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# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-067432
Article Type:	Original research
Date Submitted by the Author:	15-Aug-2022
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Keywords:	Chronic airways disease < THORACIC MEDICINE, RESPIRATORY MEDICINE (see Thoracic Medicine), ORAL MEDICINE, Emphysema < THORACIC MEDICINE

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Manuscripts



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5 **1 Title Page**  
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7 **2 Title:** Association of periodontal disease with COPD risk and clinical events: a  
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10 3 systematic review and meta-analysis  
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54 20  
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57 21 **Word count of the abstract:** 223  
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60

1  
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5 22 **Word count of the main text:** 3310  
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10 24 **Association of periodontal disease with COPD risk and**  
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13 25 **clinical events: a systematic review and meta-analysis**  
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18 27 **ABSTRACT**  
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20 28 **Objectives** Studies have suggested contradictory results of the relationship between  
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23 29 chronic obstructive pulmonary disease (COPD) and periodontal disease (PD). The aim  
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25  
26 30 of this study was to determine the association of PD with COPD risk and its clinical  
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29 31 events.

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31 32 **Methods** We systematically searched PubMed, EMBASE and CENTRAL from  
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34 33 inception to 10 August 2022, to identify relevant articles. Odds ratio (OR) with 95%  
35  
36 34 confident interval (CI) was pooled in a random-effect model with inverse variance  
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39 35 method. We also performed stratified and subgroup analyses.

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41 36 **Results** In total, 22 observational studies with 51704 participants were included in the  
42  
43  
44 37 meta-analysis. Pooled analysis of 18 studies suggested that PD was weakly associated  
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46 38 with risk of COPD (OR 1.20; 95% CI 1.09 to 1.32;  $I^2=79%$ ) after adjusting for smoking  
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48  
49 39 status. In stratified and subgroup analyses, with more strict adjustment for smoking, PD  
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51  
52 40 no longer related to COPD risk, when adjusting for smoking intensity (OR 1.14; 95% CI  
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54 41 0.86 to 1.51), smokers only (OR 1.46; 95% CI 0.92 to 2.31) and for never smokers (OR  
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57 42 0.93; 95% CI 0.72 to 1.21). Pooled analysis of 4 studies indicated that PD did not  
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5 43 increase risk of COPD-related exacerbation or mortality (OR 1.18; 95% CI 0.71 to 1.97;  
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7  
8 44  $I^2=36\%$ ).

9  
10 45 **Conclusions** PD confers no risk for COPD and COPD-related events, with adjustment  
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13 46 for confounding by smoking. Further investigations focusing on never smokers are  
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15  
16 47 warranted.

## 17 18 19 20 21 49 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

- 22  
23 50 1. This is the largest systematic review and meta-analysis on association between  
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26 51 chronic obstructive pulmonary disease (COPD) and periodontal disease (PD)  
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29 52 collecting data over 20 years.
- 30  
31 53 2. This study firstly synthesized research evidence regarding correlation of PD with  
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34 54 COPD-related exacerbation or mortality.
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36 55 3. Compared with previous reports, the present study was conducted with more strict  
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39 56 adjustment for confounding by smoking, which was the most important confounder  
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42 57 in the COPD-PD relationship.
- 43  
44 58 4. Our study provided limited evidence on the outcome of COPD-related events  
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46  
47 59 because of limited data.
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49 60 5. Clinical heterogeneity and publication bias compromised the evidence strength of  
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52 61 the study, although subgroup and stratified analyses were performed.

## 53 54 55 56 57 63 **INTRODUCTION**

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5 64 Chronic obstructive pulmonary disease (COPD) is the third leading cause of death,  
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8 65 resulting in enormous economic burden.<sup>1</sup> Commonly, COPD coexists with other  
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10 66 disorders, also called comorbidities, which play key roles in COPD progression and  
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12  
13 67 prognosis.<sup>2 3</sup> Understanding COPD-comorbidities relationship has been a momentous  
14  
15 68 prerequisite for optimizing disease prevention and management strategies.<sup>2 3</sup>  
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18 69 Given ageing and widespread use of inhaled corticosteroids in COPD, periodontal  
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20 70 disease (PD) has been a common comorbidity of COPD.<sup>4</sup> It is a chronic inflammatory  
21  
22  
23 71 condition of tissues surrounding and supporting the teeth, including gingiva, bone and  
24  
25  
26 72 ligament,<sup>5</sup> with the prevalence estimates over 10% around the world and especially  
27  
28 73 prevalent in elderly individuals.<sup>6</sup> To date, diagnosis and assessment of PD are mostly  
29  
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31 74 based on periodontal measurements including clinical attachment level (CAL), probing  
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34 75 pocket depth (PPD) and alveolar bone loss (ABL).<sup>5</sup> They are primary clinical  
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36 76 manifestations of PD, reflecting the extent of periodontal tissue destruction.<sup>5</sup>  
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39 77 Based on the nature of inflammation,<sup>5 7</sup> mounting evidence has shed light on the  
40  
41 78 association between PD and development of COPD.<sup>8 9</sup> Currently three points are  
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44 79 proposed. First, they share the same risk factors, such as age, gender, smoking and  
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47 80 socioeconomic status.<sup>2 10</sup> Second, they have similar pathogenetic mechanisms. Both  
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49 81 diseases are characterized by host susceptibility to environmental factors, immune  
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52 82 overreaction, oxidative stress and production of pro-inflammatory cytokines.<sup>7 8</sup> Most  
53  
54 83 importantly, neutrophilic inflammation plays a key role in both diseases.<sup>8 11</sup> Third, oral  
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57 84 bacteria released from the dental plaque in PD could trigger progression and acute  
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5 85 exacerbation (AE) of COPD.<sup>12 13</sup>  
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8 86 Meanwhile, epidemiological evidence has indicated that PD increased risk of COPD<sup>11</sup>  
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10 87 <sup>14 15</sup> and COPD-related events.<sup>13 16</sup> Scannapieco *et al* revealed a 4.5-fold increased risk  
11  
12 88 of developing COPD in patients with PD, compared to those without.<sup>14</sup> A dose-response  
13  
14 89 relationship was further implied between PD severity and lung function.<sup>15</sup> Among  
15  
16 90 patients with both diseases, COPD-related AE and mortality also significantly linked  
17  
18 91 with periodontal status.<sup>13 16</sup> Periodontal therapy, such as scaling and root planing  
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20 92 treatment, could ameliorate lung function and decrease frequency of AE in COPD with  
21  
22 93 chronic periodontitis.<sup>17 18</sup> However, there were some other studies revealing opposite  
23  
24 94 results, resulting in a long-standing controversy.<sup>19-21</sup> It is worth noting that, parameters  
25  
26 95 used to determine PD were apparently variable across studies, which also failed to  
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28 96 adequately control confounders, especially smoking, the most important confounder in  
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30 97 the COPD-PD relationship. Therefore, to provide the latest and most convincing  
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32 98 evidence, we systematically reviewed current available literature to investigate  
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34 99 association of PD with risk of COPD and COPD-related events. Subgroup and stratified  
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36 100 analyses were also conducted to further decrease confounding effect of smoking.  
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## 102 **Methods**

103 This systematic review and meta-analysis was conducted and reported in accordance to  
104 the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)  
105 guideline.<sup>22</sup>  
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5 106  
67 107 **Search strategy and selection criteria**  
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10 108 We searched PubMed, EMBASE and CENTRAL for records evaluating association  
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12 109 between COPD and PD, from inception to 10 August 2022. The search strategy was  
13  
14 110 described in online supplemental table S1. The language was restricted to English, for  
15  
16 111 the purpose of rapid review.<sup>23</sup> Studies meeting the following criteria were included: (1)  
17  
18 112 adult participants; (2) original studies with randomized controlled trial (RCT), cohort,  
19  
20 113 case-control or cross-sectional study designs; (3) presenting clear diagnostic or  
21  
22 114 assessment criteria for COPD and PD; (4) evaluating association between PD and risk  
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24 115 of COPD, or risk of COPD-related AE and mortality, with statistical adjustment for  
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26 116 smoking.  
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33 117 According to the inclusion criteria, two independent investigators (MY and XL)  
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35 118 performed systematical search, screened titles and abstracts of all retrieved studies to  
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37 119 exclude duplicate or irrelevant records. For articles requiring further assessment, full-  
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39 120 text reviews were carried out and references of retrieved articles and relevant reviews  
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41 121 were also manually checked to identify additional eligible studies. Disagreements were  
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43 122 resolved by discussion between the two reviewers or with the help of the third  
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45 123 investigator (RP).  
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54 125 **Data extraction and quality assessment**  
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57 126 Two investigators (MY and RP) independently extracted data from selected studies  
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5 127 using a standardized Excel (Microsoft Corporation) file. The following information was  
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8 128 extracted: author, year of publication, country, study design, number of subjects (COPD  
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10 129 and non-COPD), demographic characteristics of participants, periodontal variables  
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13 130 applied to assess PD, diagnostic criteria for COPD, definition of COPD-related AE and  
14  
15 131 mortality, adjusted odds ratio (OR), relative risk (RR) or hazard ratio (HR) for risk of  
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18 132 COPD, AE and mortality in relation to PD, as well as adjustment for confounders. The  
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20 133 primary outcome was risk of COPD. Secondary outcome was risk of COPD-related  
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23 134 adverse events, including AE and mortality. Quality of studies was independently  
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26 135 evaluated using the Newcastle-Ottawa Scale<sup>24</sup> by two investigators (MY and XL). A  
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28 136 score of  $\geq 6$  was considered a low risk while  $< 6$  a high risk of bias. Both case-control  
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31 137 and cohort studies had a maximum score of 9. Cross-sectional study was regarded as  
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34 138 case-control study when performing quality assessment. Discrepancies regarding data  
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36 139 extraction and quality assessment were resolved through discussion and consensus.  
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#### 141 **Data analysis**

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

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5 148 and cross-sectional studies, we estimated the OR whereas for cohort studies we  
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8 149 estimated the RR or HR. The random-effect model with inverse variance method were  
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10 150 applied due to potential heterogeneity resulting from methodological differences.  
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13 151 Heterogeneity across studies was identified with the  $I^2$  statistic.  $I^2$  statistic  $> 50\%$   
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15 152 indicated significant heterogeneity.

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18 153 To explore heterogeneity, subgroup analyses were conducted based on study design  
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20 154 (case-control, cross-sectional and cohort studies), geographical location (Asia, North  
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22  
23 155 America, Europe), assessment of PD (CAL, ABL and PPD), definition of COPD (Global  
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25  
26 156 Initiative for Chronic Obstructive Lung Diseases, GOLD and non-GOLD criteria) and  
27  
28 157 adjustment for smoking intensity, defined as dose and duration of smoking. To better  
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31 158 control the confounding effect of smoking, stratified analyses were also performed in  
32  
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34 159 smokers and never smokers respectively.

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36 160 To test the robustness of study findings, we performed sensitivity analysis on studies  
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39 161 with relatively large sample size ( $\geq 500$  participants), which tended to be more  
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42 162 representative of the general population and with smaller bias in the overall estimates in  
43  
44 163 meta-analyses.<sup>27</sup> Additionally, influence of a single study on the overall pooled estimate  
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47 164 was tested by omitting one study in each turn. Publication bias was visually assessed  
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49 165 using a funnel plot and quantitatively evaluated by the Egger's tests.  $p < 0.05$  was  
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52 166 considered statistically significant. Evaluation of publication bias, subgroup and  
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55 167 stratified analyses were performed only for the risk of COPD due to small number of  
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57 168 studies for the other outcome. All statistical analyses were performed using Stata version  
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5 169 16 (StataCorp) and Review manager version 5.4 (Cochrane Collaboration).  
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10 171 **Patient and public involvement**  
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12 172 No patient involved.  
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18 174 **RESULTS**

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20 175 **Study selection and characteristics**  
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23 176 A total of 30165 records were identified from the initial database search. 13662 records  
24  
25 177 were removed for duplicates, and 16227 records were excluded after titles and abstracts  
26  
27 178 screening because of irrelevant content and animal studies. The remaining 276 full-text  
28  
29 179 articles were identified for eligibility, of which 252 were excluded for reasons including  
30  
31 180 duplicates (6 studies), reviews (183 studies), insufficient information (9 studies) and  
32  
33 181 ineligible designs and outcomes (54 studies). Finally, 24 studies<sup>14-16 19-21 28-45</sup> were  
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35 182 included in the review. The selection process is shown in **figure 1**.  
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41 183 The characteristics of included 24 studies were shown in online supplemental table  
42  
43 184 S2. The number of participants was 53049 and COPD was more than 21.7%. The mean  
44  
45 185 age of patients with COPD was between 41.4 and 83.1 years while the control subjects  
46  
47 186 was between 42.2 and 80.3 years. These studies were published between 1998 and 2021.  
48  
49 187 The sample size ranged from 117 to 13792. Among included studies, 11 were case-  
50  
51 188 control studies<sup>15 19 28 29 32-34 37 39 42 44</sup> and 10 were cross-sectional studies,<sup>14 20 30 31 35 36 40 41</sup>  
52  
53 189 <sup>43 45</sup> only 3 with a cohort study design.<sup>16 21 38</sup> Additionally, 13 studies were conducted in  
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5 190 Asia,<sup>15 16 19 28 33 35 36 38-40 42-44</sup> while 6 in the North America,<sup>14 20 21 28-30</sup> 4 in Europe<sup>31 34 37</sup>  
6  
7 191 <sup>41</sup> and one in Africa.<sup>45</sup>  
8  
9

10 192 All included articles performed multivariable analyses, in which risk of COPD, or risk  
11  
12 193 of COPD-related events (AE or mortality), was identified as the dependent variable and  
13  
14 194 PD as the independent variable. Control for smoking included stratification (smokers  
15  
16 195 and never smokers) or covariance adjustment in multivariable models (the degree of  
17  
18 196 control: never smokers > adjusting for smoking intensity (duration and dose) >  
19  
20 197 adjusting for smoking status).  
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26 198 The adjustment for confounders of included studies was detailedly presented in online  
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28 199 supplemental table S3. 16 articles reported the adjusted ORs and 4 reported adjusted RRs,  
29  
30 200 2 reporting HRs. One study provided the F value of the one-way analysis of variance for  
31  
32 201 regression analysis<sup>32</sup> while the other one only provided relevant exponential of  
33  
34 202 coefficient for constant, called as Exp (B).<sup>39</sup> Definition of COPD comprised the GOLD  
35  
36 203 criteria, FEV1 <65% of predicted volume, having a history of chronic bronchitis and /  
37  
38 204 or emphysema, self-reported and others. Periodontal parameters used for PD assessment  
39  
40 205 were CAL, ABL, PPD, gingival bleeding (GB), bleeding index (BI), plaque index (PLI)  
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42 206 and oral health index (OHI).  
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## 51 208 **Assessment of bias**

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54 209 Based on the Newcastle-Ottawa Scale, quality assessment for the 24 studies is shown in  
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56 210 online supplemental table S4. Among them, 20 studies<sup>15 19-21 28-30 32-44</sup> were rated as high  
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5 211 quality with a total score of  $\geq 6$  whereas 4 studies<sup>14 16 31 45</sup> as a score of  $< 6$ , indicating  
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8 212 a high risk of bias. The main reasons for lower scores were selection bias  
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10 213 (representativeness of sample population), especially for control groups and  
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13 214 comparability of cases and control subjects.  
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15 215

### 18 216 **Primary outcome**

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20 217 In 20 studies investigating correlation between PD and risk of COPD, only 6<sup>15 19 20 29 33</sup>  
21  
22 218 <sup>36</sup> conducted stratified analyses regarding smoking status, which unanimously suggested  
23  
24 219 PD was not associated with risk of COPD in never smokers. In the remaining 14 studies  
25  
26 220 with relatively inadequate adjustment for smoking, 13 studies<sup>14 28 30-32 34 35 37 38 40-43</sup>  
27  
28 221 revealed PD was significantly correlated with COPD risk in smokers and never smokers  
29  
30 222 combined, the OR value ranging from 1.02 to 10.00. Furthermore, 18 studies<sup>14 15 19 20 28-</sup>  
31  
32 223 <sup>31 33-38 40-43</sup> providing adjusted OR or RR were included in the quantitative analysis,  
33  
34 224 which demonstrated that after adjusting for smoking status, PD increased risk of COPD,  
35  
36 225 but only by a ratio of 1.20 (95% CI 1.09 to 1.32;  $p=0.0002$ ;  $I^2=79\%$ ) (**figure 2**). Further  
37  
38 226 exclusion of any single study did not materially alter the overall pooled OR, with a range  
39  
40 227 from 1.17 (95% CI 1.06-1.28) to 1.28 (95% CI 1.12-1.46). Sensitivity analysis limited  
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42 228 to studies with larger sample size ( $\geq 500$ )<sup>15 19 20 28-30 35-38 40 41 43</sup> revealed similar results  
43  
44 229 (OR 1.24; 95% CI 1.08 to 1.43;  $p=0.003$ ;  $I^2=82\%$ ) (online supplemental figure S1).  
45  
46 230 However, significant publication bias was noted by visual inspections of the funnel plot  
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48 231 (online supplemental figure S2) and the Egger's test for small study effects (bias  
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232 coefficient 1.49; 95% CI 0.44 to 2.55; p=0.008).

233 Subgroup analyses indicated that assessment of PD (p=0.02), study design (p=0.05)  
 234 and diagnosis of COPD (p=0.05) were the potential main causes of heterogeneity (**table**  
 235 **1**). Moreover, there were several findings in subgroup analyses. First, comparing to  
 236 studies adjusting for smoking status, pooled analyses on those controlling for smoking  
 237 intensity did not show apparent correlation on PD and COPD risk (OR 1.14; 95% CI  
 238 0.86 to 1.51; p=0.38; 10 studies<sup>15 19 20 29-31 33 34 36 38</sup>), similar to those applying a GOLD  
 239 criterion (OR 1.10; 95% CI 1.00 to 1.22; p=0.06; 12 studies<sup>15 19 20 31 33-36 38 41-43</sup>). Second,  
 240 with regard to assessment of PD (CAL, ABL and PPD), only those using the parameter  
 241 of ABL presented results with statistical significance (OR 1.98; 95% CI 1.32 to 2.97;  
 242 p=0.001; 6 studies<sup>15 28 29 31 33 41</sup>). Third, in the three locations (Asia, North America and  
 243 Europe), obvious impact of PD on COPD risk was only found in studies of Europe (OR  
 244 2.05; 95% CI 1.07 to 3.95; p=0.03; 4 studies<sup>31 34 37 41</sup>).

245

246 **Table 1** Subgroup analyses regarding risk of COPD

Subgroups	No. Articles	No. Participants /Cases	OR value (95% CI)	P value	I <sup>2</sup> , %
Adjusted for smoking intensity <sup>a</sup>					
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)	<b>0.0002</b>	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)	<b>0.001</b>	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)	<b>0.03</b>	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)	<b>0.0007</b>	46
Study design					
Case-control	8	9,911 / 4,472	1.12 (1.01-1.24)	<b>0.03</b>	86
Cross-sectional	9	38,593 / 4,540	1.34 (1.08-1.66)	<b>0.007</b>	45
Cohort	1	878 / 22	3.51 (1.15-10.74)	<b>0.03</b>	-

247 <sup>a</sup>Duration and dose of smoking.

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

251 **Bold:** subgroups with positive results.

