BMJ Open

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

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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 A 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 standardised Excel file. Quality of studies was evaluated using the Newcastle-Ottawa Scale. OR with 95% 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.

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

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This systematic review and meta-analysis only included studies with statistical adjustment for smoking, to adequately control the confounding by smoking.

⇒ We defined 'periodontal disease' as a wide variety of periodontal abnormalities according to clinical and radiographic assessments, which is not limited to periodontitis.

⇒ The language was restricted to English when conducting study searching, thus some literature might have been missed.

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

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a momentous prerequisite for optimising 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 characterised 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 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 randomised controlled trial, cohort, case–control or cross-sectional study designs; (3) presenting clear diagnostic or assessment criteria for COPD and PD and (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 OR, relative risk (RR) or 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 standardised 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% 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 and 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 V.16 (StataCorp) and Review manager V.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 30 165 records were identified from the initial database search. 13 662 records were removed for duplicates, and 16 227 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 (6 studies), reviews (183 studies), insufficient information (9 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 given in table 1. The number of participants was 51 704 and there were 9973 (18.9%) patients with COPD. The mean age of patients with COPD was between 45.1 years and 83.1 years, while the mean age of the control subjects was between 42.2 years and 80.3 years. These studies were published between 1998 and 2021. The sample size ranged from 120 to 13 792. 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 3 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 6 studies in the North America,[14 20 21 28–30] 4 studies in Europe[31 33 36 39] and 1 study in Africa.[43]

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
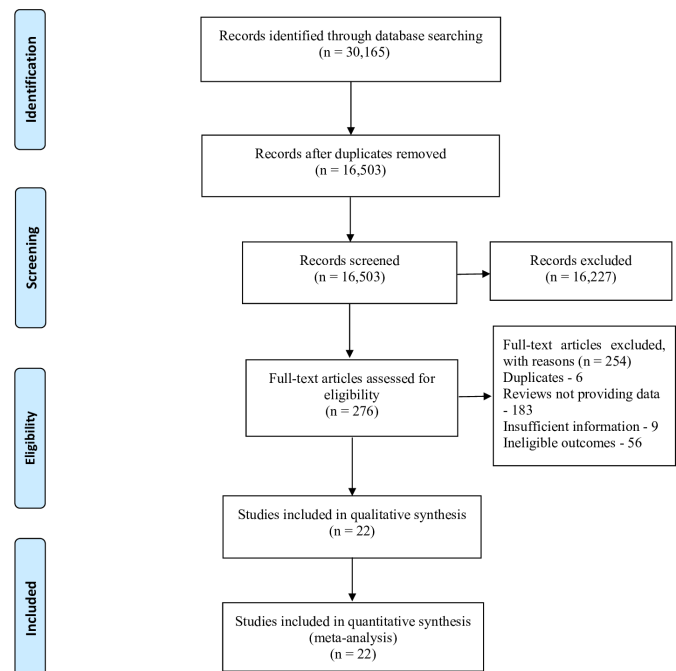

Figure 1 PRISMA flow diagram of study selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

> 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. Sixteen articles reported the adjusted ORs and four 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, bleeding index, 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 4 studies[14 16 31 43] with 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

