio (OR) with 95% confident interval (CI) was pooled in a random-effect model with inverse variance method.

Results 22 observational studies with 51704 participants were included. Pooled analysis

of 18 studies suggested that PD was weakly associated with the risk of COPD (OR 1.20, 95% CI 1.09 to 1.32). However, in stratified and subgroup analyses, with strict adjustment for smoking, PD no longer related to the risk of COPD (adjusting for smoking intensity: OR 1.14, 95% CI 0.86 to 1.51; smokers only: OR 1.46, 95% CI 0.92 to 2.31; never smokers only: OR 0.93, 95% CI 0.72 to 1.21). Moreover, PD did not increase the risk of COPD-related exacerbation or mortality (OR 1.18, 95% CI 0.71 to 1.97) in the pooled result of four studies.

Conclusions This study demonstrates PD confers no risk for COPD and COPD-related events when strictly adjusted by smoking. Large-scale prospective cohort studies with control of potential confounding factors are warranted to validate the present findings.

STRENGTHS AND LIMITATIONS OF THIS STUDY

1. This systematic review and meta-analysis only included studies with statistical adjustment for smoking, to adequately control the confounding by smoking.
2. We defined "periodontal disease" as a wide variety of periodontal abnormalities according to clinical and radiographic assessments, which is not limited to periodontitis.
3. The language was restricted to English when conducting study searching, thus some literatures might have been missed.
4. Clinical heterogeneity and publication bias compromised the evidence strength of this study, although subgroup and stratified analyses were performed.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death, resulting in enormous economic burden.[1] Commonly, COPD coexists with a variety of disorders, called comorbidities, which play significant roles in the progression and prognosis of COPD.[2 3] Understanding the COPD-comorbidities relationship has been a momentous prerequisite for optimizing disease prevention and management strategies.[2 3]

Given ageing and widespread use of inhaled corticosteroids in COPD, periodontal disease (PD) has been a common comorbidity of COPD.[4] It is a chronic inflammatory condition of tissues surrounding and supporting the teeth, including gingiva, bone and ligament,[5] with the prevalence estimates over 10% around the world and especially prevalent in elderly individuals.[6] To date, diagnosis and assessment of PD are mostly based on periodontal measurements including clinical attachment level (CAL), probing pocket depth (PPD) and alveolar bone loss (ABL).[5] They are primary clinical manifestations of PD, reflecting the extent of periodontal tissue destruction.[5]

Based on the nature of inflammation,[5 7] mounting evidence has shed light on the association between PD and development of COPD.[8 9] Currently three points are proposed. First, they share the same risk factors, such as age, gender, smoking and socioeconomic status.[2 10] Second, they have similar pathogenetic mechanisms. Both diseases are characterized by host susceptibility to environmental factors, immune

overreaction, oxidative stress and production of pro-inflammatory cytokines.[7 8] Most importantly, neutrophilic inflammation plays a key role in both diseases.[8 11] Third, oral bacteria released from the dental plaque in PD could trigger progression and acute exacerbation (AE) of COPD.[12 13]

Meanwhile, epidemiological evidence has indicated that PD increases risk of COPD[11 14 15] and COPD-related events.[13 16] Scannapieco *et al* revealed a 4.5-fold increased risk of COPD in patients with PD, compared with those without.[14] A dose-response relationship was further implied between PD severity and lung function.[15] Among patients with both diseases, COPD-related AE and mortality also significantly linked with periodontal status.[13 16] Periodontal therapy, such as scaling and root planing treatment, may ameliorate lung function and decrease frequency of AE in COPD with chronic periodontitis.[17 18] However, there were some other studies revealing opposite results, resulting in a long-standing controversy.[19-21] It is worth noting that, parameters used to determine PD apparently varied across studies, and these studies also failed to adequately control for confounders, especially smoking, the most important confounder for the COPD-PD relationship. Therefore, to provide the latest and most convincing evidence, we systematically reviewed current available literature to investigate whether PD increases the risk of COPD. The secondary objective was to evaluate the association between PD and the risk of COPD-related events. Subgroup and stratified analyses were also conducted to adjust for the confounding by smoking.

METHODS

This systematic review and meta-analysis was conducted and reported in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.[22]

Search strategy and selection criteria

We searched PubMed, Ovid EMBASE and Ovid Cochrane Central Register of Controlled Trials for records evaluating association between COPD and PD, from inception to 22 February 2023. The full search strategy was described in **online supplemental table 1**. The language was restricted to English, for the purpose of rapid review.[23] Studies meeting the following criteria were included: (1) adult participants (≥18 years); (2) original studies with randomized controlled trial (RCT), cohort, case-control or cross-sectional study designs; (3) presenting clear diagnostic or assessment criteria for COPD and PD; (4) evaluating association between PD and the risk of COPD, or risk of COPD-related events (AE and mortality), with statistical adjustment for smoking, and providing the adjusted odds ratio (OR), relative risk (RR) or hazard ratio (HR) for the risk of COPD, AE and mortality in relation to PD. Given the inconsistent diagnostic criteria of PD across studies, we predefined PD as a wide variety of periodontal abnormalities according to clinical and radiographic assessments.[24]

According to the inclusion criteria, two independent investigators (MY and XL) performed systematical search, screened titles and abstracts of all retrieved studies to

exclude duplicate or irrelevant records. For articles requiring further assessment, full-text reviews were carried out and references of retrieved articles and relevant reviews were also manually checked to identify additional eligible studies. Disagreements were resolved by discussion between the two reviewers or with the help of the third investigator (RP).

Data extraction and quality assessment

Two investigators (MY and RP) independently extracted data from selected studies using a standardized Excel (Microsoft Corporation) file. The following information was extracted: author, year of publication, country, study design, number of subjects (COPD and non-COPD), demographic characteristics of participants, diagnostic criteria for PD and COPD, definition of COPD-related AE and mortality, adjusted OR, RR or HR for the risk of COPD, AE and mortality in relation to PD, as well as adjustment for confounders. The primary outcome was the risk of COPD. Secondary outcome was the risk of COPD-related adverse events, including AE and mortality. Quality of studies was independently evaluated using the Newcastle-Ottawa Scale[25] by two investigators (MY and XL). A score of ≥6 was considered a low risk while < 6 a high risk of bias. Both case-control and cohort studies had a maximum score of 9. Cross-sectional study was regarded as case-control study when performing quality assessment. Discrepancies regarding data extraction and quality assessment were resolved through discussion and consensus.

Data analysis

The final pooled estimate was expressed as OR with 95% confident interval (CI). Considering CAL, ABL and PPD have been regarded as the primary parameters for PD,[24 26] where more than one adjusted estimate was shown in the paper, we preferentially used the estimate regarding these parameters (CAL > ABL > PPD), or the estimate being better adjusted for tobacco smoking (never smokers > adjusting for smoking intensity [duration and dose] > adjusting for smoking status), or the estimate regarding more severe PD, where available. For case-control and cross-sectional studies, we estimated the OR whereas for cohort studies we estimated the RR or HR. The random-effect model with inverse variance method were applied due to potential heterogeneity resulting from methodological differences. Heterogeneity across studies was identified with the I^2 statistic. I^2 statistic >50% indicated significant heterogeneity.