252

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



257

**258 Secondary outcome**

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

266

**267 DISCUSSION**

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

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

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5 278 articles were adjusted for age, except the study by Scannapieco *et al.*<sup>14</sup> In prior evidence,  
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8 279 PD was suggested significantly increasing risk of COPD and COPD-related events.  
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10 280 However, the majority of studies has obvious flaws, such as only applying univariate  
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13 281 analyses, not controlling confounding effect of smoking, and using parameters with  
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15 282 relatively low specificity to determine PD.<sup>13 25 45</sup> To define periodontal disease as  
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18 283 accurately as possible, we preferentially extracted results concerning the parameter of  
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21 284 CAL, ABL or PPD rather than PLI, OHI or remaining teeth. CAL, ABL and PPD are  
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23 285 clinical measurements reflecting the destruction of periodontal tissues, also the basis for  
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26 286 PD diagnosis.<sup>25</sup> Meanwhile, compared with previous meta-analyses, we enrolled more  
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29 287 studies, applied more rigorous screening criteria and most importantly, revealed opposite  
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31 288 results. In meta-analyses with incomplete adjustment for smoking, OR value for COPD  
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34 289 risk in relation to PD ranged from 1.64 to 2.08.<sup>46-48</sup> However, our findings were similar  
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36 290 to studies conducted in never smokers,<sup>15 19 20 29 33 36</sup> showing PD conferred no risk for  
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39 291 COPD. Additionally, pooled results regarding parameters of CAL, ABL and PPD  
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42 292 revealed that PD also did not increase risk of COPD-related AE or mortality. These  
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44 293 demonstrate that previously reported correlation between PD and COPD may be results  
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46 294 of flawed study design, confounding by smoking and even other factors, such as age and  
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49 295 living condition.

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51 296 As a momentous inducer in inflammation-related pathological processes, tobacco is  
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54 297 known to correlate with a variety of systemic disorders.<sup>49</sup> It is also one of the foremost  
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57 298 risk factors for both PD and COPD.<sup>5 10</sup> From the epidemiological perspective, tobacco  
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5 299 smoking is a confounder with spuriously inflated effect on the relationship between PD  
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8 300 and systemic diseases.<sup>49</sup> To investigate the true association between PD and COPD, it is  
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10 301 of great importance to rigorously control the confounding effect of smoking, which  
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13 302 means initiating research in never smokers. However, the majority of former studies  
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15 303 failed to do that. After a wide search, only six studies focusing on never smokers were  
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18 304 found, which unanimously indicated PD was not related with COPD risk. We also  
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21 305 observed decreased magnitude of the association as the control for smoking elevated in  
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23 306 the quantitative analysis. Therefore, it could be too early to make a certain conclusion  
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26 307 on the COPD-PD relationship. Although interventional studies revealed that periodontal  
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29 308 treatment reduced the risk of AE, a number of problems existed, including small sample  
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31 309 size, limited study quality and unclear history of smoking or medication during the  
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34 310 follow-up.<sup>17 18</sup> For example, compared with control subjects, patients in treatment groups  
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37 311 may reduce smoking intentionally, which could spuriously enhance the positive effect  
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39 312 of periodontal treatment. Consequently, future researches need to take these problems  
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41 313 into account.

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44 314 It is worth noting that, another possibility that smoking acts as an effect modifier in  
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47 315 the COPD-PD relationship should not be ignored. Two observational studies performed  
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50 316 stratified analyses concerning smoking status and found strong correlation of PD with  
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52 317 COPD risk was restricted to smokers.<sup>15 20</sup> However, this was not revealed in the current  
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55 318 study, thus more investigations in smokers are required.

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57 319 Besides, current evidence has demonstrated several issues to be addressed in future  
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5 320 relevant study, comprising inconsistent diagnostic criteria of COPD and PD, the lack of  
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8 321 prospective study design and differing adjustments for covariates. These contribute to  
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10 322 substantial heterogeneity among studies.<sup>46 47</sup> The present study indicated the  
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13 323 heterogeneity was partly explained by study design, diagnostic criteria of COPD and  
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15 324 periodontal indexes used to assess PD. Significant association concerning PD and risk  
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18 325 of COPD was only identified in subgroups lacking well designs, applying non-GOLD  
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21 326 criteria or utilizing ABL as the measure of PD. For one thing, this demonstrated that, as  
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24 327 sources of bias, observational study design and nonstandard diagnostic method for  
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27 328 COPD could bring apparent errors, confusing the true relationship of PD with COPD.  
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30 329 For another, given undetermined diagnostic criteria for PD, discrepancies between ABL  
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33 330 and other indexes cannot fully support the COPD-PD association. Notably, as a  
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36 331 radiographic measure, although ABL has been widely considered to reflect cumulative  
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39 332 effects of periodontal attachment loss over time by chronic inflammation,<sup>28</sup> it does not  
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42 333 only exist in PD. Non-periodontal diseases such as liver disorders, cancer and  
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45 334 osteoporosis<sup>50</sup> could also result in ABL. As mentioned previously,<sup>28</sup> the observed  
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48 335 correlation between ABL and COPD risk may relate to those non-periodontal diseases.  
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51 336 Therefore, this remains to be explored further.

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### 53 338 **Limitations**

54 339 Several potential limitations should be taken into consideration when interpreting the  
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57 340 present results. First, all included studies are observational, which are highly subject to  
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5 341 selection bias and confounding by indication. Second, substantial heterogeneity was  
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8 342 identified in current study, though we conducted subgroup and stratified analyses to  
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10 343 partly explain and reduce it. As stated above, several problems leading to heterogeneity  
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13 344 need to be addressed in future researches. Third, the number of studies on risk of COPD-  
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15 345 related events was limited, thus the result needs to be carefully understood. Limited  
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18 346 number of studies in subgroup and stratified analyses suggested more relevant studies  
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21 347 with larger sample size are required. Fourth, although confounding effects of age and  
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23 348 smoking were controlled by stratified analysis and statistical adjustment, other potential  
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26 349 confounders such as gender, living condition and socioeconomic status<sup>10</sup> could also  
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29 350 reduce reliability of the results. Fifth, obvious publication bias was noted in relevant  
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31 351 meta-analyses,<sup>46 47</sup> including the present study. For the purpose of rapid review,<sup>23</sup> we  
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34 352 only included articles in English. There could exist non-English publications and  
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37 353 unpublished evidence, despite we searched English-language studies as much as possible.  
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39 354 Finally, although smoking status and intensity were considered in subgroup analysis,  
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42 355 information regarding tobacco content and chemical composition were not collected.  
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44 356 This information is difficult to obtain, especially from self-reported smoking, leaving a  
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47 357 residual smoking-related bias. Consequently, it is advisable to explore relationship  
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49 358 between COPD and PD in never smokers.

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## 360 **CONCLUSION**

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

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5 362 associated with risk of COPD and COPD-related events. Previously reported  
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8 363 relationship between COPD and PD may be results of flawed study design and  
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10 364 confounding by smoking. However, future well-designed studies are required to validate  
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13 365 the present findings.  
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15 366

### 18 367 **Abbreviations**

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20 368 ABL: Alveolar bone loss; AE: Acute exacerbation; BI: Bleeding index; CAL: Clinical  
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23 369 attachment level; CI: Confident interval; COPD: Chronic obstructive pulmonary disease;  
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26 370 GB: Gingival bleeding; GOLD: Global Initiative for Chronic Obstructive Lung Diseases;  
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28 371 HR: Hazard ratio; OHI: Oral health index; OR: Odds ratio; PD: Periodontal disease; PLI:  
29  
30 372 Plaque index; PPD: Probing pocket depth; RR: Relative risk.  
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35  
36 374 **Contributors** LC and LL designed the study. MY and XL screened and selected relevant  
37  
38 375 studies. MY, RP and XL rated the study quality and extracted the data. MY, RP, XL and  
39  
40  
41 376 JP analyzed the data. All authors interpreted the data, and MY, RP, XL, JP drafted the  
42  
43  
44 377 paper. LC and LL critically revised the paper. All authors acknowledged and agreed with  
45  
46  
47 378 the format and content of the paper before submission for publication. LC and LL are  
48  
49 379 the guarantors and responsible for the overall contents of this study.  
50

51 380

52  
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54 381 **Funding** This research received no specific grant from any funding agency in the public,  
55  
56  
57 382 commercial or not-for-profit sectors.  
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8 384 **Competing interests** None declared.  
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10 385  
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13 386 **Patient and public involvement** Patients and/or the public were not involved in the  
14  
15 387 design, or conduct, or reporting, or dissemination plans of this research.  
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20 389 **Patient consent for publication** Not applicable.  
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25 391 **Ethics approval** Not applicable.  
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30 393 **Data availability statement** The data that support the findings of this study are available  
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32 394 from the corresponding author upon reasonable request.  
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40 397 Lei Chen <https://orcid.org/0000-0003-3476-0035>  
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## 544 **Figure legends**

545 **Figure 1** PRISMA flow diagram of study selection.

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

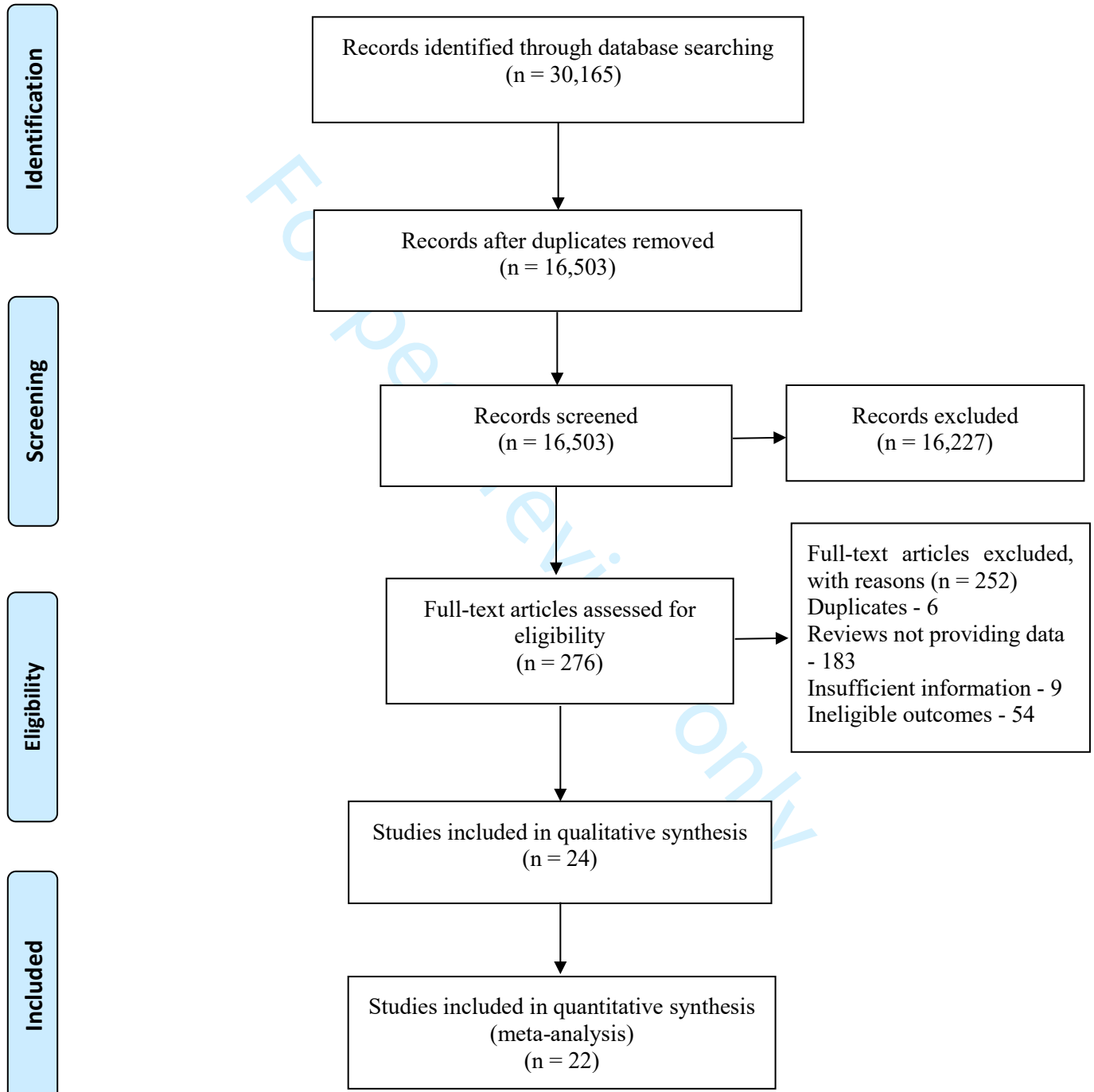
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5 547 on adjusted by smoking status and intensity versus by smoking status only. Values more  
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8 548 than one indicate a higher risk in patients with periodontal disease.

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10 549 **Figure 3** Forest plot of the risk of COPD by periodontal disease. **A** in smokers and **B** in  
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13 550 never smokers. Values more than one indicate a higher risk in patients with periodontal  
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15 551 disease.

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18 552 **Figure 4** Forest plot of the risk of COPD-related events by periodontal disease. Values  
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21 553 more than one indicate a higher risk in patients with periodontal disease.



## PRISMA 2009 Flow Diagram



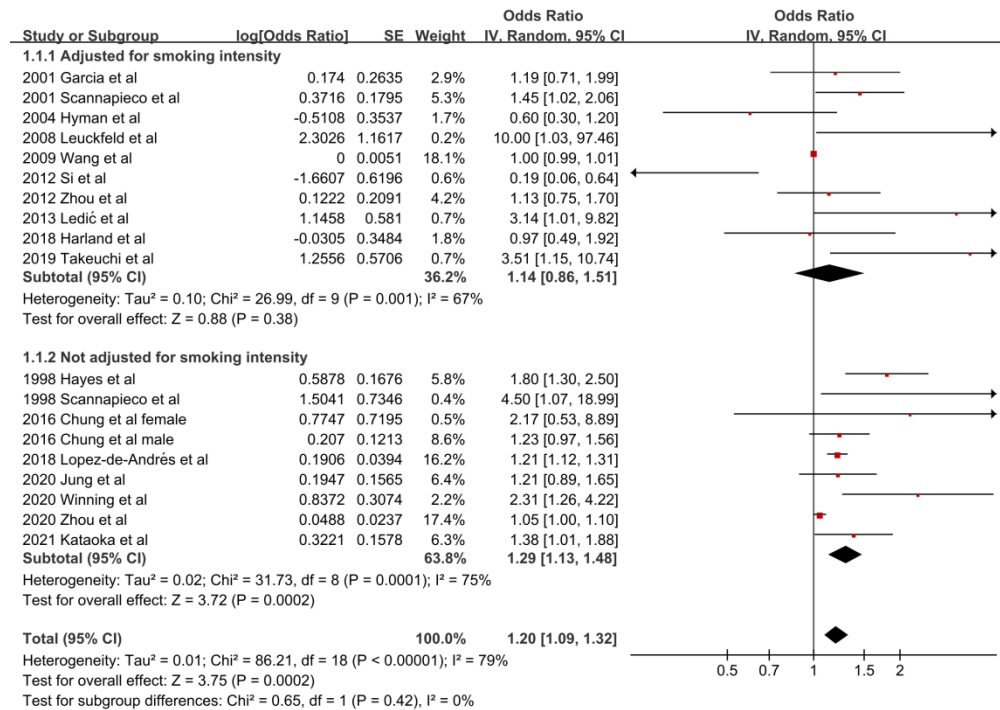


Figure 2 Forest plot of the risk of COPD by periodontal disease, subgroup analysis based on adjusted by smoking status and intensity versus by smoking status only. Values more than one indicate a higher risk in patients with periodontal disease.

536x384mm (118 x 118 DPI)

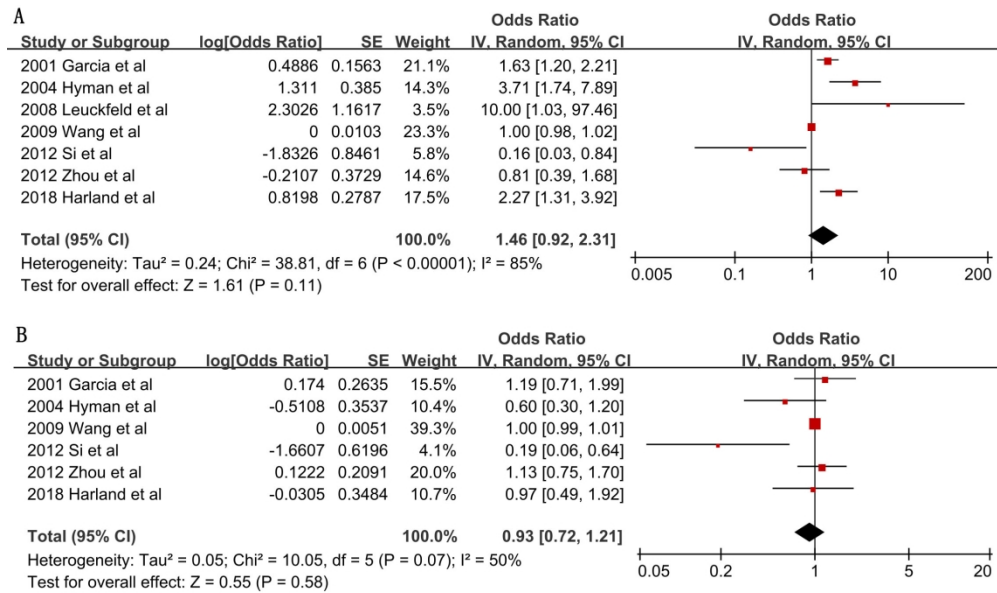


Figure 3 Forest plot of the risk of COPD by periodontal disease. A in smokers and B in never smokers. Values more than one indicate a higher risk in patients with periodontal disease.

192x118mm (300 x 300 DPI)



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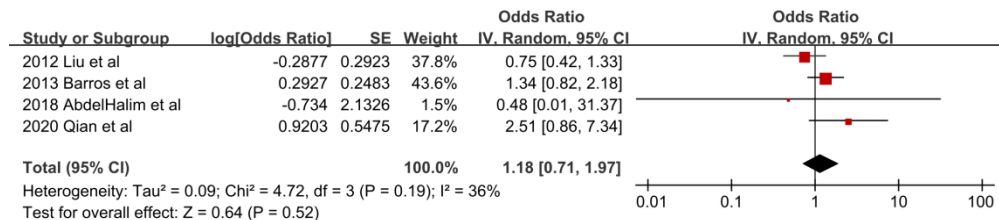


Figure 4 Forest plot of the risk of COPD-related events by periodontal disease. Values more than one indicate a higher risk in patients with periodontal disease.

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## PRISMA 2009 Checklist

Section/topic	Item No	Checklist item	Reported on Page Number/Line Number	Reported on Section/Paragraph
<b>TITLE</b>				
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1 / Line 2	Title page
<b>ABSTRACT</b>				
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
<b>INTRODUCTION</b>				
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
<b>METHODS</b>				
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 <sup>2</sup> ) 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
<b>RESULTS</b>				
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
<b>DISCUSSION</b>				
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](http://www.prisma-statement.org).