Eighteen 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

Table 1 Characteristics of included studies

Year/study	Design	Location	No. COPD/control subjects	Age (COPD/control subjects)	Assessment of PD	Assessment of COPD
Hayes et al[28] 1998	Case–control	USA	261/857	45.1±9.7/42.2±9.1	ABL	FEV_1
Scannapieco et al[14] 1998	Cross-sectional	USA	77/309	NA	OHI	Self-reported
Garcia et al[29] 2001	Case–control	USA	279/833	NA	ABL, PPD	FEV_1
Scannapieco et al[30] 2001	Cross-sectional	USA	810/12 982	51.2±17.9/43.9±17.7	CAL, GB	Self-reported
Hyman et al[20] 2004	Cross-sectional	USA	993/6 632	62.3±14.1/47.4±14.2	CAL	GOLD
Leuckfeld et al[31] 2008	Cross-sectional	Norway	130/50	54.9±4.9/47.0±9.8	ABL	GOLD
Wang et al[19] 2009	Case–control	China	306/328	63.9±9.8/63.3±9.0	CAL, PLI	GOLD
Liu et al[42] 2012	Case–control	China	183/209*	64.3±10.1/63.6±9.7	CAL, PPD, BI	GOLD
Si et al[15] 2012	Case–control	China	581/438	63.9±9.4/62.8±9.5	CAL, ABL, PPD, PLI, BI	GOLD
Zhou et al[32] 2012	Case–control	China	193/181	63.6±10.3/62.1±9.1	CAL, ABL, PPD, PLI, BI	GOLD
Barros et al[21] 2013	Cohort	USA	399/1236†	63.9±5.7/66.0±5.1	CAL, PPD	GOLD
Ledić et al[33] 2013	Case–control	Croatia	93/43	65.8±9.7/62.1±11.9	CAL	GOLD
Chung et al[34] 2016	Cross-sectional	Korea	697/5181	64.3±0.2/54.6±0.1	PPD, GB	GOLD
AbdelHalim et al[43] 2018	Cross-sectional	Egypt	134/116*	56.8±10.4/55.3±9.1	CAL, PPD, BI, PLI, OHI	GOLD
Harland et al[35] 2018	Cross-sectional	Japan	149/1325	61.3±9.1/54.5±8.7	PPD	GOLD
Lopez-de-Andrés et al[36] 2018	Case–control	Spain	2699/2699	63±14/61±14	Self-reported	Self-reported
Takeuchi et al[37] 2019	Cohort	Japan	22/878	NA	CAL, PPD	GOLD
Jung et al[38] 2020	Cross-sectional	Korea	1134/6585	62.6±0.4/53.6±0.2	PPD	FEV_1/FVC
Qian et al[16] 2020	Cohort	China	23‡/NA	83.1±4.8/80.3±3.7	ABL	NR
Winning et al[39] 2020	Cross-sectional	Sweden	86/740	NA	ABL	GOLD
Zhou et al[40] 2020	Case–control	China	60/60	63.1±10.1/60.0±9.4	CAL, PLI	GOLD
Kataoka et al[41] 2021	Cross-sectional	Japan	464/249	54.1±9.4/NA	PPD	GOLD

Continuous data are presented as mean±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 (hospitalisation 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; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GB, gingival bleeding; GOLD, Global Initiative for Chronic Obstructive Lung Disease; OHI, oral health index; PD, periodontal disease; PLI, plaque index; PPD, probing pocket depth.

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 to 1.28) to 1.28 (95% CI 1.12 to 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
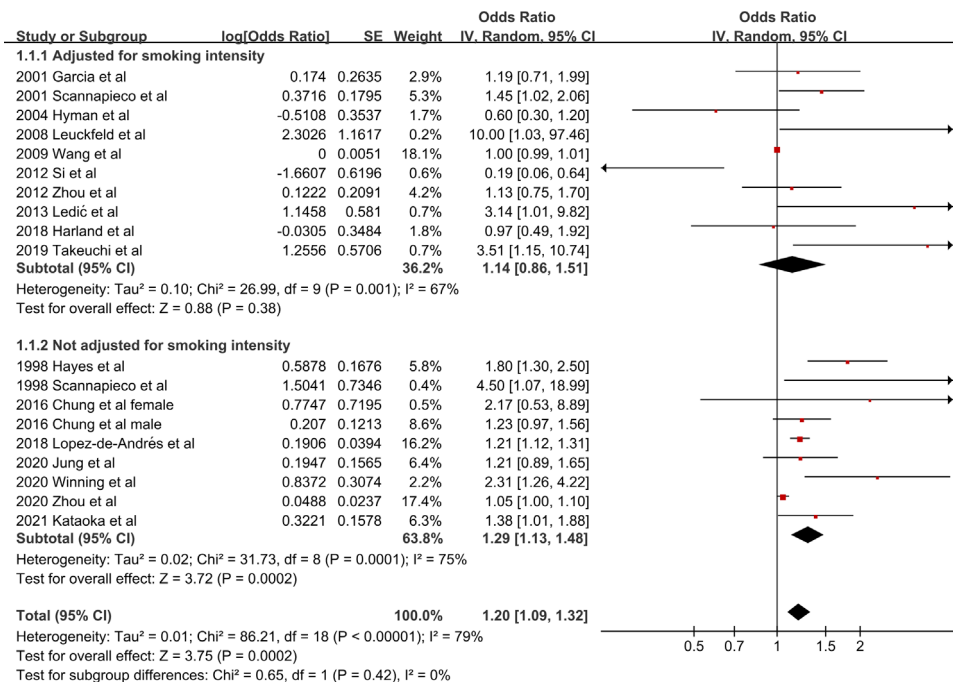
Figure 2 Forest plot of the risk of COPD by PD, subgroup analysis based on adjusted by smoking status and intensity versus by smoking status only. Values more than 1 indicate a higher risk in patients with PD. COPD, chronic obstructive pulmonary disease; PD, periodontal disease.