To explore heterogeneity, subgroup analyses were conducted based on study design (case-control, cross-sectional and cohort studies), geographical location (Asia, North America, Europe), assessment of PD (CAL, ABL and PPD), definition of COPD (Global Initiative for Chronic Obstructive Lung Diseases, GOLD and non-GOLD criteria) and adjustment for smoking intensity (dose and duration of smoking). To better control the confounding effect of smoking, stratified analyses were performed in smokers and never smokers respectively.

To test the robustness of study findings, we performed sensitivity analysis on studies

with relatively large sample size (≥500 participants), which tended to be more representative of the general population and with smaller bias in the overall estimates in meta-analyses.[27] Additionally, influence of a single study on the overall pooled estimate was tested by omitting one study in each turn. Publication bias was visually assessed using a funnel plot and quantitatively evaluated by the Egger's tests. P <0.05 was considered statistically significant. All statistical analyses were performed using Stata version 16 (StataCorp) and Review manager version 5.4 (Cochrane Collaboration).

Patient and public involvement

No patients or other individuals are involved in the design, conduct, reporting or dissemination of this research.

RESULTS

Study selection and characteristics

A total of 30165 records were identified from the initial database search. 13662 records were removed for duplicates, and 16227 records were excluded after titles and abstracts screening because of irrelevant content and animal studies. The remaining 276 full-text articles were identified for eligibility, of which 254 were excluded for reasons including duplicates (six studies), reviews (183 studies), insufficient information (nine studies) and ineligible designs and outcomes (56 studies). Finally, 22 studies[14-16 19-21 28-43] were included in the review. The selection process is shown in **figure 1**.

The characteristics of included 22 studies were shown in **table 1**. The number of participants was 51704 and there were 9973 (18.9%) patients with COPD. The mean age of patients with COPD was between 45.1 and 83.1 years while the control subjects was between 42.2 and 80.3 years. These studies were published between 1998 and 2021. The sample size ranged from 120 to 13792. Nine studies were case-control studies[15 19 28 29 32 33 36 40 42] and 10 studies were cross-sectional studies,[14 20 30 31 34 35 38 39 41 43] only three studies with a cohort study design.[16 21 37] Additionally, 11 studies were conducted in Asia,[15 16 19 32 34 35 37 38 40-42] while six studies in the North America,[14 20 21 28-30] four studies in Europe[31 33 36 39] and one study in Africa.[43]

Table 1 Characteristics of included studies

Year / Study	Design	Location	No. COPD / Control subjects	Age (COPD / Control subjects)	Assessment of PD	Assessment of COPD
1998 Hayes *et al*[28]	Case-control	United States	261/857	45.1±9.7/42.2±9.1	ABL	FEV_1
1998 Scannapieco *et al*[14]	Cross-sectional	United States	77/309	NA	OHI	Self-reported
2001 Garcia *et al*[29]	Case-control	United States	279/833	NA	ABL, PPD	FEV_1
2001 Scannapieco *et al*[30]	Cross-sectional	United States	810/12,982	51.2±17.9/43.9±17.7	CAL, GB	Self-reported
2004 Hyman *et al*[20]	Cross-sectional	United States	993/6,632	62.3±14.1/47.4±14.2	CAL	GOLD
2008 Leuckfeld *et al*[31]	Cross-sectional	Norway	130/50	54.9±4.9/47.0±9.8	ABL	GOLD
2009 Wang *et al*[19]	Case-control	China	306/328	63.9±9.8/63.3±9.0	CAL, PLI	GOLD
2012 Liu *et al*[42]	Case-control	China	183/209*	64.3±10.1/63.6±9.7	CAL, PPD, BI	GOLD

2012 Si *et al*[15]	Case-control	China	581/438	63.9±9.4/62.8±9.5	CAL, ABL, PPD, PLI, BI	GOLD
2012 Zhou *et al*[32]	Case-control	China	193/181	63.6±10.3/62.1±9.1	CAL, ABL, PPD, PLI, BI	GOLD
2013 Barros *et al*[21]	Cohort	United States	399/1,236§	63.9±5.7/66.0±5.1	CAL, PPD	GOLD
2013 Ledić *et al*[33]	Case-control	Croatia	93/43	65.8±9.7/62.1±11.9	CAL	GOLD
2016 Chung *et al*[34]	Cross-sectional	Korea	697/5,181	64.3±0.2/54.6±0.1	PPD, GB	GOLD
2018 AbdelHalim *et al*[43]	Cross-sectional	Egypt	134/116*	56.8±10.4/55.3±9.1	CAL, PPD, BI, PLI, OHI	GOLD
2018 Harland *et al*[35]	Cross-sectional	Japan	149/1,325	61.3±9.1/54.5±8.7	PPD	GOLD
2018 Lopez-de-Andrés *et al*[36]	Case-control	Spain	2,699/2,699	63±14/61±14	Self-reported	Self-reported
2019 Takeuchi *et al*[37]	Cohort	Japan	22/878	NA	CAL, PPD	GOLD
2020 Jung *et al*[38]	Cross-sectional	Korea	1,134/6,585	62.6±0.4/53.6±0.2	PPD	FEV_1 / FVC
2020 Qian *et al*[16]	Cohort	China	23‡/NA	83.1±4.8/80.3±3.7	ABL	NR
2020 Winning *et al*[39]	Cross-sectional	Sweden	86/740	NA	ABL	GOLD
2020 Zhou *et al*[40]	Case-control	China	60/60	63.1±10.1/60.0±9.4	CAL, PLI	GOLD
2021 Kataoka *et al*[41]	Cross-sectional	Japan	464/249	54.1±9.4/NA	PPD	GOLD

Continuous data are presented as mean ± standard deviation (SD) unless otherwise indicated.

*No. COPD subjects with frequent exacerbation (≥2 exacerbations in the last year)/Infrequent exacerbation (< 2 exacerbations in the last year).

§No. COPD subjects with events (hospitalization for exacerbation or COPD-related death) in the 5-year follow-up visit/COPD subjects without events in the 5-year follow-up visit.

‡No. COPD-related mortality in a follow-up visit more than 5 years.

ABL, alveolar bone loss; BI, bleeding index; CAL, clinical attachment level; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GB, gingival bleeding; GOLD, Global Initiative for Chronic Obstructive Lung

Disease; NA, not available; OHI, oral health index; PD, periodontal disease; PLI, plaque index; PPD, probing pocket depth.

All included articles performed multivariable analyses, in which the risk of COPD, or risk of COPD-related events (AE or mortality), was identified as the dependent variable and PD as the independent variable. Controlling for confounding by smoking included stratification (smokers and never smokers) or covariance adjustment in multivariable models (the degree of control: never smokers > adjusting for smoking intensity [duration and dose] > adjusting for smoking status).