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**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

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**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 <i>et al</i> <sup>1</sup>	Case-control	United States	261/857	45.1±9.7/42.2±9.1	ABL	FEV1
1998 Scannapieco <i>et al</i> <sup>2</sup>	Cross-sectional	United States	77/309	NA	OHI	Self-reported
2001 Garcia <i>et al</i> <sup>3</sup>	Case-control	United States	279/833	NA	ABL, PPD	FEV1
2001 Scannapieco <i>et al</i> <sup>4</sup>	Cross-sectional	United States	810/12,982	51.2±17.9/43.9±17.7	CAL, GB	Self-reported
2004 Hyman <i>et al</i> <sup>5</sup>	Cross-sectional	United States	993/6,632	62.3±14.1/47.4±14.2	CAL	GOLD
2008 Leuckfeld <i>et al</i> <sup>6</sup>	Cross-sectional	Norway	130/50	54.9±4.9/47.0±9.8	ABL	GOLD
2009 Deo <i>et al</i> <sup>7</sup>	Case-control	India	150/50	41.4±7.5/43.6±5.5	CAL, GB	FEV1 / FVC
2009 Wang <i>et al</i> <sup>8</sup>	Case-control	China	306/328	63.9±9.8/63.3±9.0	CAL, PLI	GOLD
2012 Liu <i>et al</i> <sup>9</sup>	Case-control	China	183/209*	64.3±10.1/63.6±9.7*	CAL, PPD, BI	GOLD
2012 Si <i>et al</i> <sup>10</sup>	Case-control	China	581/438	63.9±9.4/62.8±9.5	CAL, ABL, PPD, PLI, BI	GOLD
2012 Zhou <i>et al</i> <sup>11</sup>	Case-control	China	193/181	63.6±10.3/62.1±9.1	CAL, ABL, PPD, PLI, BI	GOLD
2013 Barros <i>et al</i> <sup>12</sup>	Cohort	United States	399/1,236 <sup>§</sup>	63.9±5.7/66.0±5.1 <sup>#</sup>	CAL, PPD	GOLD
2013 Ledić <i>et al</i> <sup>13</sup>	Case-control	Croatia	93/43	65.8±9.7/62.1±11.9	CAL	GOLD
2016 Chung <i>et al</i> <sup>14</sup>	Cross-sectional	Korea	697/5,181	64.3±0.2/54.6±0.1	PPD, GB	GOLD
2018 AbdelHalim <i>et al</i> <sup>15</sup>	Cross-sectional	Egypt	134/116*	56.8±10.4/55.3±9.1*	CAL, PPD, BI, PLI, OHI	GOLD
2018 Harland <i>et al</i> <sup>16</sup>	Cross-sectional	Japan	149/1,325	61.3±9.1/54.5±8.7	PPD	GOLD

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4	2018 Lopez-de-Andrés <i>et al</i> <sup>17</sup>	Case-control	Spain	2,699/2,699	63±14/61±14	Self-reported	Self-reported
5							
6	2019 Bomble <i>et al</i> <sup>18</sup>	Case-control	India	39/78	NA	CAL, OHI, PPD	GOLD
7							
8							
9	2019 Takeuchi <i>et al</i> <sup>19</sup>	Cohort	Japan	22/878	NA	CAL, PPD	GOLD
10							
11							
12	2020 Jung <i>et al</i> <sup>20</sup>	Cross-sectional	Korea	1,134/6,585	62.6±0.4/53.6±0.2	PPD	FEV1 / FVC
13							
14	2020 Qian <i>et al</i> <sup>21</sup>	Cohort	China	23 <sup>‡</sup> /NA	83.1±4.8/80.3±3.7	ABL	NR
15							
16							
17	2020 Winning <i>et al</i> <sup>22</sup>	Cross-sectional	Sweden	86/740	NA	ABL	GOLD
18							
19							
20	2020 Zhou <i>et al</i> <sup>23</sup>	Case-control	China	60/60	63.1±10.1/60.0±9.4	CAL, PLI	GOLD
21							
22	2021 Kataoka <i>et al</i> <sup>24</sup>	Cross-sectional	Japan	464/249	54.1±9.4/NA	PPD	GOLD
23							

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

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

27  
28 <sup>§</sup>No. COPD subjects with events (hospitalization for exacerbation or COPD-related death) in the 5-year follow-up  
29 visit/COPD subjects without events in the 5-year follow-up visit.

30  
31 <sup>‡</sup>No. COPD-related mortality in a follow-up visit more than 5 years.

32 ABL, alveolar bone loss; BI, bleeding index; CAL, clinical attachment level; FEV1, forced expiratory volume in 1  
33 second; FVC, forced vital capacity; GB, gingival bleeding; GOLD, Global Initiative for Chronic Obstructive Lung  
34 Disease; NA, not available; OHI, oral health index; PD, periodontal disease; PLI, plaque index; PPD, probing  
35 pocket depth.  
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**Table S3** Adjustment for confounders of included studies

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



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

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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 <i>et al</i> <sup>12</sup>	*	*	*	...	...	*	*	*	6
Sukeuchi <i>et al</i> <sup>19</sup>	*	*	*	*	...	*	*	*	7
Qian <i>et al</i> <sup>21</sup>	...	*	*	...	...	*	*	...	4

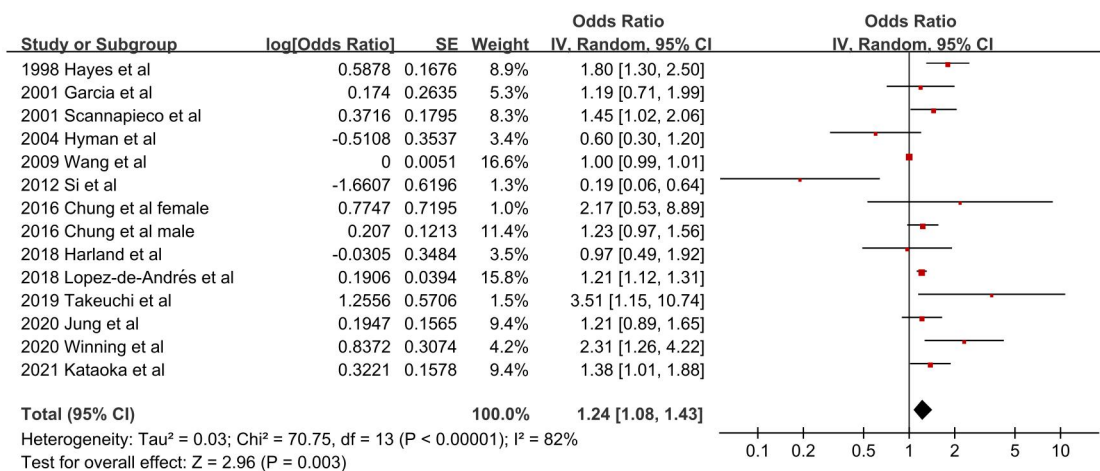
(B) Case-control / cross-sectional study

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-resp onse rate	
Hayes <i>et al</i> <sup>1</sup>	*	...	*	*	*	*	*	*	7
Scarpapico <i>et al</i> <sup>2</sup>	...	*	*	*	...	*	*	...	5
García <i>et al</i> <sup>3</sup>	*	...	*	*	*	*	*	*	7
Scarpapico <i>et al</i> <sup>4</sup>	...	*	*	*	...	*	*	*	6
Hynnian <i>et al</i> <sup>5</sup>	*	*	*	*	...	*	*	*	7
Leukfeld <i>et al</i> <sup>6</sup>	*	...	...	*	...	*	*	*	5
Deo <i>et al</i> <sup>7</sup>	*	*	...	*	*	*	*	*	7
Wang <i>et al</i> <sup>8</sup>	*	*	...	*	*	*	*	*	7
Liu <i>et al</i> <sup>9</sup>	*	*	...	*	*	*	*	*	7
Si <i>et al</i> <sup>10</sup>	*	*	...	*	*	*	*	*	7
Zhou <i>et al</i> <sup>11</sup>	*	*	...	*	*	*	*	*	7
Lečić <i>et al</i> <sup>13</sup>	*	*	...	*	*	*	*	*	7
Chung <i>et al</i> <sup>14</sup>	*	*	*	*	...	*	*	*	7
Abdel Halim <i>et al</i> <sup>15</sup>	*	...	...	*	...	*	*	*	5
Harland <i>et al</i> <sup>16</sup>	*	*	...	*	...	*	*	*	6
Lopez-de-Andrés <i>et al</i> <sup>14</sup>	...	*	*	*	*	...	*	*	6
Bomble <i>et al</i> <sup>18</sup>	*	*	...	*	**	*	*	*	8
Wang <i>et al</i> <sup>20</sup>	...	*	*	*	...	*	*	*	6
Wang <i>et al</i> <sup>22</sup>	*	*	*	*	...	*	*	*	7

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Zhou <i>et al</i> <sup>23</sup>	*	*	...	...	**	*	*	*	7
Kaboka <i>et al</i> <sup>24</sup>	*	*	*	*	...	*	*	*	7

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

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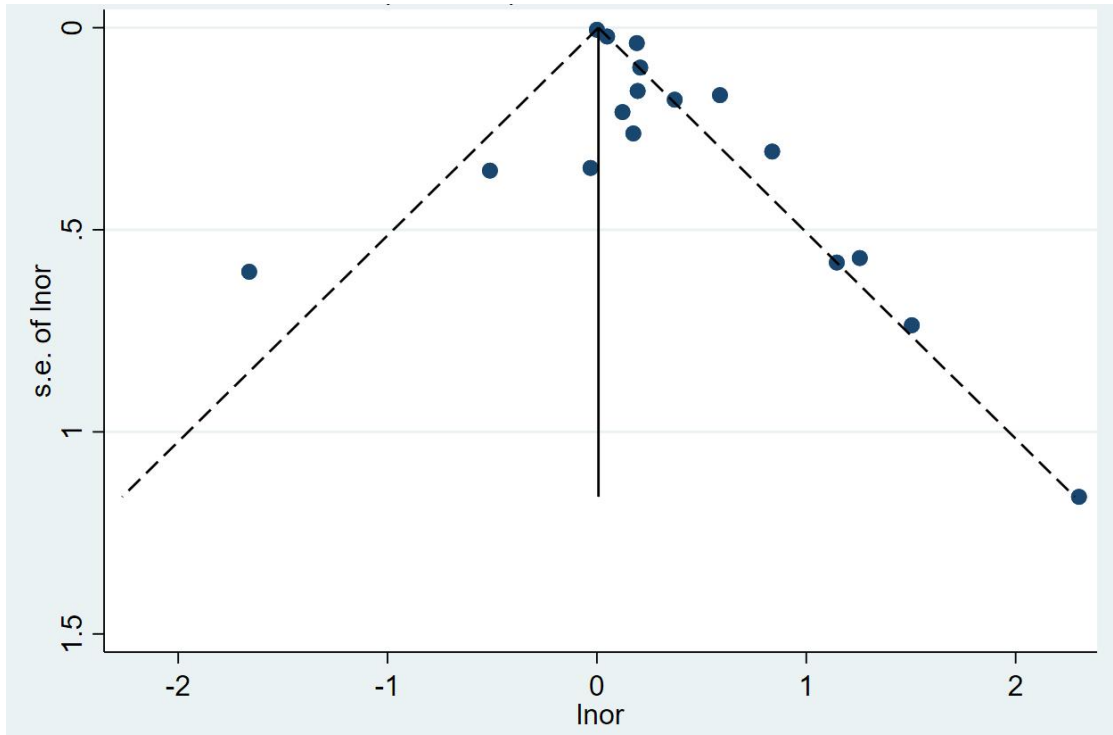


Figure S2 Funnel plot for risk of COPD, with pseudo 95% confidence limits.

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-067432.R1
Article Type:	Original research
Date Submitted by the Author:	25-Feb-2023
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<b>Primary Subject Heading</b>:	Respiratory medicine
Secondary Subject Heading:	Public health, Smoking and tobacco, Dentistry and oral medicine
Keywords:	Chronic airways disease < THORACIC MEDICINE, RESPIRATORY MEDICINE (see Thoracic Medicine), ORAL MEDICINE, Emphysema < THORACIC MEDICINE

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5 **1 Title Page**  
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7 **2 Title:** The association between chronic obstructive pulmonary disease and periodontal  
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3 disease: a systematic review and meta-analysis

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21 **Word count of the abstract:** 274

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10 24 **The association between chronic obstructive pulmonary**  
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12 **disease and periodontal disease: a systematic review and**  
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14 **meta-analysis**  
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20 28 **ABSTRACT**  
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23 29 **Objectives** Studies have suggested contradictory results on the relationship between  
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25 chronic obstructive pulmonary disease (COPD) and periodontal disease (PD). The aim  
26 30  
27 of this study was to determine whether PD increased the risk of COPD and COPD-  
28 31  
29 related clinical events.  
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33 33 **Design** Systematic review and meta-analysis.  
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36 34 **Data sources** PubMed, EMBASE and CENTRAL were searched from inception to 22  
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38 February 2023.  
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41 36 **Eligibility criteria for studies** We included trials and observational studies evaluating  
42  
43 association of PD with the risk of COPD or COPD-related events (exacerbation and  
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45 mortality), with statistical adjustment for smoking.  
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48  
49 39 **Data extraction and synthesis** Two investigators independently extracted data from  
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51 selected studies using a standardized Excel file. Quality of studies was evaluated using  
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53 the Newcastle-Ottawa Scale. Odds ratio (OR) with 95% confident interval (CI) was  
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55 pooled in a random-effect model with inverse variance method.  
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5 43 **Results** 22 observational studies with 51704 participants were included. Pooled analysis  
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8 44 of 18 studies suggested that PD was weakly associated with the risk of COPD (OR 1.20,  
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10 45 95% CI 1.09 to 1.32). However, in stratified and subgroup analyses, with strict  
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12 46 adjustment for smoking, PD no longer related to the risk of COPD (adjusting for  
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14 47 smoking intensity: OR 1.14, 95% CI 0.86 to 1.51; smokers only: OR 1.46, 95% CI 0.92  
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16 48 to 2.31; never smokers only: OR 0.93, 95% CI 0.72 to 1.21). Moreover, PD did not  
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18 49 increase the risk of COPD-related exacerbation or mortality (OR 1.18, 95% CI 0.71 to  
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20 50 1.97) in the pooled result of four studies.  
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26 51 **Conclusions** This study demonstrates PD confers no risk for COPD and COPD-related  
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28 52 events when strictly adjusted by smoking. Large-scale prospective cohort studies with  
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30 53 control of potential confounding factors are warranted to validate the present findings.  
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## 36 55 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

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39 56 1. This is the largest systematic review and meta-analysis on association between  
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41 57 chronic obstructive pulmonary disease (COPD) and periodontal disease (PD)  
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43 58 collecting data over 20 years.  
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46 59 2. This is the first meta-analysis investigating whether PD increases the risk of COPD-  
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48 60 related events (exacerbation or mortality).  
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51 61 3. Compared with previous reports, this study was conducted with more strict  
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53 62 adjustment for confounding by smoking, which was the most important confounder  
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55 63 in the COPD-PD relationship.  
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5 64 4. Our study provided limited evidence on the outcome of COPD-related events  
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8 65 because of limited data.

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10 66 5. Clinical heterogeneity and publication bias compromised the evidence strength of  
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12 67 this study, although subgroup and stratified analyses were performed.

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## 17 69 **INTRODUCTION**

20 70 Chronic obstructive pulmonary disease (COPD) is the third leading cause of death,  
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22 71 resulting in enormous economic burden.<sup>1</sup> Commonly, COPD coexists with a variety of  
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24 72 disorders, called comorbidities, which play significant roles in the progression and  
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26 73 prognosis of COPD.<sup>2,3</sup> Understanding the COPD-comorbidities relationship has been a  
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28 74 momentous prerequisite for optimizing disease prevention and management strategies.<sup>2</sup>  
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36 76 Given ageing and widespread use of inhaled corticosteroids in COPD, periodontal  
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38 77 disease (PD) has been a common comorbidity of COPD.<sup>4</sup> It is a chronic inflammatory  
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40 78 condition of tissues surrounding and supporting the teeth, including gingiva, bone and  
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42 79 ligament,<sup>5</sup> with the prevalence estimates over 10% around the world and especially  
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44 80 prevalent in elderly individuals.<sup>6</sup> To date, diagnosis and assessment of PD are mostly  
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46 81 based on periodontal measurements including clinical attachment level (CAL), probing  
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48 82 pocket depth (PPD) and alveolar bone loss (ABL).<sup>5</sup> They are primary clinical  
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50 83 manifestations of PD, reflecting the extent of periodontal tissue destruction.<sup>5</sup>

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57 84 Based on the nature of inflammation,<sup>5,7</sup> mounting evidence has shed light on the  
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5 85 association between PD and development of COPD.<sup>8 9</sup> Currently three points are  
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8 86 proposed. First, they share the same risk factors, such as age, gender, smoking and  
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10 87 socioeconomic status.<sup>2 10</sup> Second, they have similar pathogenetic mechanisms. Both  
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12 88 diseases are characterized by host susceptibility to environmental factors, immune  
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15 89 overreaction, oxidative stress and production of pro-inflammatory cytokines.<sup>7 8</sup> Most  
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18 90 importantly, neutrophilic inflammation plays a key role in both diseases.<sup>8 11</sup> Third, oral  
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20 91 bacteria released from the dental plaque in PD could trigger progression and acute  
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23 92 exacerbation (AE) of COPD.<sup>12 13</sup>

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26 93 Meanwhile, epidemiological evidence has indicated that PD increases risk of COPD<sup>11</sup>  
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28 94 <sup>14 15</sup> and COPD-related events.<sup>13 16</sup> Scannapieco *et al* revealed a 4.5-fold increased risk  
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30 95 of COPD in patients with PD, compared with those without.<sup>14</sup> A dose-response  
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33 96 relationship was further implied between PD severity and lung function.<sup>15</sup> Among  
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36 97 patients with both diseases, COPD-related AE and mortality also significantly linked  
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39 98 with periodontal status.<sup>13 16</sup> Periodontal therapy, such as scaling and root planing  
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42 99 treatment, may ameliorate lung function and decrease frequency of AE in COPD with  
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45 100 chronic periodontitis.<sup>17 18</sup> However, there were some other studies revealing opposite  
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48 101 results, resulting in a long-standing controversy.<sup>19-21</sup> It is worth noting that, parameters  
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51 102 used to determine PD apparently varied across studies, and these studies also failed to  
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54 103 adequately control for confounders, especially smoking, the most important confounder  
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57 104 for the COPD-PD relationship. Therefore, to provide the latest and most convincing  
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60 105 evidence, we systematically reviewed current available literature to investigate whether

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5 106 PD increases the risk of COPD. The secondary objective was to evaluate the association  
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7 107 between PD and the risk of COPD-related events. Subgroup and stratified analyses were  
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10 108 also conducted to adjust for the confounding by smoking.  
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## 15 110 **METHODS**

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18 111 This systematic review and meta-analysis was conducted and reported in accordance to  
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20 112 the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)  
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23 113 guideline.<sup>22</sup>  
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### 28 115 **Search strategy and selection criteria**

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31 116 We searched PubMed, EMBASE and CENTRAL for records evaluating association  
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33 117 between COPD and PD, from inception to 22 February 2023. The search strategy was  
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36 118 described in online supplemental table S1. The language was restricted to English, for  
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39 119 the purpose of rapid review.<sup>23</sup> Studies meeting the following criteria were included: (1)  
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41 120 adult participants ( $\geq 18$  years); (2) original studies with randomized controlled trial  
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44 121 (RCT), cohort, case-control or cross-sectional study designs; (3) presenting clear  
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47 122 diagnostic or assessment criteria for COPD and PD; (4) evaluating association between  
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49 123 PD and the risk of COPD, or risk of COPD-related events (AE and mortality), with  
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52 124 statistical adjustment for smoking, and providing the adjusted odds ratio (OR), relative  
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54 125 risk (RR) or hazard ratio (HR) for the risk of COPD, AE and mortality in relation to PD.

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57 126 According to the inclusion criteria, two independent investigators (MY and XL)

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5 127 performed systematical search, screened titles and abstracts of all retrieved studies to  
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7 128 exclude duplicate or irrelevant records. For articles requiring further assessment, full-  
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10 129 text reviews were carried out and references of retrieved articles and relevant reviews  
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13 130 were also manually checked to identify additional eligible studies. Disagreements were  
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15 131 resolved by discussion between the two reviewers or with the help of the third  
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18 132 investigator (RP).