Table 2 Subgroup analyses regarding the risk of COPD

Subgroups	No. studies	No. participants/Cases	OR value (95% CI)	P value	I², %
Adjusted for smoking intensity*					
Yes	10	27 246/3556	1.14 (0.86 to 1.51)	0.38	67
No	8	22 158/5478	1.29 (1.13 to 1.48)	**0.0002**	75
Assessment of PD					
CAL	8	24 600/3058	1.04 (0.96 to 1.14)	0.33	75
ABL	6	4629/1530	1.98 (1.32 to 2.97)	**0.001**	56
PPD	8	19 189/3519	1.16 (0.89 to 1.51)	0.27	63
Geographical location					
Asia	9	18 831/3606	1.07 (0.99 to 1.17)	0.08	65
North America	5	24 033/2420	1.37 (0.93 to 2.01)	0.11	63
Europe	4	6540/3008	2.05 (1.07 to 3.95)	**0.03**	71
Assessment of COPD					
GOLD	12	19 879/3774	1.10 (1.00 to 1.22)	0.06	71
Non-GOLD	6	29 525/5260	1.35 (1.14 to 1.61)	**0.0007**	46
Study design					
Case–control	8	9 911/4472	1.12 (1.01 to 1.24)	**0.03**	86
Cross-sectional	9	38 593/4540	1.34 (1.08 to 1.66)	**0.007**	45
Cohort	1	878/22	3.51 (1.15 to 10.74)	**0.03**	–

Bold: subgroups with positive results.
*Duration and dose of smoking.
ABL, alveolar bone loss; CAL, clinical attachment level; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; PD, periodontal disease; PPD, probing pocket depth.

to 2.97, p=0.001, 6 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, 4 studies).[31 33 36 39]

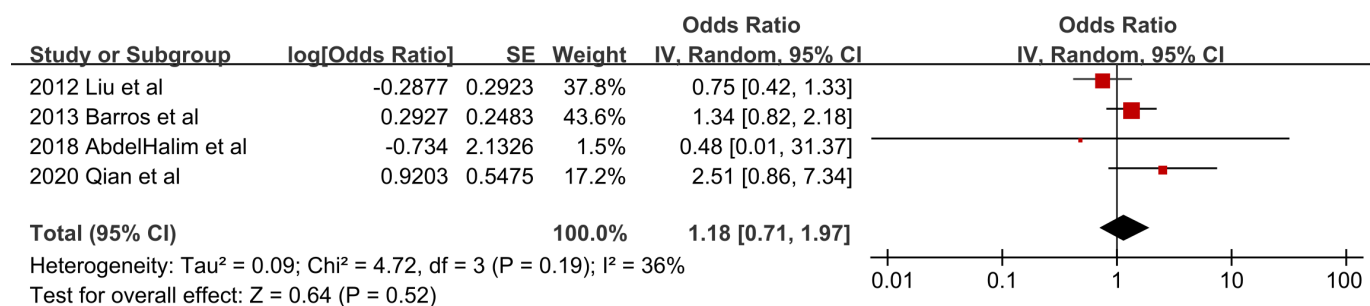| Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Odds Ratio IV, Random, 95% CI
2012 Liu et al	-0.2877	0.2923	37.8%	0.75 [0.42, 1.33]	
2013 Barros et al	0.2927	0.2483	43.6%	1.34 [0.82, 2.18]	
2018 AbdelHalim et al	-0.734	2.1326	1.5%	0.48 [0.01, 31.37]	
2020 Qian et al	0.9203	0.5475	17.2%	2.51 [0.86, 7.34]	
Total (95% CI)			100.0%	1.18 [0.71, 1.97]	

Heterogeneity: Tau² = 0.09; Chi² = 4.72, df = 3 (P = 0.19); I² = 36%
Test for overall effect: Z = 0.64 (P = 0.52)

Figure 3 Forest plot of the risk of COPD-related events by PD. Values more than 1 indicate a higher risk in patients with PD. COPD, chronic obstructive pulmonary disease; PD, periodontal disease.

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 32 35] or never smokers (OR: 0.93, 95% CI 0.72 to 1.21, p=0.58, 6 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, I²=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 using ABL as the measure of PD. For one thing, this demonstrated that, as sources of bias, observational study design and non-standard 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-PDs 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-PDs.

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 the 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 that 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.

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