The adjustment for confounders of included studies was detailedly presented in **online supplemental table 2**. 16 articles reported the adjusted ORs and 4 reported adjusted RRs, two studies reporting HRs. Definition of COPD comprised the GOLD criteria,[2] FEV_1 <65% of predicted volume, having a history of chronic bronchitis and / or emphysema, self-reported and others. Across almost all studies, periodontal examination was conducted by experienced or trained dentists. Periodontal parameters used for diagnosis of PD were CAL, ABL, PPD, gingival bleeding (GB), bleeding index (BI), plaque index (PLI) and oral health index (OHI). The detailed diagnostic criteria applied by included studies were presented in the **online supplemental table 3**.

Assessment of bias

Based on the Newcastle-Ottawa Scale, quality assessment for the 22 studies was shown in **online supplemental table 4**. Among them, 18 studies[15 19-21 28-30 32-42] were rated as high quality with a total score of ≥6 whereas four studies[14 16 31 43] as a score of <6,

indicating a high risk of bias. The main reasons for lower scores were selection bias (representativeness of sample population), especially for control groups and comparability of cases and control subjects.

Primary outcome

18 studies[14 15 19 20 28-41] provided data for the risk of COPD in relation to PD. Quantitative analysis demonstrated that after adjusting for smoking status, PD increased the risk of COPD, but only by a ratio of 1.20 (95% CI 1.09 to 1.32, p=0.0002, I^2=79%) (**figure 2**). Further exclusion of any single study did not materially alter the overall pooled OR, with a range from 1.17 (95% CI 1.06-1.28) to 1.28 (95% CI 1.12-1.46). Sensitivity analysis limited to studies with larger sample size (≥500)[15 19 20 28-30 34-39 41] revealed similar results (OR 1.24, 95% CI 1.08 to 1.43, p=0.003, I^2=82%) (**online supplemental figure 1**). However, significant publication bias was noted by visual inspections of the funnel plot (**online supplemental figure 2**) and the Egger' s test for small study effects (bias coefficient 1.49, 95% CI 0.44 to 2.55, p=0.008).

Subgroup analyses indicated that assessment parameters of PD (p=0.02), study design (p=0.05) and diagnosis of COPD (p=0.05) were the potential main causes of heterogeneity (**table 2**). Moreover, there were several findings in subgroup analyses. First, after further controlling for smoking intensity, PD did not increase the risk of COPD (OR 1.14, 95% CI 0.86 to 1.51, p=0.38, 10 studies[15 19 20 29-33 35 37]), similar to the subgroup applying a GOLD criterion (OR 1.10, 95% CI 1.00 to 1.22, p=0.06, 12

studies[15 19 20 31-35 37 39-41]). Second, among the parameters of CAL, ABL and PPD, only subgroup using the parameter of ABL showed a significant association between PD and the risk of COPD (OR 1.98, 95% CI 1.32 to 2.97, p=0.001, six studies[15 28 29 31 32 39]). Third, in the three geographical locations (Asia, North America and Europe), only the subgroup of Europe indicated that PD increased the risk of COPD (OR 2.05, 95% CI 1.07 to 3.95, p=0.03, four studies[31 33 36 39]).

Table 2 Subgroup analyses regarding the risk of COPD

Subgroups	No. Studies	No. Participants /Cases	OR value (95% CI)	P value	I^2, %
Adjusted for smoking intensity[a]					
Yes	10	27,246 / 3,556	1.14 (0.86-1.51)	0.38	67
No	8	22,158 / 5,478	1.29 (1.13-1.48)	**0.0002**	75
Assessment of PD					
CAL	8	24,600 / 3,058	1.04 (0.96-1.14)	0.33	75
ABL	6	4,629 / 1,530	1.98 (1.32-2.97)	**0.001**	56
PPD	8	19,189 / 3,519	1.16 (0.89-1.51)	0.27	63
Geographical location					
Asia	9	18,831 / 3,606	1.07 (0.99-1.17)	0.08	65
North America	5	24,033 / 2,420	1.37 (0.93-2.01)	0.11	63
Europe	4	6,540 / 3,008	2.05 (1.07-3.95)	**0.03**	71

Assessment of COPD					
GOLD	12	19,879 / 3,774	1.10 (1.00-1.22)	0.06	71
Non-GOLD	6	29,525 / 5,260	1.35 (1.14-1.61)	**0.0007**	46
Study design					
Case-control	8	9,911 / 4,472	1.12 (1.01-1.24)	**0.03**	86
Cross-sectional	9	38,593 / 4,540	1.34 (1.08-1.66)	**0.007**	45
Cohort	1	878 / 22	3.51 (1.15-10.74)	**0.03**	-

[a]Duration and dose of smoking.

ABL, alveolar bone loss; CAL, clinical attachment level; CI, confident interval; GOLD, Global Initiative for Chronic Obstructive Lung Disease; OR, odds ratio; PD, periodontal disease; PPD, probing pocket depth.

Bold: subgroups with positive results.

Stratified analyses regarding smoking status revealed that PD did not increase the risk of COPD whether in smokers (OR 1.46, 95% CI 0.92 to 2.31, p=0.11, seven studies[15 19 20 29 31 32 35]) or never smokers (OR 0.93, 95% CI 0.72 to 1.21, p=0.58, six studies[15 19 20 29 32 35]) (**online supplemental figure 3**).

Secondary outcome

Only four studies evaluated the risk of COPD-related AE or mortality.[16 21 42 43] Definition of AE was acute deterioration in clinical presentations according to the recommendation in GOLD guideline.[21 42 43] Pooled analysis showed that after adjusting for smoking status, PD did not increase the risk of COPD-related AE or mortality (OR 1.18, 95% CI 0.71 to 1.97, p=0.52, I^2=36%) (**figure 3**).

DISCUSSION

This systematic review and meta-analysis identified 22 observational studies to investigate the association between COPD and PD. The results indicated that, after strictly adjusting for confounding by smoking, PD did not increase the risk of COPD, as well as the risk of COPD-related AE or mortality. Moreover, these findings were consistent across the subgroup and stratified analyses.

To the best of our knowledge, this is the first and largest meta-analysis investigating the association of PD with the risk of COPD and its clinical events, with adequately controlling the confounding effect of smoking. Besides, nearly all included articles were adjusted for age, except the study by Scannapieco *et al*.[14] Prior publications have suggested that PD significantly increased the risk of COPD and COPD-related events. However, the majority of studies have non-negligible flaws, such as only performing univariate analyses, not controlling the confounding by smoking, and using parameters with relatively low specificity for determining PD.[13 24 43] In the present study, to define PD as accurately as possible, we preferentially extracted data concerning the parameters of CAL, ABL and PPD rather than PLI, OHI or remaining teeth. CAL, ABL and PPD are clinical measurements reflecting the destruction of periodontal tissues and momentous parameters for diagnosis of PD.[24 44] Meanwhile, compared with previous meta-analyses, we enrolled more studies, applied more rigorous screening criteria and most importantly, revealed opposite results. In the meta-analyses with incomplete

adjustment for smoking, OR value for the risk of COPD ranged from 1.28 to 2.08.[45-48] However, our findings were similar to studies conducted in never smokers,[15 19 20 29 32 35] which showed that PD conferred no risk for COPD. Additionally, pooled analyses regarding parameters of CAL, ABL and PPD revealed that PD also did not increase the risk of COPD-related AE or mortality. These findings demonstrate that previously reported correlation between PD and COPD may be results of flawed study design, confounding by smoking and even other factors, such as age and living condition.