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### 22 23 134 **Data extraction and quality assessment**

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25 135 Two investigators (MY and RP) independently extracted data from selected studies  
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27 136 using a standardized Excel (Microsoft Corporation) file. The following information was  
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30 137 extracted: author, year of publication, country, study design, number of subjects (COPD  
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33 138 and non-COPD), demographic characteristics of participants, periodontal variables  
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36 139 applied to assess PD, diagnostic criteria for COPD, definition of COPD-related AE and  
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39 140 mortality, adjusted OR, RR or HR for the risk of COPD, AE and mortality in relation to  
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42 141 PD, as well as adjustment for confounders. The primary outcome was the risk of COPD.  
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44 142 Secondary outcome was the risk of COPD-related adverse events, including AE and  
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47 143 mortality. Quality of studies was independently evaluated using the Newcastle-Ottawa  
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49 144 Scale<sup>24</sup> by two investigators (MY and XL). A score of  $\geq 6$  was considered a low risk  
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52 145 while  $< 6$  a high risk of bias. Both case-control and cohort studies had a maximum score  
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55 146 of 9. Cross-sectional study was regarded as case-control study when performing quality  
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57 147 assessment. Discrepancies regarding data extraction and quality assessment were  
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5 148 resolved through discussion and consensus.  
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10 150 **Data analysis**  
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13 151 The final pooled estimate was expressed as OR with 95% confident interval (CI).  
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15 152 Considering CAL, ABL and PPD have been regarded as the primary parameters for  
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18 153 PD,<sup>25 26</sup> where more than one adjusted estimate was shown in the paper, we preferentially  
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21 154 used the estimate regarding these parameters (CAL > ABL > PPD), or the estimate being  
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23 155 better adjusted for tobacco smoking (never smokers > adjusting for smoking intensity  
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26 156 [duration and dose] > adjusting for smoking status), or the estimate regarding more  
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28 157 severe PD, where available. For case-control and cross-sectional studies, we estimated  
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31 158 the OR whereas for cohort studies we estimated the RR or HR. The random-effect model  
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33 159 with inverse variance method were applied due to potential heterogeneity resulting from  
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36 160 methodological differences. Heterogeneity across studies was identified with the I<sup>2</sup>  
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39 161 statistic. I<sup>2</sup> statistic >50% indicated significant heterogeneity.  
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41 162 To explore heterogeneity, subgroup analyses were conducted based on study design  
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44 163 (case-control, cross-sectional and cohort studies), geographical location (Asia, North  
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46 164 America, Europe), assessment of PD (CAL, ABL and PPD), definition of COPD (Global  
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49 165 Initiative for Chronic Obstructive Lung Diseases, GOLD and non-GOLD criteria) and  
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52 166 adjustment for smoking intensity (dose and duration of smoking). To better control the  
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54 167 confounding effect of smoking, stratified analyses were performed in smokers and never  
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57 168 smokers respectively.  
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5 169 To test the robustness of study findings, we performed sensitivity analysis on studies  
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8 170 with relatively large sample size ( $\geq 500$  participants), which tended to be more  
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10 171 representative of the general population and with smaller bias in the overall estimates in  
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13 172 meta-analyses.<sup>27</sup> Additionally, influence of a single study on the overall pooled estimate  
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15 173 was tested by omitting one study in each turn. Publication bias was visually assessed  
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18 174 using a funnel plot and quantitatively evaluated by the Egger's tests.  $P < 0.05$  was  
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21 175 considered statistically significant. All statistical analyses were performed using Stata  
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23 176 version 16 (StataCorp) and Review manager version 5.4 (Cochrane Collaboration).  
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## 28 178 **Patient and public involvement**

30 179 No patient involved.  
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## 36 181 **RESULTS**

### 38 182 **Study selection and characteristics**

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41 183 A total of 30165 records were identified from the initial database search. 13662 records  
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43 184 were removed for duplicates, and 16227 records were excluded after titles and abstracts  
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45 185 screening because of irrelevant content and animal studies. The remaining 276 full-text  
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47 186 articles were identified for eligibility, of which 254 were excluded for reasons including  
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50 187 duplicates (six studies), reviews (183 studies), insufficient information (nine studies) and  
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53 188 ineligible designs and outcomes (56 studies). Finally, 22 studies<sup>14-16 19-21 28-43</sup> were  
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56 189 included in the review. The selection process is shown in **figure 1**.  
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5 190 The characteristics of included 22 studies were shown in **table 1**. The number of  
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8 191 participants was 51704 and there were 9973 (18.9%) patients with COPD. The mean age  
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10 192 of patients with COPD was between 45.1 and 83.1 years while the control subjects was  
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13 193 between 42.2 and 80.3 years. These studies were published between 1998 and 2021. The  
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15 194 sample size ranged from 120 to 13792. Nine studies were case-control studies<sup>15 19 28 29 32</sup>  
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18 195 <sup>33 36 40 42</sup> and 10 studies were cross-sectional studies,<sup>14 20 30 31 34 35 38 39 41 43</sup> only three  
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20 196 studies with a cohort study design.<sup>16 21 37</sup> Additionally, 11 studies were conducted in  
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23 197 Asia,<sup>15 16 19 32 34 35 37 38 40-42</sup> while six studies in the North America,<sup>14 20 21 28-30</sup> four studies  
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26 198 in Europe<sup>31 33 36 39</sup> and one study in Africa.<sup>43</sup>

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**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 <i>et al</i> <sup>28</sup>	Case-control	United States	261/857	45.1±9.7/42.2±9.1	ABL	FEV <sub>1</sub>
1998 Scannapieco <i>et al</i> <sup>14</sup>	Cross-sectional	United States	77/309	NA	OHI	Self-reported
2001 Garcia <i>et al</i> <sup>29</sup>	Case-control	United States	279/833	NA	ABL, PPD	FEV <sub>1</sub>
2001 Scannapieco <i>et al</i> <sup>30</sup>	Cross-sectional	United States	810/12,982	51.2±17.9/43.9±17.7	CAL, GB	Self-reported
2004 Hyman <i>et al</i> <sup>20</sup>	Cross-sectional	United States	993/6,632	62.3±14.1/47.4±14.2	CAL	GOLD
2008 Leuckfeld <i>et al</i> <sup>31</sup>	Cross-sectional	Norway	130/50	54.9±4.9/47.0±9.8	ABL	GOLD
2009 Wang <i>et al</i> <sup>19</sup>	Case-control	China	306/328	63.9±9.8/63.3±9.0	CAL, PLI	GOLD
2012 Liu <i>et al</i> <sup>42</sup>	Case-control	China	183/209*	64.3±10.1/63.6±9.7	CAL, PPD, BI	GOLD

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2012 Si <i>et al</i> <sup>15</sup>	Case-control	China	581/438	63.9±9.4/62.8±9.5	CAL, ABL, PPD, PLI, BI	GOLD
2012 Zhou <i>et al</i> <sup>32</sup>	Case-control	China	193/181	63.6±0.3/62.1±9.1	CAL, ABL, PPD, PLI, BI	GOLD
2013 Barros <i>et al</i> <sup>21</sup>	Cohort	United States	399/1,236 <sup>§</sup>	63.9±5.7/66.0±5.1	CAL, PPD	GOLD
2013 Ledić <i>et al</i> <sup>33</sup>	Case-control	Croatia	93/43	65.8±9.7/62.1±11.9	CAL	GOLD
2016 Chung <i>et al</i> <sup>34</sup>	Cross-sectional	Korea	697/5,181	64.3±0.2/54.6±0.1	PPD, GB	GOLD
2018 AbdelHalim <i>et al</i> <sup>43</sup>	Cross-sectional	Egypt	134/116*	56.8±10.4/55.3±9.1	CAL, PPD, BI, PLI, OHI	GOLD
2018 Harland <i>et al</i> <sup>35</sup>	Cross-sectional	Japan	149/1,325	61.3±9.1/54.5±8.7	PPD	GOLD
2018 Lopez-de-Andrés <i>et al</i> <sup>36</sup>	Case-control	Spain	2,699/2,699	63±14/61±14	Self-reported	Self-reported
2019 Takeuchi <i>et al</i> <sup>37</sup>	Cohort	Japan	22/878	NA	CAL, PPD	GOLD
2020 Jung <i>et al</i> <sup>38</sup>	Cross-sectional	Korea	1,134/6,585	62.6±0.4/53.6±0.2	PPD	FEV <sub>1</sub> / FVC
2020 Qian <i>et al</i> <sup>16</sup>	Cohort	China	23 <sup>‡</sup> /NA	83.1±4.8/80.3±3.7	ABL	NR
2020 Winning <i>et al</i> <sup>39</sup>	Cross-sectional	Sweden	86/740	NA	ABL	GOLD
2020 Zhou <i>et al</i> <sup>40</sup>	Case-control	China	60/60	63.1±10.1/60.0±9.4	CAL, PLI	GOLD
2021 Kataoka <i>et al</i> <sup>41</sup>	Cross-sectional	Japan	464/249	54.1±9.4/NA	PPD	GOLD

- 201 Continuous data are presented as mean ± standard deviation (SD) unless otherwise indicated.
- 202 \*No. COPD subjects with frequent exacerbation (≥2 exacerbations in the last year)/Infrequent exacerbation (< 2
- 203 exacerbations in the last year).
- 204 <sup>§</sup>No. COPD subjects with events (hospitalization for exacerbation or COPD-related death) in the 5-year follow-up
- 205 visit/COPD subjects without events in the 5-year follow-up visit.
- 206 <sup>‡</sup>No. COPD-related mortality in a follow-up visit more than 5 years.
- 207 ABL, alveolar bone loss; BI, bleeding index; CAL, clinical attachment level; FEV<sub>1</sub>, forced expiratory volume in 1
- 208 second; FVC, forced vital capacity; GB, gingival bleeding; GOLD, Global Initiative for Chronic Obstructive Lung

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4 209 Disease; NA, not available; OHI, oral health index; PD, periodontal disease; PLI, plaque index; PPD, probing pocket  
5 210 depth.  
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9 212 All included articles performed multivariable analyses, in which the risk of COPD, or  
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11 213 risk of COPD-related events (AE or mortality), was identified as the dependent variable  
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14 214 and PD as the independent variable. Controlling for confounding by smoking included  
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16 215 stratification (smokers and never smokers) or covariance adjustment in multivariable  
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18 216 models (the degree of control: never smokers > adjusting for smoking intensity [duration  
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20 217 and dose] > adjusting for smoking status).  
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24 218 The adjustment for confounders of included studies was detailedly presented in online  
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26 219 supplemental table S2. 16 articles reported the adjusted ORs and 4 reported adjusted RRs,  
27  
28 220 two studies reporting HRs. Definition of COPD comprised the GOLD criteria,<sup>2</sup> FEV<sub>1</sub>  
29  
30 221 <65% of predicted volume, having a history of chronic bronchitis and / or emphysema,  
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32 222 self-reported and others. Periodontal parameters used for PD assessment were CAL,  
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34 223 ABL, PPD, gingival bleeding (GB), bleeding index (BI), plaque index (PLI) and oral  
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36 224 health index (OHI).  
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#### 45 226 **Assessment of bias**

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47 227 Based on the Newcastle-Ottawa Scale, quality assessment for the 22 studies was shown  
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49 228 in online supplemental table S3. Among them, 18 studies<sup>15 19-21 28-30 32-42</sup> were rated as  
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51 229 high quality with a total score of  $\geq 6$  whereas four studies<sup>14 16 31 43</sup> as a score of <6,  
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53 230 indicating a high risk of bias. The main reasons for lower scores were selection bias  
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56 231 (representativeness of sample population), especially for control groups and  
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232 comparability of cases and control subjects.

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### 234 **Primary outcome**

235 18 studies<sup>14 15 19 20 28-41</sup> provided data for the risk of COPD in relation to PD. Quantitative  
236 analysis demonstrated that after adjusting for smoking status, PD increased the risk of  
237 COPD, but only by a ratio of 1.20 (95% CI 1.09 to 1.32,  $p=0.0002$ ,  $I^2=79\%$ ) (**figure 2**).

238 Further exclusion of any single study did not materially alter the overall pooled OR, with  
239 a range from 1.17 (95% CI 1.06-1.28) to 1.28 (95% CI 1.12-1.46). Sensitivity analysis  
240 limited to studies with larger sample size ( $\geq 500$ )<sup>15 19 20 28-30 34-39 41</sup> revealed similar results  
241 (OR 1.24, 95% CI 1.08 to 1.43,  $p=0.003$ ,  $I^2=82\%$ ) (online supplemental figure S1).

242 However, significant publication bias was noted by visual inspections of the funnel plot  
243 (online supplemental figure S2) and the Egger's test for small study effects (bias  
244 coefficient 1.49, 95% CI 0.44 to 2.55,  $p=0.008$ ).

245 Subgroup analyses indicated that assessment parameters of PD ( $p=0.02$ ), study design  
246 ( $p=0.05$ ) and diagnosis of COPD ( $p=0.05$ ) were the potential main causes of  
247 heterogeneity (**table 2**). Moreover, there were several findings in subgroup analyses.

248 First, after further controlling for smoking intensity, PD did not increase the risk of  
249 COPD (OR 1.14, 95% CI 0.86 to 1.51,  $p=0.38$ , 10 studies<sup>15 19 20 29-33 35 37</sup>), similar to the  
250 subgroup applying a GOLD criterion (OR 1.10, 95% CI 1.00 to 1.22,  $p=0.06$ , 12  
251 studies<sup>15 19 20 31-35 37 39-41</sup>). Second, among the parameters of CAL, ABL and PPD, only  
252 subgroup using the parameter of ABL showed a significant association between PD and

253 the risk of COPD (OR 1.98, 95% CI 1.32 to 2.97,  $p=0.001$ , six studies<sup>15 28 29 31 32 39</sup>).

254 Third, in the three geographical locations (Asia, North America and Europe), only the

255 subgroup of Europe indicated that PD increased the risk of COPD (OR 2.05, 95% CI

256 1.07 to 3.95,  $p=0.03$ , four studies<sup>31 33 36 39</sup>).

257

258 **Table 2** Subgroup analyses regarding the risk of COPD

Subgroups	No. Studies	No. Participants /Cases	OR value (95% CI)	P value	I <sup>2</sup> , %
Adjusted for smoking intensity <sup>a</sup>					
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)	<b>0.0002</b>	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)	<b>0.001</b>	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)	<b>0.03</b>	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)	<b>0.0007</b>	46
Study design					
Case-control	8	9,911 / 4,472	1.12 (1.01-1.24)	<b>0.03</b>	86
Cross-sectional	9	38,593 / 4,540	1.34 (1.08-1.66)	<b>0.007</b>	45
Cohort	1	878 / 22	3.51 (1.15-10.74)	<b>0.03</b>	-

259 <sup>a</sup>Duration and dose of smoking.

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

263 **Bold:** subgroups with positive results.

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

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## 270 Secondary outcome

271 Only four studies evaluated the risk of COPD-related AE or mortality.<sup>16 21 42 43</sup> Definition  
 272 of AE was acute deterioration in clinical presentations according to the recommendation  
 273 in GOLD guideline.<sup>21 42 43</sup> Pooled analysis showed that after adjusting for smoking status,  
 274 PD did not increase the risk of COPD-related AE or mortality (OR 1.18, 95% CI 0.71 to  
 275 1.97, p=0.52, I<sup>2</sup>=36%) (**figure 4**).

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## 277 DISCUSSION



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5 278 This systematic review and meta-analysis identified 22 observational studies to  
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8 279 investigate the association between COPD and PD. The results indicated that, after  
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10 280 strictly adjusting for confounding by smoking, PD did not increase the risk of COPD, as  
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13 281 well as the risk of COPD-related AE or mortality. Moreover, these findings were  
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15 282 consistent across the subgroup and stratified analyses.

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18 283 To the best of our knowledge, this is the first and largest meta-analysis investigating  
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20 284 the association of PD with the risk of COPD and its clinical events, with adequately  
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23 285 controlling the confounding effect of smoking. Besides, nearly all included articles were  
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25 286 adjusted for age, except the study by Scannapieco *et al.*<sup>14</sup> Prior publications have  
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28 287 suggested that PD significantly increased the risk of COPD and COPD-related events.  
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31 288 However, the majority of studies have non-negligible flaws, such as only performing  
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34 289 univariate analyses, not controlling the confounding by smoking, and using parameters  
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36 290 with relatively low specificity for determining PD.<sup>13 25 43</sup> In the present study, to define  
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39 291 PD as accurately as possible, we preferentially extracted data concerning the parameters  
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41 292 of CAL, ABL and PPD rather than PLI, OHI or remaining teeth. CAL, ABL and PPD  
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44 293 are clinical measurements reflecting the destruction of periodontal tissues and  
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46 294 momentous parameters for diagnosis of PD.<sup>25 44</sup> Meanwhile, compared with previous  
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49 295 meta-analyses, we enrolled more studies, applied more rigorous screening criteria and  
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52 296 most importantly, revealed opposite results. In the meta-analyses with incomplete  
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54 297 adjustment for smoking, OR value for the risk of COPD ranged from 1.28 to 2.08.<sup>45-48</sup>  
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57 298 However, our findings were similar to studies conducted in never smokers,<sup>15 19 20 29 32 35</sup>

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5 299 which showed that PD conferred no risk for COPD. Additionally, pooled analyses  
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8 300 regarding parameters of CAL, ABL and PPD revealed that PD also did not increase the  
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10 301 risk of COPD-related AE or mortality. These findings demonstrate that previously  
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12 302 reported correlation between PD and COPD may be results of flawed study design,  
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15 303 confounding by smoking and even other factors, such as age and living condition.  
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18 304 As a momentous inducer for inflammation-related pathological processes, tobacco is  
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20 305 known to correlate with a variety of systemic disorders.<sup>49</sup> It is also one of the foremost  
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22 306 risk factors for both COPD and PD.<sup>5 10</sup> From the epidemiological perspective, tobacco  
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24 307 smoking is a confounder with spuriously inflated effect on the relationship between PD  
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26 308 and systemic diseases.<sup>49</sup> To investigate the true association between PD and COPD, it is  
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28 309 of great importance to rigorously control the confounding effect of smoking, which  
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30 310 means initiating research in never smokers. However, the majority of former studies  
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32 311 failed to do that. After a wide search, only six studies focusing on never smokers were  
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34 312 found, which unanimously indicated PD was not related with the risk of COPD. We also  
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36 313 observed a decreased intensity of the association between both diseases with the increase  
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38 314 of control for smoking. Therefore, it could be too early to make a certain conclusion on  
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40 315 the COPD-PD relationship. Although interventional studies revealed that periodontal  
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42 316 treatment reduced the risk of AE, a number of problems existed, including small sample  
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44 317 size, limited study quality and unclear history of smoking or medication during the  
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46 318 follow-up.<sup>17 18</sup> For example, compared with control subjects, patients in treatment groups  
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57 319 may reduce smoking intentionally, which could spuriously enhance the positive effect  
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5 320 of periodontal treatment. Consequently, future researches need to take these problems  
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10 322 It is worth noting that, another possibility that smoking acts as an effect modifier in  
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13 323 the COPD-PD relationship should not be ignored. Two observational studies performing  
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15 324 stratified analyses concerning smoking status found that the strong correlation of PD  
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18 325 with the risk of COPD was restricted to smokers.<sup>15 20</sup> However, this was not revealed in  
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21 326 the present study, thus more investigations in smokers and never smokers respectively  
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23 327 are required.