As a momentous inducer for inflammation-related pathological processes, tobacco is known to correlate with a variety of systemic disorders.[49] It is also one of the foremost risk factors for both COPD and PD.[5 10] From the epidemiological perspective, tobacco smoking is a confounder with spuriously inflated effect on the relationship between PD and systemic diseases.[49] To investigate the true association between PD and COPD, it is of great importance to rigorously control the confounding effect of smoking, which means initiating research in never smokers. However, the majority of former studies failed to do that. After a wide search, only six studies focusing on never smokers were found, which unanimously indicated PD was not related with the risk of COPD. We also observed a decreased intensity of the association between both diseases with the increase of control for smoking. Therefore, it could be too early to make a certain conclusion on the COPD-PD relationship. Although interventional studies revealed that periodontal treatment reduced the risk of AE, a number of problems existed, including small sample size, limited study quality and unclear history of smoking or medication during the

follow-up.[17 18] For example, compared with control subjects, patients in treatment groups may reduce smoking intentionally, which could spuriously enhance the positive effect of periodontal treatment. Consequently, future researches need to take these problems into account.

It is worth noting that, another possibility that smoking acts as an effect modifier in the COPD-PD relationship should not be ignored. Two observational studies performing stratified analyses concerning smoking status found that the strong correlation of PD with the risk of COPD was restricted to smokers.[15 20] However, this was not revealed in the present study, thus more investigations in smokers and never smokers respectively are required.

Besides, current evidence has demonstrated several issues to be addressed in future study, comprising inconsistent diagnostic criteria of COPD and PD, the lack of prospective study design and differing adjustments for covariates. These contribute to substantial heterogeneity among studies.[45 46] The present study indicated the heterogeneity was partly explained by study design, diagnostic criteria of COPD and PD. Significant association concerning PD and risk of COPD was only identified in subgroups lacking well designs, applying non-GOLD criteria or utilizing ABL as the measure of PD. For one thing, this demonstrated that, as sources of bias, observational study design and nonstandard diagnostic method for COPD could induce apparent deviations, confusing the true relationship between COPD and PD. For another, given undetermined diagnostic criteria for PD, discrepancies between ABL and other indexes

cannot fully support the COPD-PD association. Notably, as a radiographic measure, although ABL has been widely considered to reflect cumulative effects of periodontal attachment loss over time by chronic inflammation,[28] it does not only exist in PD. Non-periodontal diseases such as liver disorders, cancer and osteoporosis[50] could also result in ABL. As mentioned previously,[28] the observed correlation between ABL and risk of COPD may relate to those non-periodontal diseases.

Limitations

Several potential limitations should be taken into consideration when interpreting the present results. First, all included studies are observational, which are highly subject to selection bias and confounding by indication. Second, substantial heterogeneity was identified in current study, though we conducted subgroup and stratified analyses to partly explain and reduce it. As stated above, several problems leading to heterogeneity need to be addressed in future researches. Third, the number of studies on risk of COPD-related events was limited, thus the result needs to be carefully understood. Limited number of studies in subgroup and stratified analyses suggested more relevant studies with larger sample size are required. Fourth, although confounding effects of age and smoking were controlled by stratified analysis and statistical adjustment, other potential confounders such as gender, living condition and socioeconomic status[10] could also reduce reliability of the results. Fifth, obvious publication bias was noted in relevant meta-analyses,[45 46] including the present study. For the purpose of rapid review,[23] we

only included articles in English. There could exist non-English publications and unpublished evidence, although we searched English-language studies as much as possible. Finally, although smoking status and intensity were considered in subgroup analysis, information regarding tobacco content and chemical composition were not collected. This information is difficult to obtain, especially from self-reported smoking, leaving a residual smoking-related bias. Consequently, it is advisable to explore relationship between COPD and PD in never smokers.

CONCLUSION

In summary, this systematic review and meta-analysis suggests that PD is not associated with the risk of COPD and COPD-related events after strict adjustment for smoking, although the positive relationship between COPD and PD was previously reported. Large-scale prospective cohort studies with control of potential confounding factors are warranted to validate the present findings.

Abbreviations

ABL: Alveolar bone loss; AE: Acute exacerbation; BI: Bleeding index; CAL: Clinical attachment level; CI: Confident interval; COPD: Chronic obstructive pulmonary disease; GB: Gingival bleeding; GOLD: Global Initiative for Chronic Obstructive Lung Diseases; HR: Hazard ratio; OHI: Oral health index; OR: Odds ratio; PD: Periodontal disease; PLI: Plaque index; PPD: Probing pocket depth; RR: Relative risk.

Contributors LC and LL designed the study. MY and XL screened and selected relevant studies. MY, RP and XL rated the study quality and extracted the data. MY, RP, XL and JP analyzed the data. All authors interpreted the data, and MY, RP, XL, JP drafted the paper. LC and LL critically revised the paper. All authors acknowledged and agreed with the format and content of the paper before submission for publication. LC and LL are the guarantors and responsible for the overall contents of this study.

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Figure legends

Figure 1 PRISMA flow diagram of study selection.

Figure 2 Forest plot of the risk of COPD by periodontal disease, subgroup analysis based

on adjusted by smoking status and intensity versus by smoking status only. Values more than one indicate a higher risk in patients with periodontal disease.

Figure 3 Forest plot of the risk of COPD-related events by periodontal disease. Values more than one indicate a higher risk in patients with periodontal disease.

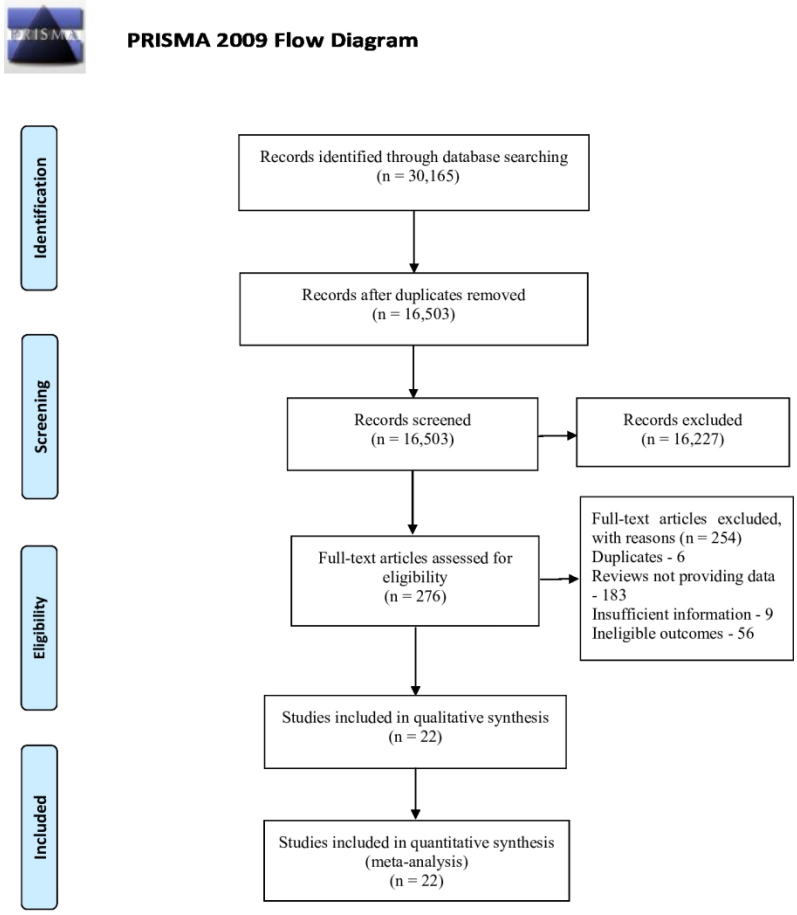

Figure 1 PRISMA flow diagram of study selection.

215x279mm (200 x 200 DPI)

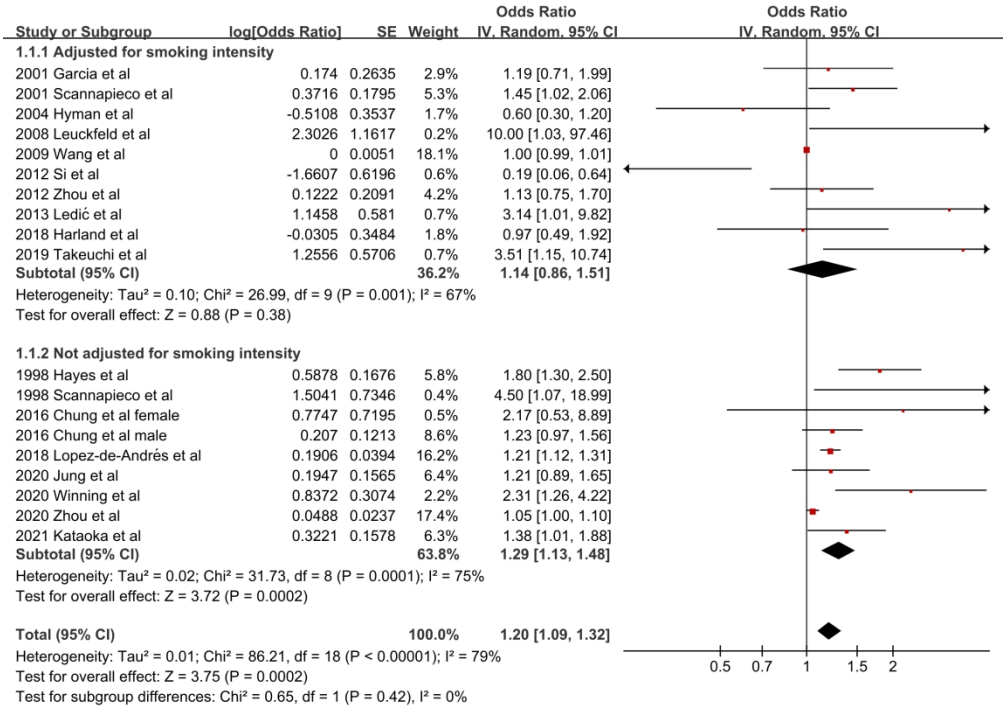

Figure 2 Forest plot of the risk of COPD by periodontal disease, subgroup analysis based on adjusted by smoking status and intensity versus by smoking status only. Values more than one indicate a higher risk in patients with periodontal disease.

536x384mm (118 x 118 DPI)

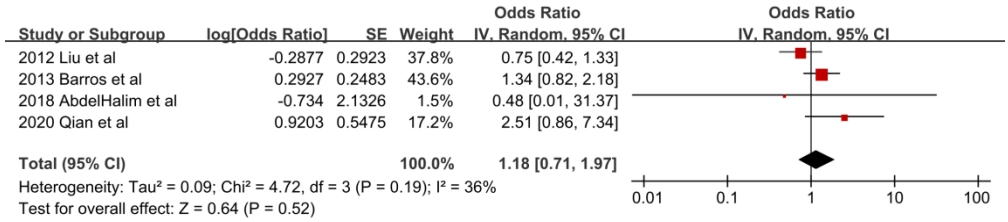

Figure 3 Forest plot of the risk of COPD-related events by periodontal disease. Values more than one indicate a higher risk in patients with periodontal disease.

497x118mm (118 x 118 DPI)

Table 1 Search strategy

Database 1: PubMed

(("oral health"[MeSH Terms] OR ("oral"[All Fields] AND "health"[All Fields]) OR "oral health"[All Fields] OR ("periodontal diseases"[MeSH Terms] OR ("periodontal"[All Fields] AND "diseases"[All Fields]) OR "periodontal diseases"[All Fields] OR ("periodontal"[All Fields] AND "disease"[All Fields]) OR "periodontal disease"[All Fields]) OR (("periodontal"[All Fields] OR "periodontally"[All Fields] OR "periodontically"[All Fields] OR "periodontics"[MeSH Terms] OR "periodontics"[All Fields] OR "periodontic"[All Fields] OR "periodontitis"[MeSH Terms] OR "periodontitis"[All Fields] OR "periodontitides"[All Fields]) AND ("health"[MeSH Terms] OR "health"[All Fields] OR "health s"[All Fields] OR "healthful"[All Fields] OR "healthfulness"[All Fields] OR "healths"[All Fields])) OR ("periodontal"[All Fields] OR "periodontally"[All Fields] OR "periodontically"[All Fields] OR "periodontics"[MeSH Terms] OR "periodontics"[All Fields] OR "periodontic"[All Fields] OR "periodontitis"[MeSH Terms] OR "periodontitis"[All Fields] OR "periodontitides"[All Fields]) OR (("ambulatory care facilities"[MeSH Terms] OR ("ambulatory"[All Fields] AND "care"[All Fields] AND "facilities"[All Fields]) OR "ambulatory care facilities"[All Fields] OR "clinic"[All Fields] OR "clinic s"[All Fields] OR "clinical"[All Fields] OR "clinically"[All Fields] OR "clinicals"[All Fields] OR "clinics"[All Fields]) AND ("attach"[All Fields] OR "attachable"[All Fields] OR "attached"[All Fields] OR "attachement"[All Fields] OR "attaches"[All Fields] OR "attaching"[All Fields] OR "attachment"[All Fields] OR "attachments"[All Fields]) AND ("level"[All Fields] OR "levels"[All Fields])) OR ("alveolar bone loss"[MeSH Terms] OR ("alveolar"[All Fields] AND "bone"[All Fields] AND "loss"[All Fields]) OR "alveolar bone loss"[All Fields]) OR (("probe"[All Fields] OR "probe s"[All Fields] OR "probed"[All Fields] OR "probes"[All Fields] OR "probing"[All Fields] OR "probings"[All Fields]) AND ("depth"[All Fields] OR "depths"[All Fields]))) AND ("respiratory tract diseases"[MeSH Terms] OR ("respiratory"[All Fields] AND "tract"[All Fields] AND "diseases"[All Fields]) OR "respiratory tract diseases"[All Fields] OR ("respiratory"[All Fields] AND "disease"[All Fields]) OR "respiratory disease"[All Fields] OR "respiration disorders"[MeSH Terms] OR ("respiration"[All Fields] AND "disorders"[All Fields]) OR "respiration disorders"[All Fields] OR ("respiratory"[All Fields] AND "disease"[All Fields]) OR ("pulmonary disease, chronic obstructive"[MeSH Terms] OR ("pulmonary"[All Fields] AND "disease"[All Fields] AND "chronic"[All Fields] AND "obstructive"[All Fields]) OR "chronic obstructive pulmonary disease"[All Fields] OR ("chronic"[All Fields]