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26 328 Besides, current evidence has demonstrated several issues to be addressed in future  
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29 329 study, comprising inconsistent diagnostic criteria of COPD and PD, the lack of  
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32 330 prospective study design and differing adjustments for covariates. These contribute to  
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34 331 substantial heterogeneity among studies.<sup>45 46</sup> The present study indicated the  
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37 332 heterogeneity was partly explained by study design, diagnostic criteria of COPD and  
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40 333 periodontal indexes used to assess PD. Significant association concerning PD and risk  
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43 334 of COPD was only identified in subgroups lacking well designs, applying non-GOLD  
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45 335 criteria or utilizing ABL as the measure of PD. For one thing, this demonstrated that, as  
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48 336 sources of bias, observational study design and nonstandard diagnostic method for  
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51 337 COPD could induce apparent deviations, confusing the true relationship between COPD  
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54 338 and PD. For another, given undetermined diagnostic criteria for PD, discrepancies  
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57 339 between ABL and other indexes cannot fully support the COPD-PD association. Notably,  
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60 340 as a radiographic measure, although ABL has been widely considered to reflect

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5 341 cumulative effects of periodontal attachment loss over time by chronic inflammation,<sup>28</sup>  
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8 342 it does not only exist in PD. Non-periodontal diseases such as liver disorders, cancer and  
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10 343 osteoporosis<sup>50</sup> could also result in ABL. As mentioned previously,<sup>28</sup> the observed  
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13 344 correlation between ABL and risk of COPD may relate to those non-periodontal diseases.  
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### 17 18 346 **Limitations**

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20 347 Several potential limitations should be taken into consideration when interpreting the  
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23 348 present results. First, all included studies are observational, which are highly subject to  
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26 349 selection bias and confounding by indication. Second, substantial heterogeneity was  
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29 350 identified in current study, though we conducted subgroup and stratified analyses to  
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31 351 partly explain and reduce it. As stated above, several problems leading to heterogeneity  
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34 352 need to be addressed in future researches. Third, the number of studies on risk of COPD-  
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36 353 related events was limited, thus the result needs to be carefully understood. Limited  
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39 354 number of studies in subgroup and stratified analyses suggested more relevant studies  
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41 355 with larger sample size are required. Fourth, although confounding effects of age and  
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44 356 smoking were controlled by stratified analysis and statistical adjustment, other potential  
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47 357 confounders such as gender, living condition and socioeconomic status<sup>10</sup> could also  
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49 358 reduce reliability of the results. Fifth, obvious publication bias was noted in relevant  
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52 359 meta-analyses,<sup>45 46</sup> including the present study. For the purpose of rapid review,<sup>23</sup> we  
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55 360 only included articles in English. There could exist non-English publications and  
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57 361 unpublished evidence, although we searched English-language studies as much as  
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5 362 possible. Finally, although smoking status and intensity were considered in subgroup  
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7 363 analysis, information regarding tobacco content and chemical composition were not  
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9 364 collected. This information is difficult to obtain, especially from self-reported smoking,  
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12 365 leaving a residual smoking-related bias. Consequently, it is advisable to explore  
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15 366 relationship between COPD and PD in never smokers.  
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## 368 **CONCLUSION**

369 In summary, this systematic review and meta-analysis suggests that PD is not associated  
370 with the risk of COPD and COPD-related events after strict adjustment for smoking,  
371 although the positive relationship between COPD and PD was previously reported.  
372 Large-scale prospective cohort studies with control of potential confounding factors are  
373 warranted to validate the present findings.  
374

## 375 **Abbreviations**

376 ABL: Alveolar bone loss; AE: Acute exacerbation; BI: Bleeding index; CAL: Clinical  
377 attachment level; CI: Confident interval; COPD: Chronic obstructive pulmonary disease;  
378 GB: Gingival bleeding; GOLD: Global Initiative for Chronic Obstructive Lung Diseases;  
379 HR: Hazard ratio; OHI: Oral health index; OR: Odds ratio; PD: Periodontal disease; PLI:  
380 Plaque index; PPD: Probing pocket depth; RR: Relative risk.  
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382 **Contributors** LC and LL designed the study. MY and XL screened and selected relevant

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5 383 studies. MY, RP and XL rated the study quality and extracted the data. MY, RP, XL and  
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8 384 JP analyzed the data. All authors interpreted the data, and MY, RP, XL, JP drafted the  
9  
10 385 paper. LC and LL critically revised the paper. All authors acknowledged and agreed with  
11  
12  
13 386 the format and content of the paper before submission for publication. LC and LL are  
14  
15 387 the guarantors and responsible for the overall contents of this study.  
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20 389 **Funding** This study was supported in part by grant 2016YFC0901100 from the National  
21  
22  
23 390 Key Research and Development Program of China.  
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28 392 **Competing interests** None declared.  
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33 394 **Patient and public involvement** Patients and/or the public were not involved in the  
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36 395 design, or conduct, or reporting, or dissemination plans of this research.  
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41 397 **Patient consent for publication** Not applicable.  
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46 399 **Ethics approval** Not applicable.  
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51 401 **Data availability statement** All data relevant to the study are included in the article or  
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54 402 uploaded as supplementary information.  
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54 **Figure legends**

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57 **Figure 1** PRISMA flow diagram of study selection.  
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5 550 **Figure 2** Forest plot of the risk of COPD by periodontal disease, subgroup analysis based  
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8 551 on adjusted by smoking status and intensity versus by smoking status only. Values more  
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10 552 than one indicate a higher risk in patients with periodontal disease.

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13 553 **Figure 3** Forest plot of the risk of COPD by periodontal disease. **A** in smokers and **B** in  
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15 554 never smokers. Values more than one indicate a higher risk in patients with periodontal  
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21 556 **Figure 4** Forest plot of the risk of COPD-related events by periodontal disease. Values  
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23 557 more than one indicate a higher risk in patients with periodontal disease.  
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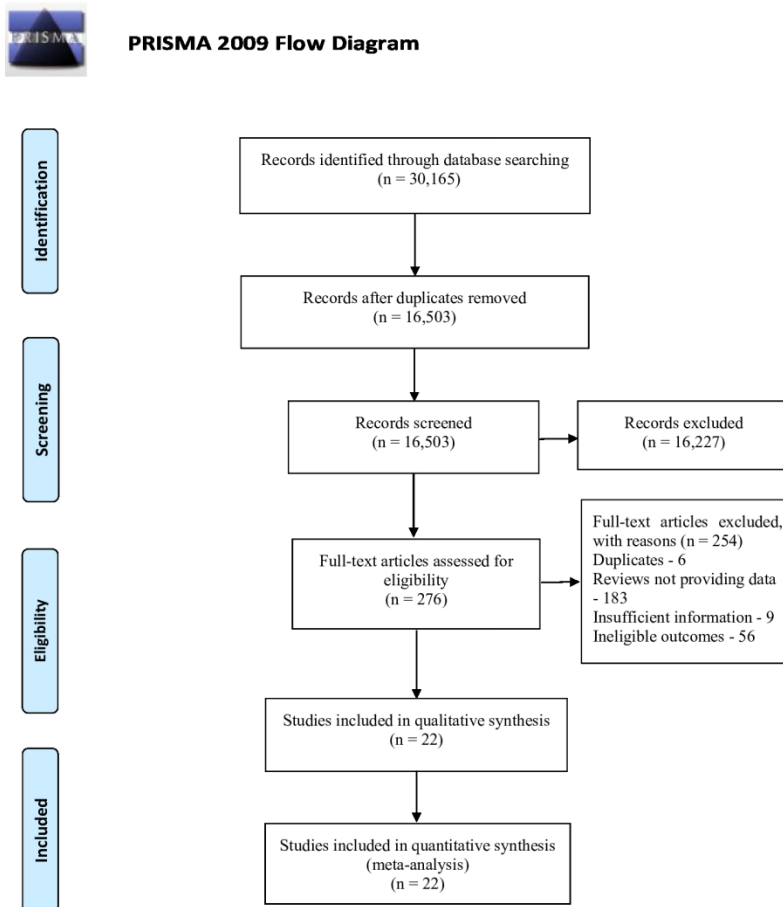


Figure 1 PRISMA flow diagram of study selection.

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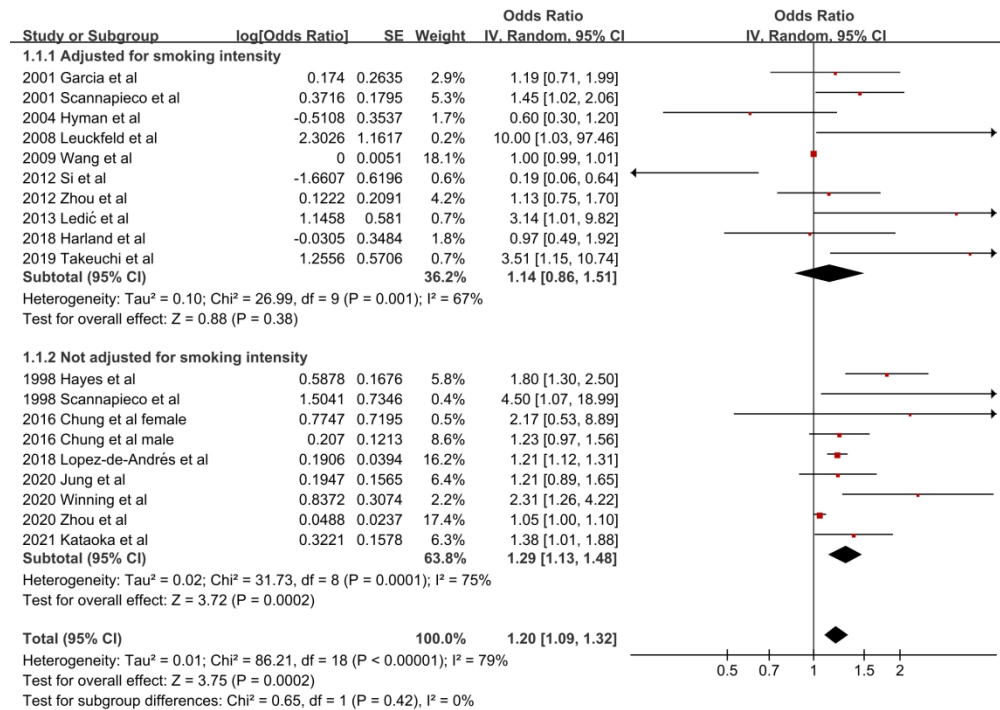


Figure 2 Forest plot of the risk of COPD by periodontal disease, subgroup analysis based on adjusted by smoking status and intensity versus by smoking status only. Values more than one indicate a higher risk in patients with periodontal disease.

536x384mm (118 x 118 DPI)

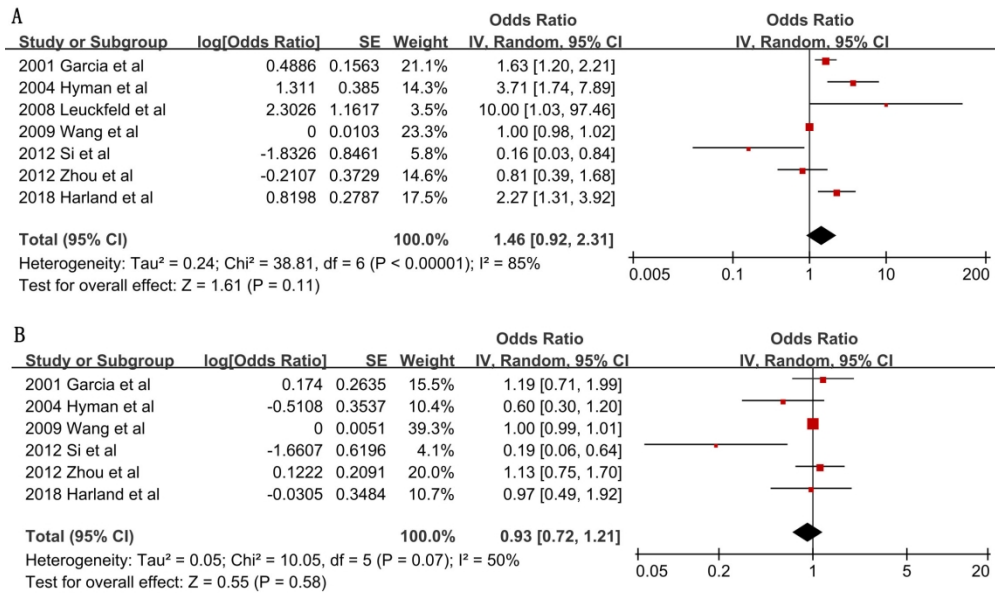


Figure 3 Forest plot of the risk of COPD by periodontal disease. A in smokers and B in never smokers. Values more than one indicate a higher risk in patients with periodontal disease.

192x118mm (300 x 300 DPI)

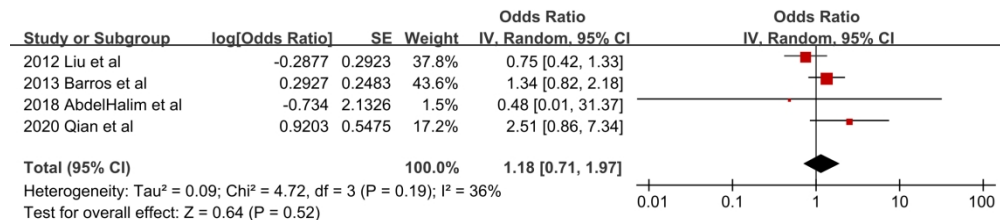


Figure 4 Forest plot of the risk of COPD-related events by periodontal disease. Values more than one indicate a higher risk in patients with periodontal disease.

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

For peer review only



**Table S2** Adjustment for confounders of included studies

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

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

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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.

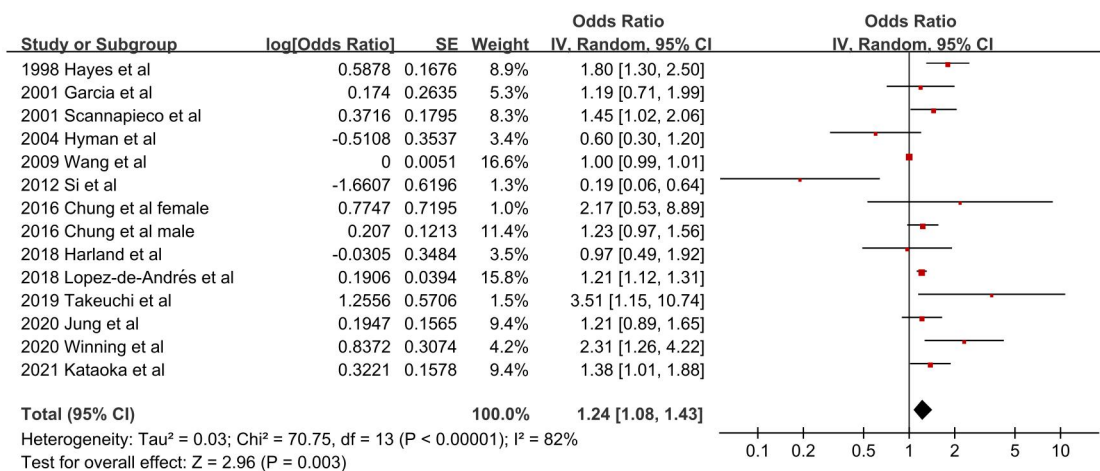
**Bold:** the covariate of smoking intensity (duration and dose) or stratified analyses on smoking status.

**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 <i>et al</i> <sup>14</sup>	*	*	*	...	...	*	*	*	6
Takeuchi <i>et al</i> <sup>19</sup>	*	*	*	*	...	*	*	*	7
Qian <i>et al</i> <sup>13</sup>	...	*	*	...	...	*	*	...	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 <i>et al</i> <sup>1</sup>	*	...	*	*	*	*	*	*	7
Scannapieco <i>et al</i> <sup>2</sup>	...	*	*	*	...	*	*	...	5
Garcia <i>et al</i> <sup>3</sup>	*	...	*	*	*	*	*	*	7
Scannapieco <i>et al</i> <sup>15</sup>	...	*	*	*	...	*	*	*	6
Hyman <i>et al</i> <sup>16</sup>	*	*	*	*	...	*	*	*	7
Leuckfeld <i>et al</i> <sup>4</sup>	*	...	...	*	...	*	*	*	5
Wang <i>et al</i> <sup>6</sup>	*	*	...	*	*	*	*	*	7
Liu <i>et al</i> <sup>5</sup>	*	*	...	*	*	*	*	*	7
Si <i>et al</i> <sup>7</sup>	*	*	...	*	*	*	*	*	7
Zhou <i>et al</i> <sup>8</sup>	*	*	...	*	*	*	*	*	7
Ledić <i>et al</i> <sup>9</sup>	*	*	...	*	*	*	*	*	7
Chung <i>et al</i> <sup>17</sup>	*	*	*	*	...	*	*	*	7
AbdelHalim <i>et al</i> <sup>22</sup>	*	...	...	*	...	*	*	*	5
Harland <i>et al</i> <sup>18</sup>	*	*	...	*	...	*	*	*	6
Lopez-de-Andrés <i>et al</i> <sup>10</sup>	...	*	*	*	*	...	*	*	6
Jung <i>et al</i> <sup>20</sup>	...	*	*	*	...	*	*	*	6
Winning <i>et al</i> <sup>21</sup>	*	*	*	*	...	*	*	*	7
Zhou <i>et al</i> <sup>11</sup>	*	*	...	...	**	*	*	*	7
Kataoka <i>et al</i> <sup>12</sup>	*	*	*	*	...	*	*	*	7



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

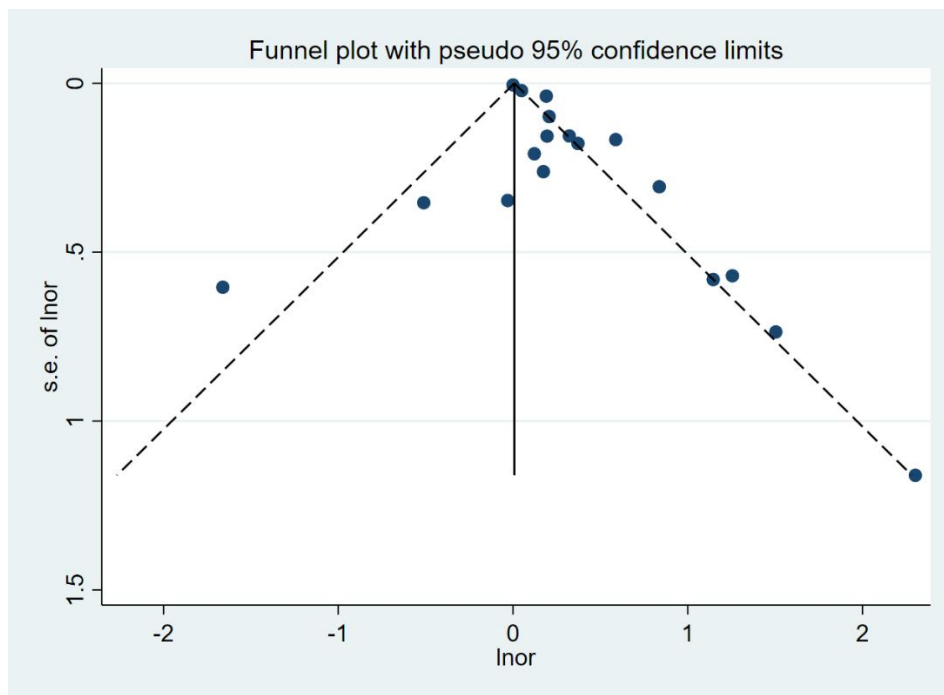


Figure S2 Funnel plot for the risk of COPD, with pseudo 95% confidence limits.

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  22. Abdelhalim H, Aboelnaga H, Aggour R. Chronic obstructive pulmonary disease exacerbations and periodontitis: a possible association. *Egyptian Journal of Bronchology* 2018;12.



## PRISMA 2009 Checklist

Section/topic	Item No	Checklist item	Reported on Page Number/Line Number	Reported on Section/Paragraph
<b>TITLE</b>				
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1 / Line 2,3	Title page
<b>ABSTRACT</b>				
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
<b>INTRODUCTION</b>				
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
<b>METHODS</b>				
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 <sup>2</sup> ) 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
<b>RESULTS</b>				
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
<b>DISCUSSION</b>				
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

**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

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# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-067432.R2
Article Type:	Original research
Date Submitted by the Author:	16-May-2023
Complete List of Authors:	Yang, Mei; Sichuan University West China Hospital, Department of Pulmonary and Critical Care Medicine Peng, Ran; Sichuan University West China Hospital, Department of Pulmonary and Critical Care Medicine; 363 Hospital, Department of Respiratory and Critical Care Medicine Li, Xiaoou; Sichuan University West China Hospital, Department of Pulmonary and Critical Care Medicine Peng, Junjie; Sichuan University West China Hospital, Department of Pulmonary and Critical Care Medicine Liu, Lin; 363 Hospital, Department of Respiratory and Critical Care Medicine Chen, Lei; Sichuan University West China Hospital, Department of Pulmonary and Critical Care Medicine
<b>Primary Subject Heading</b>:	Respiratory medicine
Secondary Subject Heading:	Public health, Smoking and tobacco, Dentistry and oral medicine
Keywords:	Chronic airways disease < THORACIC MEDICINE, RESPIRATORY MEDICINE (see Thoracic Medicine), ORAL MEDICINE, Emphysema < THORACIC MEDICINE

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## 1 **Title Page**

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

4  
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18  
19 **Word count of the abstract:** 274

20 **Word count of the main text:** 3168

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8 23 **The association between chronic obstructive pulmonary**  
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10 24 **disease and periodontal disease: a systematic review and**  
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13 25 **meta-analysis**  
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18 27 **ABSTRACT**

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20 28 **Objectives** Studies have suggested contradictory results on the relationship between  
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23 29 chronic obstructive pulmonary disease (COPD) and periodontal disease (PD). The aim  
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26 30 of this study was to determine whether PD increased the risk of COPD and COPD-  
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28  
29 31 related clinical events.