AND "obstructive"[All Fields] AND "pulmonary"[All Fields] AND "disease"[All Fields])) OR (("lung"[MeSH Terms] OR "lung"[All Fields] OR "pulmonary"[All Fields]) AND ("functional"[All Fields] OR "functional s"[All Fields] OR "functionalities"[All Fields] OR "functionality"[All Fields] OR "functionalization"[All Fields] OR "functionalizations"[All Fields] OR "functionalize"[All Fields] OR "functionalized"[All Fields] OR "functionalizes"[All Fields] OR "functionalizing"[All Fields] OR "functionally"[All Fields] OR "functionals"[All Fields] OR "functioned"[All Fields] OR "functioning"[All Fields] OR "functionings"[All Fields] OR "functions"[All Fields] OR "physiology"[MeSH Subheading] OR "physiology"[All Fields] OR "function"[All Fields] OR "physiology"[MeSH Terms])) OR (("airflow"[All Fields] OR "airflows"[All Fields]) AND ("limit"[All Fields] OR "limitation"[All Fields] OR "limitations"[All Fields] OR "limited"[All Fields] OR "limiting"[All Fields] OR "limits"[All Fields])))) AND (english[Filter])

Database 2: Ovid EMBASE

Sequence	Query
1	((Oral health) OR (periodontal disease) OR (periodontal health) OR (periodontitis) OR (clinical attachment level) OR (alveolar bone loss) OR (probing depth)) AND ((Respiratory disease) OR (chronic obstructive pulmonary disease) OR (pulmonary function) OR (airflow limitation)) {Including Related Terms}
2	limit **1** to (full text and human and english language)
3	limit **1** to english language

Database 3: Ovid Cochrane Central Register of Controlled Trials

Sequence	Query
1	((Oral health) OR (periodontal disease) OR (periodontal health) OR (periodontitis) OR (clinical attachment level) OR (alveolar bone loss) OR (probing depth)) AND ((Respiratory disease) OR (chronic obstructive pulmonary disease) OR (pulmonary function) OR (airflow limitation)) {Including Related Terms}
2	limit **1** to english language

Table 2 Adjustment for confounders of included studies

Study Author	Covariates in logistic regression multivariable model
Hayes *et al*[1]	Age, smoking, education, height
Scannapieco *et al*[2]	Smoking
Garcia *et al*[3]	Age, height, alcohol, education **(with stratified analysis on smoking)**
Leuckfeld *et al*[4]	Age, female gender, **pack years of smoking**
Liu *et al*[5]	Age, gender, BMI and smoking
Wang *et al*[6]	Age, gender, BMI **(with stratified analysis on smoking)**
Si *et al*[7]	Age, gender, occupation, educational level **(with stratified analysis on smoking)**
Zhou *et al*[8]	Age, gender, smoking, BMI, season **(with stratified analysis on smoking)**
Ledić *et al*[9]	Age, gender, **pack years of smoking**, BMI
Lopez-de-Andrés *et al*[10]	Age, gender, smoking, educational level, DM, obesity
Zhou *et al*[11]	Age, gender, smoking, BMI
Kataoka *et al*[12]	Age, smoking
Qian *et al*[13]	Age, sex, education levels, BMI, smoking, drinking, hypertension, DM
Barros *et al*[14]	Age, gender, Race, BMI, education, **pack years of smoking**, hypertension
Scannapieco *et al*[15]	Age, gender, **pack years of smoking**, Race, education, income, dental visits, alcohol, DM
Hyman *et al*[16]	Age, gender, Race, history of hypertension and heart attack, dental visit within 1 year, BMI, family income **(with stratified analysis on smoking)**
Chung *et al*[17]	Age, smoking, family income, education, alcohol, exercise, BMI, tooth brushing frequency, DM, number of natural teeth
Harland *et al*[18]	Age, number of present teeth, BMI, alcohol consumption, occupation, hypertension, DM **(with stratified analysis on smoking)**
Takeuchi *et al*[19]	Age, gender, **pack years of smoking**, occupation, DM, BMI, physical activity, alcohol intake, number of present teeth

Jung *et al*[20]	Age, gender, smoking, educational level, household income, alcohol consumption, periodontal status, number of missing teeth, oral health factors
Winning *et al*[21]	Age, gender, smoking, height, BMI, exercise, DM, hypertension, MI, education level, living condition
AbdelHalim *et al*[22]	Age, BMI, low-level of education, **pack years of smoking**, MRC, CAT, hospitalizations, COPD category (C-D), FVC (% predicted), FEV1 (% predicted), FEV1 / FVC (% predicted), MMEF (% predicted), PEF (% predicted), CRP

BMI, body mass index; CAT, chronic obstructive pulmonary disease assessment test; CRP, C-reactive protein; DM, diabetes mellitus; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; MI, myocardial infarction; MMEF, maximum mid-expiratory flow; MRC, Medical Research Council; PEF, peak expiratory flow.
Bold: the covariate of smoking intensity (duration and dose) or stratified analyses on smoking status.

Table 3 Diagnostic criteria for PD of included studies in quantitative analysis

Study Author	Diagnostic parameter/criteria	Measurement/Calculation
Hayes *et al*[1]	**Worst alveolar bone loss (ABL) quintile vs all others**	Worst ABL quintile had mean whole-mouth ABL scores of 20% or greater, i.e., an average of 20% or more ABL for each mesial and distal site measured.
Scannapieco *et al*[2]	**Simplified oral hygiene index=6**	Calculated by adding together the simplified debris index and the simplified calculus index scores.
Garcia *et al*[3]	**ABL**	Periodontitis measure is mean, whole mouth, radiographic alveolar bone loss used as a continuous variable, with each unit of ABL representing 20% increments of bone loss.
Scannapieco *et al*[15]	**Mean attachment loss (AL)≥ 3mm**	AL was obtained by subtracting the distance from the free gingival margin (FGM) to the cemento-enamel junction (CEJ) of each tooth, from the distance from the FGM to the bottom of the sulcus.
Hyman *et al*[16]	**Mean AL≥4mm**	AL was calculated based on the probe distance in millimeters from the FGM to the CEJ and the base of the sulcus.
Leuckfeld *et al*[4]	**Mean marginal bone level≥ 4mm**	The marginal bone level distance was measured from the CEJ to the alveolar bone crest, at the mesial and distal aspects of approximal tooth sites, and was rounded off to the nearest 0.1mm.
Wang *et al*[6]	**Clinical attachment level (CAL)≥4mm**	Probing depth + CEJ = CAL; probing depth and CEJ were measured with a Williams periodontal probe at six sites of all teeth (excluding third molars) and recorded in millimetres.
Liu *et al*[5]	**CAL>4mm**	Consistent with the study by Wang *et al*[6].
Si *et al*[7]	**Probing depth≥5mm and CAL≥4mm**	The two indices were recorded on six sites of each tooth.
Zhou *et al*[8]	**CAL**	Consistent with the study by Wang *et al*[6].
Barros *et al*[14]	**≥2 interproximal sites with CAL≥6mm (not on same tooth) and≥1 interproximal site with probing depth≥5mm**	Using the consensus definitions published by the joint Center for Disease Control/American Association of Periodontology working group.
Ledić *et al*[9]	**CAL≥4mm at at least 60% of the measured sites**	CAL was determined as the distance from the CEJ to the bottom of the pocket. The aforementioned value

		was recorded on the nearest milimeter by one calibrated examiner on six places per tooth (mesiobuccally, buccally, distobuccally, mesiolingually, lingually and distolingually).
Chung *et al*[17]	**Community periodontal index (CPI) >5.5mm pocket (deep periodontal pocket)**	WHO criteria (Oral health surveys: basic methods-5th edition).
AbdelHalim *et al*[22]	**CAL≥5mm**	Calculations of CAL were done by summation of probing pocket depth (PPD) and recession value. Periodontal examination was performed on all existing teeth (excluding the third molar teeth).
Harland *et al*[18]	**CPI score ≥3 (at least one sextant with a pocket depth ≥4 mm)**	WHO criteria.
Lopez-de-Andrés *et al*[10]	**Teeth bleeding spontaneously or while brushing, or/and teeth moving**	Questionnaire investigation.
Takeuchi *et al*[19]	**Severe periodontitis (2 or more interproximal sites with ≥6mm CAL [not on same tooth] and 1 or more interproximal sites with ≥5mm PPD)**	According to the suggested Centers for Disease Control and American Academy of Periodontology case definitions for periodontitis surveillance.
Jung *et al*[20]	**CPI=3-4 (periodontal pockets ≥4mm)**	The central incisor, first and second molars were selected as index teeth, and the highest score adopted as the participant's final CPI score.
Qian *et al*[13]	**Proportion of remaining bone height of the teeth (calculated from total root length and total bone height)**	Measurements of ABL were made from the CEJ to the tooth apex (total root length) and from the marginal bone crest to the tooth apex (total bone height).
Winning *et al*[21]	**A distance between the alveolar bone level and CEJ based on a threshold of ≥4mm found at ≥30% of teeth.**	The extent of ABL was measured at the mesial and distal aspects of all teeth excluding third molars.
Zhou *et al*[11]	**CAL ≥5mm**	Consistent with the study by Wang *et al*[6]
Kataoka *et al*[12]	**PPD ≥4mm**	The PPD was measured at the disto-, mid-, and mesio-buccal, as well as the disto-, mid-, and mesio-lingual buccal surfaces of all the teeth.

Table 4 Quality assessment based on the Newcastle-Ottawa Scale

(A) Cohort study

Study Author	Selection				Comparability	Outcome			Total score
	Exposed cohort	Nonexposed cohort	Ascertainment of exposure	Outcome of interest		Assessment of outcome	Length of follow-up	Adequacy of follow-up	
Barros *et al*[14]	*	*	*	…	…	*	*	*	6
Takeuchi *et al*[19]	*	*	*	*	…	*	*	*	7
Qian *et al*[13]	…	*	*	…	…	*	*	…	4

(B) Case-control / cross-sectional study

Study Author	Selection				Comparability	Outcome			Total score
	Case definition	Representati--veness of the cases	Control selection	Control definition		Ascertainment of exposure	Same method of ascertainment for cases and controls	Non--response rate	
Hayes *et al*[1]	*	…	*	*	*	*	*	*	7
Scannapieco *et al*[2]	…	*	*	*	…	*	*	…	5
Garcia *et al*[3]	*	…	*	*	*	*	*	*	7
Scannapieco *et al*[15]	…	*	*	*	…	*	*	*	6
Hyman *et al*[16]	*	*	*	*	…	*	*	*	7
Leuckfeld *et al*[4]	*	…	…	*	…	*	*	*	5
Wang *et al*[6]	*	*	…	*	*	*	*	*	7
Liu *et al*[5]	*	*	…	*	*	*	*	*	7
Si *et al*[7]	*	*	…	*	*	*	*	*	7
Zhou *et al*[8]	*	*	…	*	*	*	*	*	7
Pedić *et al*[9]	*	*	…	*	*	*	*	*	7
Chung *et al*[17]	*	*	*	*	…	*	*	*	7
AbdelHalim *et al*[22]	*	…	…	*	…	*	*	*	5
Harland *et al*[18]	*	*	…	*	…	*	*	*	6
Lopez-de-Andrés *et al*[10]	…	*	*	*	*	…	*	*	6
Jung *et al*[20]	…	*	*	*	…	*	*	*	6
Winning *et al*[21]	*	*	*	*	…	*	*	*	7
Zhou *et al*[11]	*	*	…	…	**	*	*	*	7
Kataoka *et al*[12]	*	*	*	*	…	*	*	*	7

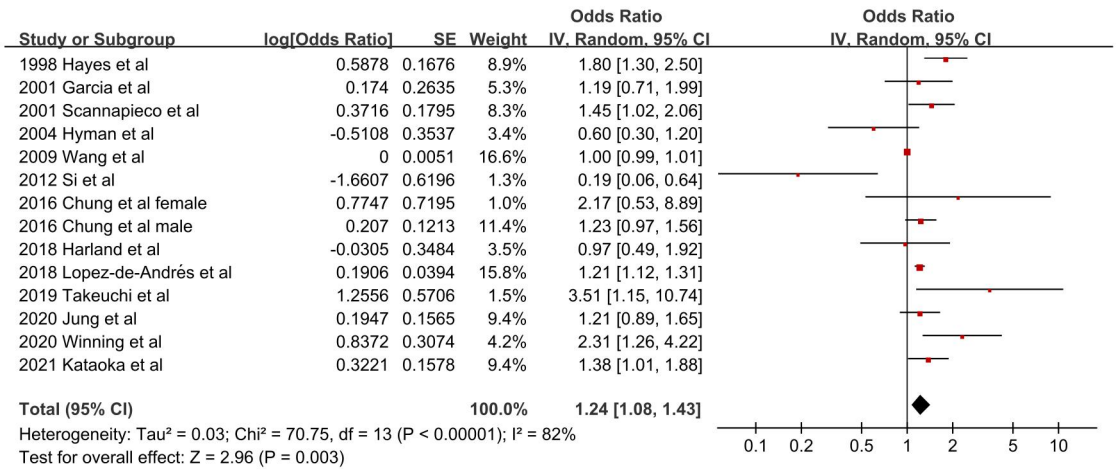

Figure 1 Sensitivity analysis on studies with larger sample size (N ≥500). Values more than one indicate a higher risk of COPD in patients with PD.