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31 32 **Design** Systematic review and meta-analysis.

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33 33 **Data sources** PubMed, EMBASE and CENTRAL were searched from inception to 22  
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36 34 February 2023.

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38 35 **Eligibility criteria for studies** We included trials and observational studies evaluating  
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41 36 association of PD with the risk of COPD or COPD-related events (exacerbation and  
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44 37 mortality), with statistical adjustment for smoking.

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46 38 **Data extraction and synthesis** Two investigators independently extracted data from  
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49 39 selected studies using a standardized Excel file. Quality of studies was evaluated using  
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52 40 the Newcastle-Ottawa Scale. Odds ratio (OR) with 95% confident interval (CI) was  
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55 41 pooled in a random-effect model with inverse variance method.

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57 42 **Results** 22 observational studies with 51704 participants were included. Pooled analysis  
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5 43 of 18 studies suggested that PD was weakly associated with the risk of COPD (OR 1.20,  
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8 44 95% CI 1.09 to 1.32). However, in stratified and subgroup analyses, with strict  
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10 45 adjustment for smoking, PD no longer related to the risk of COPD (adjusting for  
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13 46 smoking intensity: OR 1.14, 95% CI 0.86 to 1.51; smokers only: OR 1.46, 95% CI 0.92  
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15 47 to 2.31; never smokers only: OR 0.93, 95% CI 0.72 to 1.21). Moreover, PD did not  
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18 48 increase the risk of COPD-related exacerbation or mortality (OR 1.18, 95% CI 0.71 to  
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21 49 1.97) in the pooled result of four studies.

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23 50 **Conclusions** This study demonstrates PD confers no risk for COPD and COPD-related  
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26 51 events when strictly adjusted by smoking. Large-scale prospective cohort studies with  
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29 52 control of potential confounding factors are warranted to validate the present findings.

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## 32 33 54 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

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36 55 1. This is the largest systematic review and meta-analysis on association between  
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39 56 chronic obstructive pulmonary disease (COPD) and periodontal disease (PD)  
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42 57 collecting data over 20 years.
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44 58 2. This is the first meta-analysis investigating whether PD increases the risk of COPD-  
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47 59 related events (exacerbation or mortality).
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49 60 3. Compared with previous reports, this study was conducted with more strict  
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52 61 adjustment for confounding by smoking, which was the most important confounder  
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55 62 in the COPD-PD relationship.
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57 63 4. Our study provided limited evidence on the outcome of COPD-related events  
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5 64 because of limited data.  
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8 65 5. Clinical heterogeneity and publication bias compromised the evidence strength of  
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10 66 this study, although subgroup and stratified analyses were performed.  
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## 15 68 **INTRODUCTION**

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18 69 Chronic obstructive pulmonary disease (COPD) is the third leading cause of death,  
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20 70 resulting in enormous economic burden.<sup>1</sup> Commonly, COPD coexists with a variety of  
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22 71 disorders, called comorbidities, which play significant roles in the progression and  
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24 72 prognosis of COPD.<sup>2 3</sup> Understanding the COPD-comorbidities relationship has been a  
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26 73 momentous prerequisite for optimizing disease prevention and management strategies.<sup>2</sup>  
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34 75 Given ageing and widespread use of inhaled corticosteroids in COPD, periodontal  
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36 76 disease (PD) has been a common comorbidity of COPD.<sup>4</sup> It is a chronic inflammatory  
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38 77 condition of tissues surrounding and supporting the teeth, including gingiva, bone and  
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40 78 ligament,<sup>5</sup> with the prevalence estimates over 10% around the world and especially  
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42 79 prevalent in elderly individuals.<sup>6</sup> To date, diagnosis and assessment of PD are mostly  
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44 80 based on periodontal measurements including clinical attachment level (CAL), probing  
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46 81 pocket depth (PPD) and alveolar bone loss (ABL).<sup>5</sup> They are primary clinical  
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48 82 manifestations of PD, reflecting the extent of periodontal tissue destruction.<sup>5</sup>  
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54 83 Based on the nature of inflammation,<sup>5 7</sup> mounting evidence has shed light on the  
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56 84 association between PD and development of COPD.<sup>8 9</sup> Currently three points are  
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5 85 proposed. First, they share the same risk factors, such as age, gender, smoking and  
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8 86 socioeconomic status.<sup>2 10</sup> Second, they have similar pathogenetic mechanisms. Both  
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10 87 diseases are characterized by host susceptibility to environmental factors, immune  
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13 88 overreaction, oxidative stress and production of pro-inflammatory cytokines.<sup>7 8</sup> Most  
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16 89 importantly, neutrophilic inflammation plays a key role in both diseases.<sup>8 11</sup> Third, oral  
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18 90 bacteria released from the dental plaque in PD could trigger progression and acute  
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21 91 exacerbation (AE) of COPD.<sup>12 13</sup>

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23 92 Meanwhile, epidemiological evidence has indicated that PD increases risk of COPD<sup>11</sup>  
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26 93 <sup>14 15</sup> and COPD-related events.<sup>13 16</sup> Scannapieco *et al* revealed a 4.5-fold increased risk  
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29 94 of COPD in patients with PD, compared with those without.<sup>14</sup> A dose-response  
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32 95 relationship was further implied between PD severity and lung function.<sup>15</sup> Among  
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35 96 patients with both diseases, COPD-related AE and mortality also significantly linked  
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38 97 with periodontal status.<sup>13 16</sup> Periodontal therapy, such as scaling and root planing  
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41 98 treatment, may ameliorate lung function and decrease frequency of AE in COPD with  
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44 99 chronic periodontitis.<sup>17 18</sup> However, there were some other studies revealing opposite  
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47 100 results, resulting in a long-standing controversy.<sup>19-21</sup> It is worth noting that, parameters  
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50 101 used to determine PD apparently varied across studies, and these studies also failed to  
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53 102 adequately control for confounders, especially smoking, the most important confounder  
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56 103 for the COPD-PD relationship. Therefore, to provide the latest and most convincing  
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59 104 evidence, we systematically reviewed current available literature to investigate whether  
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62 105 PD increases the risk of COPD. The secondary objective was to evaluate the association

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5 106 between PD and the risk of COPD-related events. Subgroup and stratified analyses were  
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7 107 also conducted to adjust for the confounding by smoking.  
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## 12 109 **METHODS**

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15 110 This systematic review and meta-analysis was conducted and reported in accordance to  
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18 111 the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)  
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20 112 guideline.<sup>22</sup>  
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### 24 114 **Search strategy and selection criteria**

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27 115 We searched PubMed, EMBASE and CENTRAL for records evaluating association  
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30 116 between COPD and PD, from inception to 22 February 2023. The search strategy was  
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33 117 described in **online supplemental table 1**. The language was restricted to English, for  
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36 118 the purpose of rapid review.<sup>23</sup> Studies meeting the following criteria were included: (1)  
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38 119 adult participants ( $\geq 18$  years); (2) original studies with randomized controlled trial  
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41 120 (RCT), cohort, case-control or cross-sectional study designs; (3) presenting clear  
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44 121 diagnostic or assessment criteria for COPD and PD; (4) evaluating association between  
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46 122 PD and the risk of COPD, or risk of COPD-related events (AE and mortality), with  
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49 123 statistical adjustment for smoking, and providing the adjusted odds ratio (OR), relative  
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52 124 risk (RR) or hazard ratio (HR) for the risk of COPD, AE and mortality in relation to PD.

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54 125 According to the inclusion criteria, two independent investigators (MY and XL)  
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57 126 performed systematical search, screened titles and abstracts of all retrieved studies to  
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5 127 exclude duplicate or irrelevant records. For articles requiring further assessment, full-  
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8 128 text reviews were carried out and references of retrieved articles and relevant reviews  
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10 129 were also manually checked to identify additional eligible studies. Disagreements were  
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13 130 resolved by discussion between the two reviewers or with the help of the third  
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15 131 investigator (RP).

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### 19 20 133 **Data extraction and quality assessment**

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23 134 Two investigators (MY and RP) independently extracted data from selected studies  
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26 135 using a standardized Excel (Microsoft Corporation) file. The following information was  
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29 136 extracted: author, year of publication, country, study design, number of subjects (COPD  
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31 137 and non-COPD), demographic characteristics of participants, periodontal variables  
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34 138 applied to assess PD, diagnostic criteria for COPD, definition of COPD-related AE and  
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36 139 mortality, adjusted OR, RR or HR for the risk of COPD, AE and mortality in relation to  
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39 140 PD, as well as adjustment for confounders. The primary outcome was the risk of COPD.  
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42 141 Secondary outcome was the risk of COPD-related adverse events, including AE and  
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44 142 mortality. Quality of studies was independently evaluated using the Newcastle-Ottawa  
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46 143 Scale<sup>24</sup> by two investigators (MY and XL). A score of  $\geq 6$  was considered a low risk  
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49 144 while  $< 6$  a high risk of bias. Both case-control and cohort studies had a maximum score  
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52 145 of 9. Cross-sectional study was regarded as case-control study when performing quality  
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54 146 assessment. Discrepancies regarding data extraction and quality assessment were  
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57 147 resolved through discussion and consensus.  
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78 149 **Data analysis**  
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10 150 The final pooled estimate was expressed as OR with 95% confident interval (CI).  
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12 151 Considering CAL, ABL and PPD have been regarded as the primary parameters for  
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14 152 PD,<sup>25 26</sup> where more than one adjusted estimate was shown in the paper, we preferentially  
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16 153 used the estimate regarding these parameters (CAL > ABL > PPD), or the estimate being  
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18 154 better adjusted for tobacco smoking (never smokers > adjusting for smoking intensity  
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20 155 [duration and dose] > adjusting for smoking status), or the estimate regarding more  
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22 156 severe PD, where available. For case-control and cross-sectional studies, we estimated  
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24 157 the OR whereas for cohort studies we estimated the RR or HR. The random-effect model  
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26 158 with inverse variance method were applied due to potential heterogeneity resulting from  
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28 159 methodological differences. Heterogeneity across studies was identified with the I<sup>2</sup>  
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30 160 statistic. I<sup>2</sup> statistic >50% indicated significant heterogeneity.  
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39 161 To explore heterogeneity, subgroup analyses were conducted based on study design  
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41 162 (case-control, cross-sectional and cohort studies), geographical location (Asia, North  
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43 163 America, Europe), assessment of PD (CAL, ABL and PPD), definition of COPD (Global  
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45 164 Initiative for Chronic Obstructive Lung Diseases, GOLD and non-GOLD criteria) and  
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47 165 adjustment for smoking intensity (dose and duration of smoking). To better control the  
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49 166 confounding effect of smoking, stratified analyses were performed in smokers and never  
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51 167 smokers respectively.  
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57 168 To test the robustness of study findings, we performed sensitivity analysis on studies  
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5 169 with relatively large sample size ( $\geq 500$  participants), which tended to be more  
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8 170 representative of the general population and with smaller bias in the overall estimates in  
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10 171 meta-analyses.<sup>27</sup> Additionally, influence of a single study on the overall pooled estimate  
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13 172 was tested by omitting one study in each turn. Publication bias was visually assessed  
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15 173 using a funnel plot and quantitatively evaluated by the Egger's tests.  $P < 0.05$  was  
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18 174 considered statistically significant. All statistical analyses were performed using Stata  
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20 175 version 16 (StataCorp) and Review manager version 5.4 (Cochrane Collaboration).  
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### 24 25 177 **Patient and public involvement**

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28 178 No patients or other individuals are involved in the design, conduct, reporting or  
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31 179 dissemination of this research.  
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## 34 35 181 **RESULTS**

### 36 37 182 **Study selection and characteristics**

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39 183 A total of 30165 records were identified from the initial database search. 13662 records  
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42 184 were removed for duplicates, and 16227 records were excluded after titles and abstracts  
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45 185 screening because of irrelevant content and animal studies. The remaining 276 full-text  
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48 186 articles were identified for eligibility, of which 254 were excluded for reasons including  
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51 187 duplicates (six studies), reviews (183 studies), insufficient information (nine studies) and  
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54 188 ineligible designs and outcomes (56 studies). Finally, 22 studies<sup>14-16 19-21 28-43</sup> were  
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57 189 included in the review. The selection process is shown in **figure 1**.  
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5 190 The characteristics of included 22 studies were shown in **table 1**. The number of  
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8 191 participants was 51704 and there were 9973 (18.9%) patients with COPD. The mean age  
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10 192 of patients with COPD was between 45.1 and 83.1 years while the control subjects was  
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13 193 between 42.2 and 80.3 years. These studies were published between 1998 and 2021. The  
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15 194 sample size ranged from 120 to 13792. Nine studies were case-control studies<sup>15 19 28 29 32</sup>  
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18 195 <sup>33 36 40 42</sup> and 10 studies were cross-sectional studies,<sup>14 20 30 31 34 35 38 39 41 43</sup> only three  
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20 196 studies with a cohort study design.<sup>16 21 37</sup> Additionally, 11 studies were conducted in  
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23 197 Asia,<sup>15 16 19 32 34 35 37 38 40-42</sup> while six studies in the North America,<sup>14 20 21 28-30</sup> four studies  
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26 198 in Europe<sup>31 33 36 39</sup> and one study in Africa.<sup>43</sup>

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**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 <i>et al</i> <sup>28</sup>	Case-control	United States	261/857	45.1±9.7/42.2±9.1	ABL	FEV <sub>1</sub>
1998 Scannapieco <i>et al</i> <sup>14</sup>	Cross-sectional	United States	77/309	NA	OHI	Self-reported
2001 Garcia <i>et al</i> <sup>29</sup>	Case-control	United States	279/833	NA	ABL, PPD	FEV <sub>1</sub>
2001 Scannapieco <i>et al</i> <sup>30</sup>	Cross-sectional	United States	810/12,982	51.2±17.9/43.9±17.7	CAL, GB	Self-reported
2004 Hyman <i>et al</i> <sup>20</sup>	Cross-sectional	United States	993/6,632	62.3±14.1/47.4±14.2	CAL	GOLD
2008 Leuckfeld <i>et al</i> <sup>31</sup>	Cross-sectional	Norway	130/50	54.9±4.9/47.0±9.8	ABL	GOLD
2009 Wang <i>et al</i> <sup>19</sup>	Case-control	China	306/328	63.9±9.8/63.3±9.0	CAL, PLI	GOLD
2012 Liu <i>et al</i> <sup>42</sup>	Case-control	China	183/209*	64.3±10.1/63.6±9.7	CAL, PPD, BI	GOLD

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2012 Si <i>et al</i> <sup>15</sup>	Case-control	China	581/438	63.9±9.4/62.8±9.5	CAL, ABL, PPD, PLI, BI	GOLD
2012 Zhou <i>et al</i> <sup>32</sup>	Case-control	China	193/181	63.6±0.3/62.1±9.1	CAL, ABL, PPD, PLI, BI	GOLD
2013 Barros <i>et al</i> <sup>21</sup>	Cohort	United States	399/1,236 <sup>§</sup>	63.9±5.7/66.0±5.1	CAL, PPD	GOLD
2013 Ledić <i>et al</i> <sup>33</sup>	Case-control	Croatia	93/43	65.8±9.7/62.1±11.9	CAL	GOLD
2016 Chung <i>et al</i> <sup>34</sup>	Cross-sectional	Korea	697/5,181	64.3±0.2/54.6±0.1	PPD, GB	GOLD
2018 AbdelHalim <i>et al</i> <sup>43</sup>	Cross-sectional	Egypt	134/116*	56.8±10.4/55.3±9.1	CAL, PPD, BI, PLI, OHI	GOLD
2018 Harland <i>et al</i> <sup>35</sup>	Cross-sectional	Japan	149/1,325	61.3±9.1/54.5±8.7	PPD	GOLD
2018 Lopez-de-Andrés <i>et al</i> <sup>36</sup>	Case-control	Spain	2,699/2,699	63±14/61±14	Self-reported	Self-reported
2019 Takeuchi <i>et al</i> <sup>37</sup>	Cohort	Japan	22/878	NA	CAL, PPD	GOLD
2020 Jung <i>et al</i> <sup>38</sup>	Cross-sectional	Korea	1,134/6,585	62.6±0.4/53.6±0.2	PPD	FEV <sub>1</sub> / FVC
2020 Qian <i>et al</i> <sup>16</sup>	Cohort	China	23 <sup>‡</sup> /NA	83.1±4.8/80.3±3.7	ABL	NR
2020 Winning <i>et al</i> <sup>39</sup>	Cross-sectional	Sweden	86/740	NA	ABL	GOLD
2020 Zhou <i>et al</i> <sup>40</sup>	Case-control	China	60/60	63.1±10.1/60.0±9.4	CAL, PLI	GOLD
2021 Kataoka <i>et al</i> <sup>41</sup>	Cross-sectional	Japan	464/249	54.1±9.4/NA	PPD	GOLD

- 201 Continuous data are presented as mean ± standard deviation (SD) unless otherwise indicated.
- 202 \*No. COPD subjects with frequent exacerbation (≥2 exacerbations in the last year)/Infrequent exacerbation (< 2
- 203 exacerbations in the last year).
- 204 <sup>§</sup>No. COPD subjects with events (hospitalization for exacerbation or COPD-related death) in the 5-year follow-up
- 205 visit/COPD subjects without events in the 5-year follow-up visit.
- 206 <sup>‡</sup>No. COPD-related mortality in a follow-up visit more than 5 years.
- 207 ABL, alveolar bone loss; BI, bleeding index; CAL, clinical attachment level; FEV<sub>1</sub>, forced expiratory volume in 1
- 208 second; FVC, forced vital capacity; GB, gingival bleeding; GOLD, Global Initiative for Chronic Obstructive Lung

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

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

218 The adjustment for confounders of included studies was detailedly presented in **online**  
219 **supplemental table 2**. 16 articles reported the adjusted ORs and 4 reported adjusted RRs,  
220 two studies reporting HRs. Definition of COPD comprised the GOLD criteria,<sup>2</sup> FEV<sub>1</sub>  
221 <65% of predicted volume, having a history of chronic bronchitis and / or emphysema,  
222 self-reported and others. Periodontal parameters used for PD assessment were CAL,  
223 ABL, PPD, gingival bleeding (GB), bleeding index (BI), plaque index (PLI) and oral  
224 health index (OHI).

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### 226 **Assessment of bias**

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



232 comparability of cases and control subjects.

233

234 **Primary outcome**

235 18 studies<sup>14 15 19 20 28-41</sup> provided data for the risk of COPD in relation to PD. Quantitative  
236 analysis demonstrated that after adjusting for smoking status, PD increased the risk of  
237 COPD, but only by a ratio of 1.20 (95% CI 1.09 to 1.32,  $p=0.0002$ ,  $I^2=79\%$ ) (**figure 2**).  
238 Further exclusion of any single study did not materially alter the overall pooled OR, with  
239 a range from 1.17 (95% CI 1.06-1.28) to 1.28 (95% CI 1.12-1.46). Sensitivity analysis  
240 limited to studies with larger sample size ( $\geq 500$ )<sup>15 19 20 28-30 34-39 41</sup> revealed similar results  
241 (OR 1.24, 95% CI 1.08 to 1.43,  $p=0.003$ ,  $I^2=82\%$ ) (**online supplemental figure 1**).  
242 However, significant publication bias was noted by visual inspections of the funnel plot  
243 (**online supplemental figure 2**) and the Egger's test for small study effects (bias  
244 coefficient 1.49, 95% CI 0.44 to 2.55,  $p=0.008$ ).

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

253 the risk of COPD (OR 1.98, 95% CI 1.32 to 2.97,  $p=0.001$ , six studies<sup>15 28 29 31 32 39</sup>).