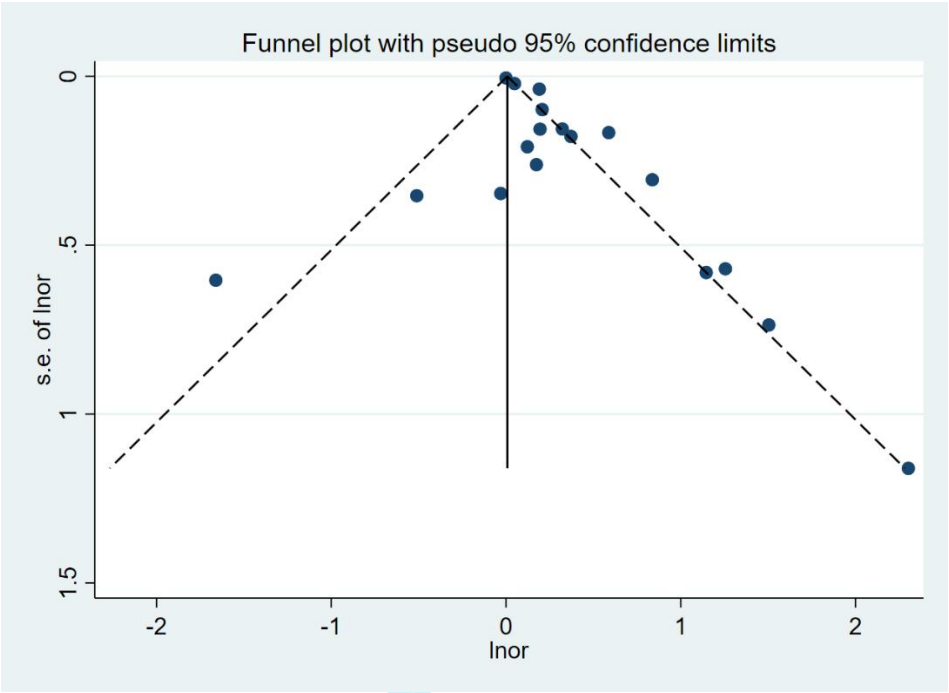

Figure 2 Funnel plot for the risk of COPD, with pseudo 95% confidence limits.

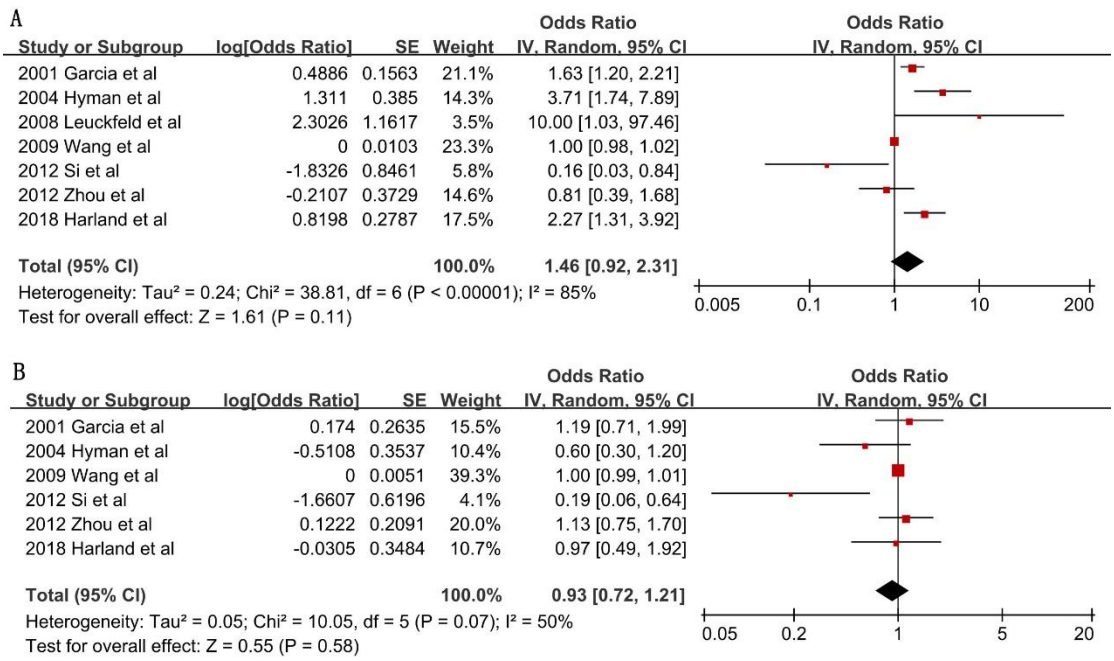

Figure 3 Forest plot of the risk of COPD by periodontal disease. A in smokers and B in never smokers. Values more than one indicate a higher risk in patients with periodontal disease.

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PRISMA 2009 Checklist

Section/topic	Item No	Checklist item	Reported on Page Number/Line Number	Reported on Section/Paragraph
TITLE				
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1 / Line 2,3	Title page
ABSTRACT				
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2,3 / Line 28-52	Abstract
INTRODUCTION				
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 3-5 / Line 66-100	Introduction / Paragraph 1-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 5 / Line 100-104	Introduction / Paragraph 4
METHODS				
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Page 5 / Line 107-109	Methods / Paragraph 1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 6 / Line 116-122	Methods / Paragraph 2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 6 / Line 112-114	Methods / Paragraph 2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 6 / Line 114-116	Methods / Paragraph 2 Supplemental table 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 6 / Line 125-131	Methods / Paragraph 3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 7 / Line 134,135	Methods / Paragraph 4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 7 / Line 135-140	Methods / Paragraph 4

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 7 / Line 141-147	Methods / Paragraph 4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 7 / Line 150	Methods / Paragraph 5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 8 / Line 156-160	Methods / Paragraph 5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 8 / Line 172, 173	Methods / Paragraph 7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 8 / Line 161-172	Methods / Paragraph 6,7
RESULTS				
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 9 / Line 183-189	Results / Paragraph 1; Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 9-12 / Line 190-226	Results / Paragraph 2-4; Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 12 / Line 229-234	Results / Paragraph 5; Supplemental table 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 12 / Line 239; Page 15 / Line 277	Results / Paragraph 6, 9; Figure 2 and 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 12 / Line 237-239 Page 15 / Line 275-277	Results / Paragraph 6,9; Figure 2 and 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 13 / Line 244-246	Results / Paragraph 6; Supplemental figure 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page 12 / Line 240-243; Page 13-15 / Line 247-270	Results / Paragraph 6-8; Table 2, Figure 2
DISCUSSION				
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 15-18 / Line 280-346	Discussion / Paragraph 1-5
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 18,19 / Line 349-368	Discussion / Paragraph 6
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 19 / Line 371-375	Conclusion / Paragraph 1

FUNDING				
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 20 / Line 391,392	Funding

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