254 Third, in the three geographical locations (Asia, North America and Europe), only the

255 subgroup of Europe indicated that PD increased the risk of COPD (OR 2.05, 95% CI

256 1.07 to 3.95,  $p=0.03$ , four studies<sup>31 33 36 39</sup>).

257

258 **Table 2** Subgroup analyses regarding the risk of COPD

Subgroups	No. Studies	No. Participants /Cases	OR value (95% CI)	P value	I <sup>2</sup> , %
Adjusted for smoking intensity <sup>a</sup>					
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)	<b>0.0002</b>	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)	<b>0.001</b>	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)	<b>0.03</b>	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)	<b>0.0007</b>	46
Study design					
Case-control	8	9,911 / 4,472	1.12 (1.01-1.24)	<b>0.03</b>	86
Cross-sectional	9	38,593 / 4,540	1.34 (1.08-1.66)	<b>0.007</b>	45
Cohort	1	878 / 22	3.51 (1.15-10.74)	<b>0.03</b>	-

259 <sup>a</sup>Duration and dose of smoking.

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

263 **Bold:** subgroups with positive results.

264

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

269

## 270 Secondary outcome

271 Only four studies evaluated the risk of COPD-related AE or mortality.<sup>16 21 42 43</sup> Definition  
 272 of AE was acute deterioration in clinical presentations according to the recommendation  
 273 in GOLD guideline.<sup>21 42 43</sup> Pooled analysis showed that after adjusting for smoking status,  
 274 PD did not increase the risk of COPD-related AE or mortality (OR 1.18, 95% CI 0.71 to  
 275 1.97, p=0.52, I<sup>2</sup>=36%) (**figure 3**).

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## 277 DISCUSSION

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5 278 This systematic review and meta-analysis identified 22 observational studies to  
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8 279 investigate the association between COPD and PD. The results indicated that, after  
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10 280 strictly adjusting for confounding by smoking, PD did not increase the risk of COPD, as  
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13 281 well as the risk of COPD-related AE or mortality. Moreover, these findings were  
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15 282 consistent across the subgroup and stratified analyses.

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18 283 To the best of our knowledge, this is the first and largest meta-analysis investigating  
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20 284 the association of PD with the risk of COPD and its clinical events, with adequately  
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23 285 controlling the confounding effect of smoking. Besides, nearly all included articles were  
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26 286 adjusted for age, except the study by Scannapieco *et al.*<sup>14</sup> Prior publications have  
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28 287 suggested that PD significantly increased the risk of COPD and COPD-related events.  
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31 288 However, the majority of studies have non-negligible flaws, such as only performing  
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34 289 univariate analyses, not controlling the confounding by smoking, and using parameters  
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36 290 with relatively low specificity for determining PD.<sup>13 25 43</sup> In the present study, to define  
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39 291 PD as accurately as possible, we preferentially extracted data concerning the parameters  
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41 292 of CAL, ABL and PPD rather than PLI, OHI or remaining teeth. CAL, ABL and PPD  
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44 293 are clinical measurements reflecting the destruction of periodontal tissues and  
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46 294 momentous parameters for diagnosis of PD.<sup>25 44</sup> Meanwhile, compared with previous  
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49 295 meta-analyses, we enrolled more studies, applied more rigorous screening criteria and  
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52 296 most importantly, revealed opposite results. In the meta-analyses with incomplete  
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54 297 adjustment for smoking, OR value for the risk of COPD ranged from 1.28 to 2.08.<sup>45-48</sup>  
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57 298 However, our findings were similar to studies conducted in never smokers,<sup>15 19 20 29 32 35</sup>

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5 299 which showed that PD conferred no risk for COPD. Additionally, pooled analyses  
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8 300 regarding parameters of CAL, ABL and PPD revealed that PD also did not increase the  
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10 301 risk of COPD-related AE or mortality. These findings demonstrate that previously  
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12 302 reported correlation between PD and COPD may be results of flawed study design,  
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15 303 confounding by smoking and even other factors, such as age and living condition.  
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18 304 As a momentous inducer for inflammation-related pathological processes, tobacco is  
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20 305 known to correlate with a variety of systemic disorders.<sup>49</sup> It is also one of the foremost  
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22 306 risk factors for both COPD and PD.<sup>5 10</sup> From the epidemiological perspective, tobacco  
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24 307 smoking is a confounder with spuriously inflated effect on the relationship between PD  
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26 308 and systemic diseases.<sup>49</sup> To investigate the true association between PD and COPD, it is  
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28 309 of great importance to rigorously control the confounding effect of smoking, which  
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30 310 means initiating research in never smokers. However, the majority of former studies  
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32 311 failed to do that. After a wide search, only six studies focusing on never smokers were  
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34 312 found, which unanimously indicated PD was not related with the risk of COPD. We also  
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36 313 observed a decreased intensity of the association between both diseases with the increase  
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38 314 of control for smoking. Therefore, it could be too early to make a certain conclusion on  
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40 315 the COPD-PD relationship. Although interventional studies revealed that periodontal  
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42 316 treatment reduced the risk of AE, a number of problems existed, including small sample  
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44 317 size, limited study quality and unclear history of smoking or medication during the  
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46 318 follow-up.<sup>17 18</sup> For example, compared with control subjects, patients in treatment groups  
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48 319 may reduce smoking intentionally, which could spuriously enhance the positive effect  
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5 320 of periodontal treatment. Consequently, future researches need to take these problems  
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8 321 into account.

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10 322 It is worth noting that, another possibility that smoking acts as an effect modifier in  
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13 323 the COPD-PD relationship should not be ignored. Two observational studies performing  
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15 324 stratified analyses concerning smoking status found that the strong correlation of PD  
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18 325 with the risk of COPD was restricted to smokers.<sup>15 20</sup> However, this was not revealed in  
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21 326 the present study, thus more investigations in smokers and never smokers respectively  
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23 327 are required.

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26 328 Besides, current evidence has demonstrated several issues to be addressed in future  
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29 329 study, comprising inconsistent diagnostic criteria of COPD and PD, the lack of  
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32 330 prospective study design and differing adjustments for covariates. These contribute to  
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34 331 substantial heterogeneity among studies.<sup>45 46</sup> The present study indicated the  
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37 332 heterogeneity was partly explained by study design, diagnostic criteria of COPD and  
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40 333 periodontal indexes used to assess PD. Significant association concerning PD and risk  
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43 334 of COPD was only identified in subgroups lacking well designs, applying non-GOLD  
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46 335 criteria or utilizing ABL as the measure of PD. For one thing, this demonstrated that, as  
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49 336 sources of bias, observational study design and nonstandard diagnostic method for  
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52 337 COPD could induce apparent deviations, confusing the true relationship between COPD  
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55 338 and PD. For another, given undetermined diagnostic criteria for PD, discrepancies  
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58 339 between ABL and other indexes cannot fully support the COPD-PD association. Notably,  
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60 340 as a radiographic measure, although ABL has been widely considered to reflect

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5 341 cumulative effects of periodontal attachment loss over time by chronic inflammation,<sup>28</sup>  
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8 342 it does not only exist in PD. Non-periodontal diseases such as liver disorders, cancer and  
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10 343 osteoporosis<sup>50</sup> could also result in ABL. As mentioned previously,<sup>28</sup> the observed  
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13 344 correlation between ABL and risk of COPD may relate to those non-periodontal diseases.  
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### 17 18 346 **Limitations**

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20 347 Several potential limitations should be taken into consideration when interpreting the  
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23 348 present results. First, all included studies are observational, which are highly subject to  
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26 349 selection bias and confounding by indication. Second, substantial heterogeneity was  
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29 350 identified in current study, though we conducted subgroup and stratified analyses to  
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31 351 partly explain and reduce it. As stated above, several problems leading to heterogeneity  
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34 352 need to be addressed in future researches. Third, the number of studies on risk of COPD-  
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36 353 related events was limited, thus the result needs to be carefully understood. Limited  
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39 354 number of studies in subgroup and stratified analyses suggested more relevant studies  
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41 355 with larger sample size are required. Fourth, although confounding effects of age and  
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44 356 smoking were controlled by stratified analysis and statistical adjustment, other potential  
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47 357 confounders such as gender, living condition and socioeconomic status<sup>10</sup> could also  
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49 358 reduce reliability of the results. Fifth, obvious publication bias was noted in relevant  
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52 359 meta-analyses,<sup>45 46</sup> including the present study. For the purpose of rapid review,<sup>23</sup> we  
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55 360 only included articles in English. There could exist non-English publications and  
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57 361 unpublished evidence, although we searched English-language studies as much as  
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5 362 possible. Finally, although smoking status and intensity were considered in subgroup  
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7 363 analysis, information regarding tobacco content and chemical composition were not  
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9 364 collected. This information is difficult to obtain, especially from self-reported smoking,  
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12 365 leaving a residual smoking-related bias. Consequently, it is advisable to explore  
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15 366 relationship between COPD and PD in never smokers.  
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## 20 368 **CONCLUSION**

23 369 In summary, this systematic review and meta-analysis suggests that PD is not associated  
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25 370 with the risk of COPD and COPD-related events after strict adjustment for smoking,  
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27 371 although the positive relationship between COPD and PD was previously reported.  
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29 372 Large-scale prospective cohort studies with control of potential confounding factors are  
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31 373 warranted to validate the present findings.  
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## 38 375 **Abbreviations**

41 376 ABL: Alveolar bone loss; AE: Acute exacerbation; BI: Bleeding index; CAL: Clinical  
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43 377 attachment level; CI: Confident interval; COPD: Chronic obstructive pulmonary disease;  
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45 378 GB: Gingival bleeding; GOLD: Global Initiative for Chronic Obstructive Lung Diseases;  
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47 379 HR: Hazard ratio; OHI: Oral health index; OR: Odds ratio; PD: Periodontal disease; PLI:  
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49 380 Plaque index; PPD: Probing pocket depth; RR: Relative risk.  
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57 382 **Contributors** LC and LL designed the study. MY and XL screened and selected relevant  
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5 383 studies. MY, RP and XL rated the study quality and extracted the data. MY, RP, XL and  
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8 384 JP analyzed the data. All authors interpreted the data, and MY, RP, XL, JP drafted the  
9  
10 385 paper. LC and LL critically revised the paper. All authors acknowledged and agreed with  
11  
12  
13 386 the format and content of the paper before submission for publication. LC and LL are  
14  
15 387 the guarantors and responsible for the overall contents of this study.  
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388

20 389 **Funding** This study was supported in part by grant 2016YFC0901100 from the National  
21  
22  
23 390 Key Research and Development Program of China.  
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28 392 **Competing interests** None declared.  
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33 394 **Patient and public involvement** No patients or other individuals are involved in the  
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36 395 design, conduct, reporting or dissemination of this research.  
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41 397 **Patient consent for publication** Not applicable.  
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46 399 **Ethics approval** Not applicable.  
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51 401 **Data availability statement** All data relevant to the study are included in the article or  
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54 402 uploaded as supplementary information.  
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547 **Figure legends**

548 **Figure 1** PRISMA flow diagram of study selection.

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

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5 550 on adjusted by smoking status and intensity versus by smoking status only. Values more  
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8 551 than one indicate a higher risk in patients with periodontal disease.  
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10 552 **Figure 3** Forest plot of the risk of COPD-related events by periodontal disease. Values  
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13 553 more than one indicate a higher risk in patients with periodontal disease.  
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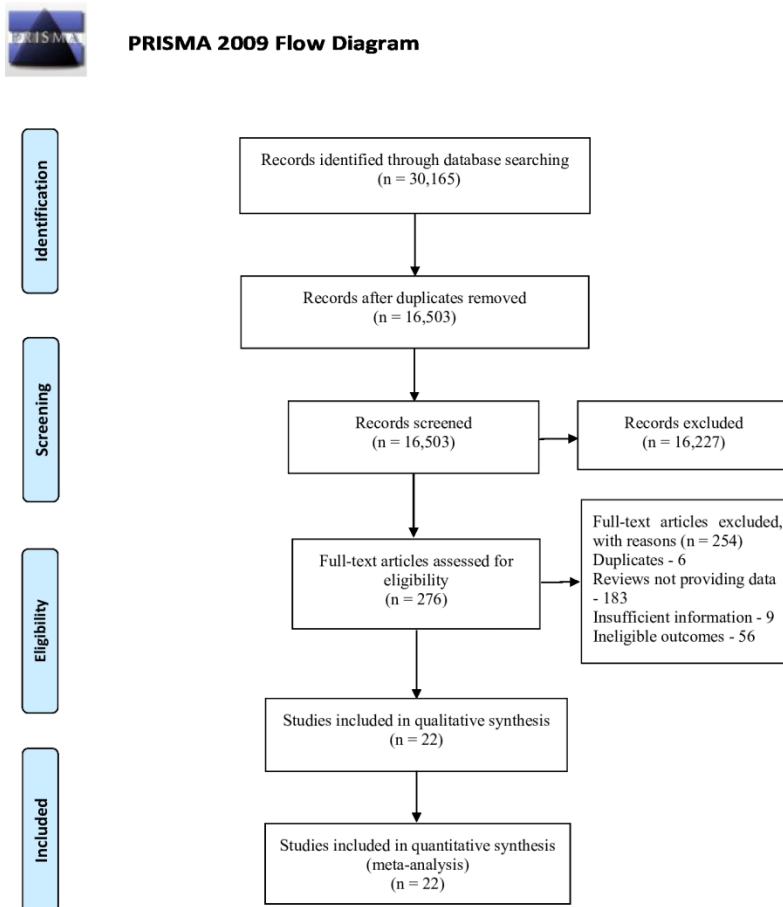


Figure 1 PRISMA flow diagram of study selection.

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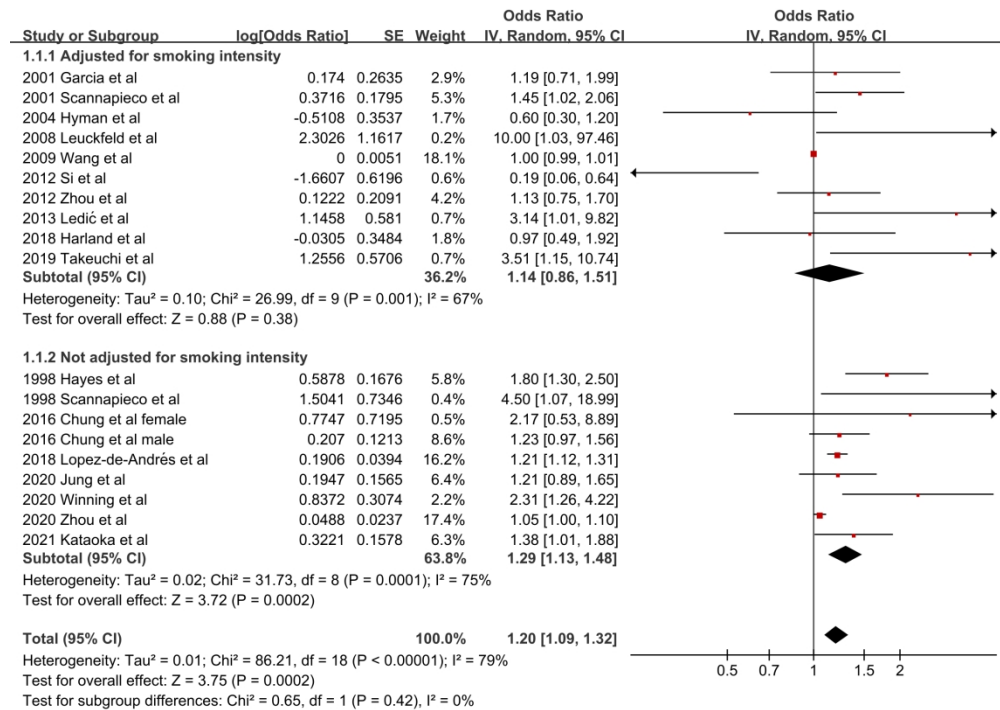


Figure 2 Forest plot of the risk of COPD by periodontal disease, subgroup analysis based on adjusted by smoking status and intensity versus by smoking status only. Values more than one indicate a higher risk in patients with periodontal disease.

536x384mm (118 x 118 DPI)



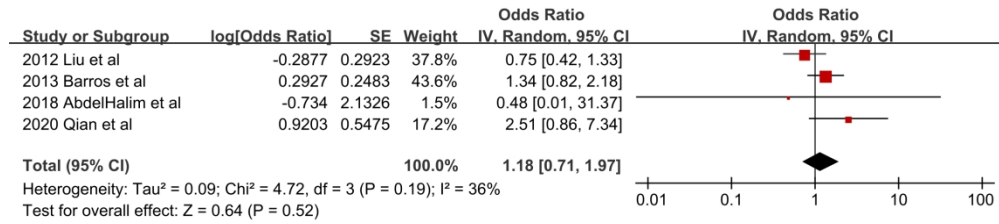


Figure 3 Forest plot of the risk of COPD-related events by periodontal disease. Values more than one indicate a higher risk in patients with periodontal disease.

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

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**Table 2** Adjustment for confounders of included studies

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

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

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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.

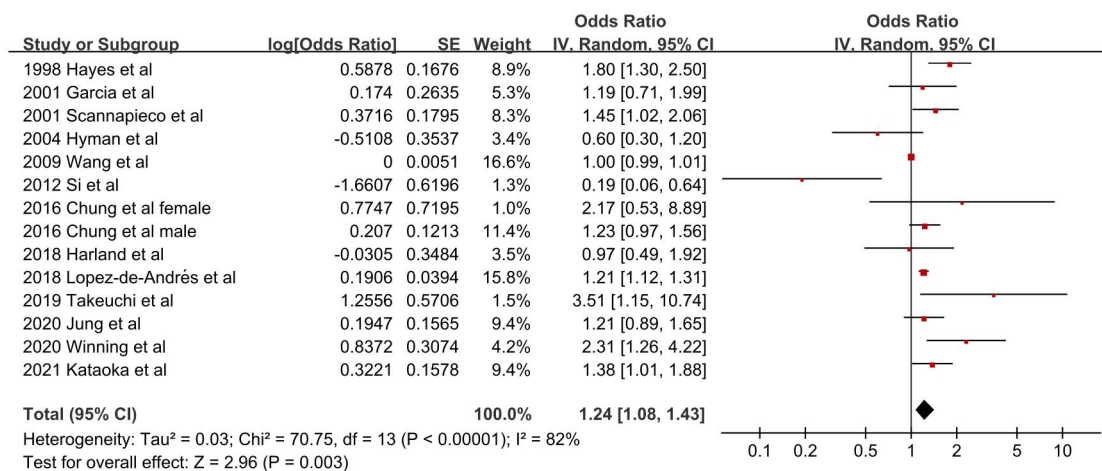
**Table 3** Quality assessment based on the Newcastle-Ottawa Scale

**(A) Cohort study**

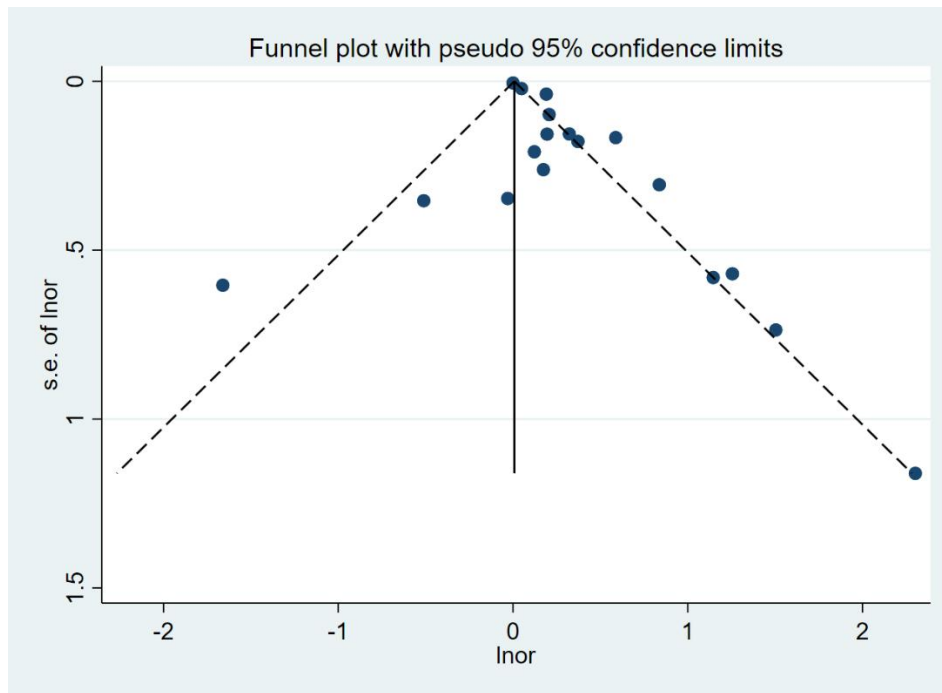
Study Author	Selection				Comparability	Outcome			Total score
	Exposed cohort	Nonexposed cohort	Ascertainment of exposure	Outcome of interest		Assessment of outcome	Length of follow-up	Adequacy of follow-up	
Barros <i>et al</i> <sup>14</sup>	*	*	*	...	...	*	*	*	6
Takeuchi <i>et al</i> <sup>19</sup>	*	*	*	*	...	*	*	*	7
Qian <i>et al</i> <sup>13</sup>	...	*	*	...	...	*	*	...	4

**(B) Case-control / cross-sectional study**

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

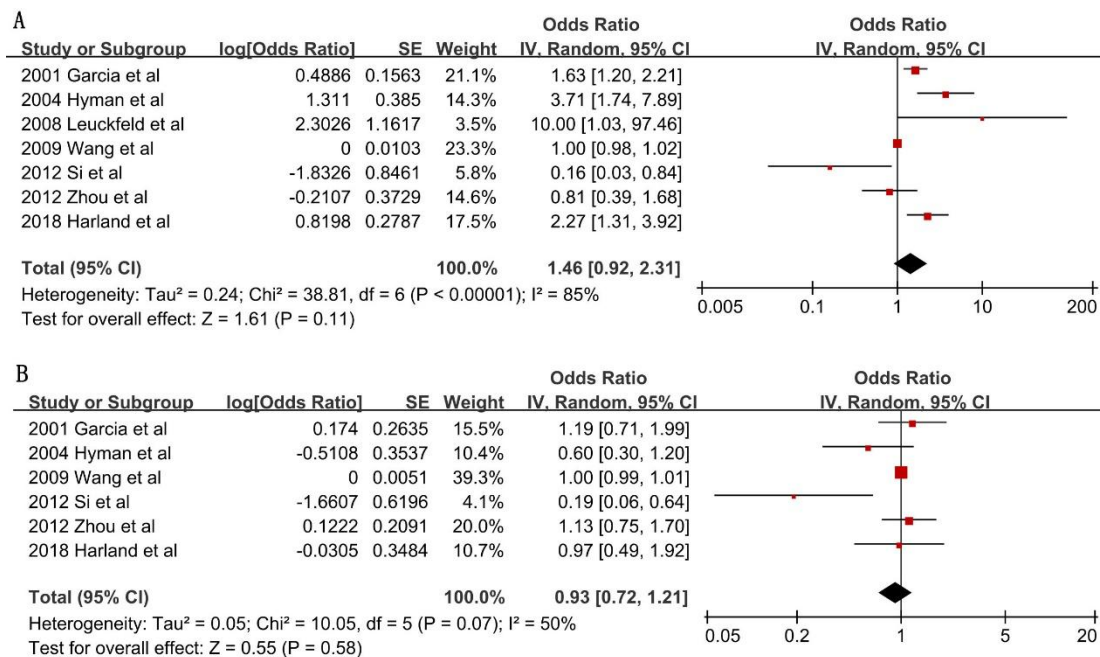


**Figure 1** Sensitivity analysis on studies with larger sample size ( $N \geq 500$ ). Values more than one indicate a higher risk of COPD in patients with PD.



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

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**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
<b>TITLE</b>				
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1 / Line 2,3	Title page
<b>ABSTRACT</b>				
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
<b>INTRODUCTION</b>				
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
<b>METHODS</b>				
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 <sup>2</sup> ) 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
<b>RESULTS</b>				
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
<b>DISCUSSION</b>				
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

**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

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# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-067432.R3
Article Type:	Original research
Date Submitted by the Author:	02-Jun-2023
Complete List of Authors:	Yang, Mei; Sichuan University West China Hospital, Department of Pulmonary and Critical Care Medicine Peng, Ran; Sichuan University West China Hospital, Department of Pulmonary and Critical Care Medicine; 363 Hospital, Department of Pulmonary and Critical Care Medicine Li, Xiaoou; Sichuan University West China Hospital, Department of Pulmonary and Critical Care Medicine Peng, Junjie; Sichuan University West China Hospital, Department of Pulmonary and Critical Care Medicine Liu, Lin; 363 Hospital, Department of Pulmonary and Critical Care Medicine Chen, Lei; Sichuan University West China Hospital, Department of Pulmonary and Critical Care Medicine
<b>Primary Subject Heading</b>:	Respiratory medicine
Secondary Subject Heading:	Public health, Smoking and tobacco, Dentistry and oral medicine
Keywords:	Chronic airways disease < THORACIC MEDICINE, RESPIRATORY MEDICINE (see Thoracic Medicine), ORAL MEDICINE, Emphysema < THORACIC MEDICINE

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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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**Word count of the abstract:** 276

**Word count of the main text:** 3224



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8 23 **The association between chronic obstructive pulmonary**  
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10 24 **disease and periodontal disease: a systematic review and**  
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13 25 **meta-analysis**  
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16 26

17  
18 27 **ABSTRACT**

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20 28 **Objectives** Studies have suggested contradictory results on the relationship between  
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23 29 chronic obstructive pulmonary disease (COPD) and periodontal disease (PD). The aim  
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26 30 of this study was to determine whether PD increased the risk of COPD and COPD-  
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29 31 related clinical events.

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31 32 **Design** Systematic review and meta-analysis.

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33 33 **Data sources** PubMed, Ovid EMBASE and Ovid CENTRAL were searched from  
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36 34 inception to 22 February 2023.

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38 35 **Eligibility criteria for studies** We included trials and observational studies evaluating  
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41 36 association of PD with the risk of COPD or COPD-related events (exacerbation and  
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44 37 mortality), with statistical adjustment for smoking.

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46 38 **Data extraction and synthesis** Two investigators independently extracted data from  
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49 39 selected studies using a standardized Excel file. Quality of studies was evaluated using  
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52 40 the Newcastle-Ottawa Scale. Odds ratio (OR) with 95% confident interval (CI) was  
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55 41 pooled in a random-effect model with inverse variance method.

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57 42 **Results** 22 observational studies with 51704 participants were included. Pooled analysis  
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5 43 of 18 studies suggested that PD was weakly associated with the risk of COPD (OR 1.20,  
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8 44 95% CI 1.09 to 1.32). However, in stratified and subgroup analyses, with strict  
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10 45 adjustment for smoking, PD no longer related to the risk of COPD (adjusting for  
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12  
13 46 smoking intensity: OR 1.14, 95% CI 0.86 to 1.51; smokers only: OR 1.46, 95% CI 0.92  
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16 47 to 2.31; never smokers only: OR 0.93, 95% CI 0.72 to 1.21). Moreover, PD did not  
17  
18 48 increase the risk of COPD-related exacerbation or mortality (OR 1.18, 95% CI 0.71 to  
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21 49 1.97) in the pooled result of four studies.

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23 50 **Conclusions** This study demonstrates PD confers no risk for COPD and COPD-related  
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26 51 events when strictly adjusted by smoking. Large-scale prospective cohort studies with  
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29 52 control of potential confounding factors are warranted to validate the present findings.

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## 32 33 54 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

- 34  
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36 55 1. This systematic review and meta-analysis only included studies with statistical  
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39 56 adjustment for smoking, to adequately control the confounding by smoking.
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41 57 2. We defined “periodontal disease” as a wide variety of periodontal abnormalities  
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44 58 according to clinical and radiographic assessments, which is not limited to  
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47 59 periodontitis.
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49 60 3. The language was restricted to English when conducting study searching, thus some  
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52 61 literatures might have been missed.
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54 62 4. Clinical heterogeneity and publication bias compromised the evidence strength of  
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57 63 this study, although subgroup and stratified analyses were performed.
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## 65 INTRODUCTION

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

71 <sup>3</sup>

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

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

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5 85 overreaction, oxidative stress and production of pro-inflammatory cytokines.<sup>7 8</sup> Most  
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8 86 importantly, neutrophilic inflammation plays a key role in both diseases.<sup>8 11</sup> Third, oral  
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10 87 bacteria released from the dental plaque in PD could trigger progression and acute  
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13 88 exacerbation (AE) of COPD.<sup>12 13</sup>

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15 89 Meanwhile, epidemiological evidence has indicated that PD increases risk of COPD<sup>11</sup>  
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18 90 <sup>14 15</sup> and COPD-related events.<sup>13 16</sup> Scannapieco *et al* revealed a 4.5-fold increased risk  
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21 91 of COPD in patients with PD, compared with those without.<sup>14</sup> A dose-response  
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23 92 relationship was further implied between PD severity and lung function.<sup>15</sup> Among  
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26 93 patients with both diseases, COPD-related AE and mortality also significantly linked  
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29 94 with periodontal status.<sup>13 16</sup> Periodontal therapy, such as scaling and root planing  
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31 95 treatment, may ameliorate lung function and decrease frequency of AE in COPD with  
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34 96 chronic periodontitis.<sup>17 18</sup> However, there were some other studies revealing opposite  
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37 97 results, resulting in a long-standing controversy.<sup>19-21</sup> It is worth noting that, parameters  
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40 98 used to determine PD apparently varied across studies, and these studies also failed to  
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43 99 adequately control for confounders, especially smoking, the most important confounder  
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46 100 for the COPD-PD relationship. Therefore, to provide the latest and most convincing  
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49 101 evidence, we systematically reviewed current available literature to investigate whether  
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52 102 PD increases the risk of COPD. The secondary objective was to evaluate the association  
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55 103 between PD and the risk of COPD-related events. Subgroup and stratified analyses were  
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58 104 also conducted to adjust for the confounding by smoking.

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## 106 **METHODS**

107 This systematic review and meta-analysis was conducted and reported in accordance to  
108 the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)  
109 guideline.<sup>22</sup>

### 111 **Search strategy and selection criteria**

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

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

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5 127 exclude duplicate or irrelevant records. For articles requiring further assessment, full-  
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8 128 text reviews were carried out and references of retrieved articles and relevant reviews  
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10 129 were also manually checked to identify additional eligible studies. Disagreements were  
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13 130 resolved by discussion between the two reviewers or with the help of the third  
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15 131 investigator (RP).

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### 19 20 133 **Data extraction and quality assessment**

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23 134 Two investigators (MY and RP) independently extracted data from selected studies  
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25  
26 135 using a standardized Excel (Microsoft Corporation) file. The following information was  
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29 136 extracted: author, year of publication, country, study design, number of subjects (COPD  
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31 137 and non-COPD), demographic characteristics of participants, diagnostic criteria for PD  
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34 138 and COPD, definition of COPD-related AE and mortality, adjusted OR, RR or HR for  
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36 139 the risk of COPD, AE and mortality in relation to PD, as well as adjustment for  
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39 140 confounders. The primary outcome was the risk of COPD. Secondary outcome was the  
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42 141 risk of COPD-related adverse events, including AE and mortality. Quality of studies was  
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45 142 independently evaluated using the Newcastle-Ottawa Scale<sup>25</sup> by two investigators (MY  
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47 143 and XL). A score of  $\geq 6$  was considered a low risk while  $< 6$  a high risk of bias. Both  
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50 144 case-control and cohort studies had a maximum score of 9. Cross-sectional study was  
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53 145 regarded as case-control study when performing quality assessment. Discrepancies  
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56 146 regarding data extraction and quality assessment were resolved through discussion and  
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59 147 consensus.  
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78 149 **Data analysis**

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10 150 The final pooled estimate was expressed as OR with 95% confident interval (CI).  
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12 151 Considering CAL, ABL and PPD have been regarded as the primary parameters for  
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14 152 PD,<sup>24,26</sup> where more than one adjusted estimate was shown in the paper, we preferentially  
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16 153 used the estimate regarding these parameters (CAL > ABL > PPD), or the estimate being  
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18 154 better adjusted for tobacco smoking (never smokers > adjusting for smoking intensity  
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20 155 [duration and dose] > adjusting for smoking status), or the estimate regarding more  
21  
22 156 severe PD, where available. For case-control and cross-sectional studies, we estimated  
23  
24 157 the OR whereas for cohort studies we estimated the RR or HR. The random-effect model  
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26 158 with inverse variance method were applied due to potential heterogeneity resulting from  
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28 159 methodological differences. Heterogeneity across studies was identified with the I<sup>2</sup>  
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30 160 statistic. I<sup>2</sup> statistic >50% indicated significant heterogeneity.

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38 161 To explore heterogeneity, subgroup analyses were conducted based on study design  
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40 162 (case-control, cross-sectional and cohort studies), geographical location (Asia, North  
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42 163 America, Europe), assessment of PD (CAL, ABL and PPD), definition of COPD (Global  
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44 164 Initiative for Chronic Obstructive Lung Diseases, GOLD and non-GOLD criteria) and  
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46 165 adjustment for smoking intensity (dose and duration of smoking). To better control the  
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48 166 confounding effect of smoking, stratified analyses were performed in smokers and never  
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50 167 smokers respectively.

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56 168 To test the robustness of study findings, we performed sensitivity analysis on studies  
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5 169 with relatively large sample size ( $\geq 500$  participants), which tended to be more  
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8 170 representative of the general population and with smaller bias in the overall estimates in  
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10 171 meta-analyses.<sup>27</sup> Additionally, influence of a single study on the overall pooled estimate  
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13 172 was tested by omitting one study in each turn. Publication bias was visually assessed  
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15 173 using a funnel plot and quantitatively evaluated by the Egger's tests.  $P < 0.05$  was  
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18 174 considered statistically significant. All statistical analyses were performed using Stata  
19  
20 175 version 16 (StataCorp) and Review manager version 5.4 (Cochrane Collaboration).  
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### 24 25 177 **Patient and public involvement**

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28 178 No patients or other individuals are involved in the design, conduct, reporting or  
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31 179 dissemination of this research.  
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## 34 35 181 **RESULTS**

### 36 37 182 **Study selection and characteristics**

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40 183 A total of 30165 records were identified from the initial database search. 13662 records  
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43 184 were removed for duplicates, and 16227 records were excluded after titles and abstracts  
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46 185 screening because of irrelevant content and animal studies. The remaining 276 full-text  
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49 186 articles were identified for eligibility, of which 254 were excluded for reasons including  
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52 187 duplicates (six studies), reviews (183 studies), insufficient information (nine studies) and  
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55 188 ineligible designs and outcomes (56 studies). Finally, 22 studies<sup>14-16 19-21 28-43</sup> were  
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57 189 included in the review. The selection process is shown in **figure 1**.  
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5 190 The characteristics of included 22 studies were shown in **table 1**. The number of  
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8 191 participants was 51704 and there were 9973 (18.9%) patients with COPD. The mean age  
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10 192 of patients with COPD was between 45.1 and 83.1 years while the control subjects was  
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13 193 between 42.2 and 80.3 years. These studies were published between 1998 and 2021. The  
14  
15 194 sample size ranged from 120 to 13792. Nine studies were case-control studies<sup>15 19 28 29 32</sup>  
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18 195 <sup>33 36 40 42</sup> and 10 studies were cross-sectional studies,<sup>14 20 30 31 34 35 38 39 41 43</sup> only three  
19  
20 196 studies with a cohort study design.<sup>16 21 37</sup> Additionally, 11 studies were conducted in  
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23 197 Asia,<sup>15 16 19 32 34 35 37 38 40-42</sup> while six studies in the North America,<sup>14 20 21 28-30</sup> four studies  
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26 198 in Europe<sup>31 33 36 39</sup> and one study in Africa.<sup>43</sup>

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**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 <i>et al</i> <sup>28</sup>	Case-control	United States	261/857	45.1±9.7/42.2±9.1	ABL	FEV <sub>1</sub>
1998 Scannapieco <i>et al</i> <sup>14</sup>	Cross-sectional	United States	77/309	NA	OHI	Self-reported
2001 Garcia <i>et al</i> <sup>29</sup>	Case-control	United States	279/833	NA	ABL, PPD	FEV <sub>1</sub>
2001 Scannapieco <i>et al</i> <sup>30</sup>	Cross-sectional	United States	810/12,982	51.2±17.9/43.9±17.7	CAL, GB	Self-reported
2004 Hyman <i>et al</i> <sup>20</sup>	Cross-sectional	United States	993/6,632	62.3±14.1/47.4±14.2	CAL	GOLD
2008 Leuckfeld <i>et al</i> <sup>31</sup>	Cross-sectional	Norway	130/50	54.9±4.9/47.0±9.8	ABL	GOLD
2009 Wang <i>et al</i> <sup>19</sup>	Case-control	China	306/328	63.9±9.8/63.3±9.0	CAL, PLI	GOLD
2012 Liu <i>et al</i> <sup>42</sup>	Case-control	China	183/209*	64.3±10.1/63.6±9.7	CAL, PPD, BI	GOLD

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

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

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

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

206 <sup>‡</sup>No. COPD-related mortality in a follow-up visit more than 5 years.

207 ABL, alveolar bone loss; BI, bleeding index; CAL, clinical attachment level; FEV<sub>1</sub>, forced expiratory volume in 1

208 second; FVC, forced vital capacity; GB, gingival bleeding; GOLD, Global Initiative for Chronic Obstructive Lung

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4 209 Disease; NA, not available; OHI, oral health index; PD, periodontal disease; PLI, plaque index; PPD, probing pocket  
5 210 depth.  
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9 212 All included articles performed multivariable analyses, in which the risk of COPD, or  
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11 213 risk of COPD-related events (AE or mortality), was identified as the dependent variable  
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13  
14 214 and PD as the independent variable. Controlling for confounding by smoking included  
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16 215 stratification (smokers and never smokers) or covariance adjustment in multivariable  
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18 216 models (the degree of control: never smokers > adjusting for smoking intensity [duration  
19  
20 217 and dose] > adjusting for smoking status).  
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24 218 The adjustment for confounders of included studies was detailedly presented in **online**  
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26 219 **supplemental table 2**. 16 articles reported the adjusted ORs and 4 reported adjusted RRs,  
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28 220 two studies reporting HRs. Definition of COPD comprised the GOLD criteria,<sup>2</sup> FEV<sub>1</sub>  
29  
30 221 <65% of predicted volume, having a history of chronic bronchitis and / or emphysema,  
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33 222 self-reported and others. Across almost all studies, periodontal examination was  
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35 223 conducted by experienced or trained dentists. Periodontal parameters used for diagnosis  
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37 224 of PD were CAL, ABL, PPD, gingival bleeding (GB), bleeding index (BI), plaque index  
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39 225 (PLI) and oral health index (OHI). The detailed diagnostic criteria applied by included  
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41 226 studies were presented in the **online supplemental table 3**.  
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#### 49 228 **Assessment of bias**

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53 229 Based on the Newcastle-Ottawa Scale, quality assessment for the 22 studies was shown  
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55 230 in **online supplemental table 4**. Among them, 18 studies<sup>15 19-21 28-30 32-42</sup> were rated as  
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57 231 high quality with a total score of  $\geq 6$  whereas four studies<sup>14 16 31 43</sup> as a score of <6,  
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5 232 indicating a high risk of bias. The main reasons for lower scores were selection bias  
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8 233 (representativeness of sample population), especially for control groups and  
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10 234 comparability of cases and control subjects.  
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### 15 236 **Primary outcome**

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18 237 18 studies<sup>14 15 19 20 28-41</sup> provided data for the risk of COPD in relation to PD. Quantitative  
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20 238 analysis demonstrated that after adjusting for smoking status, PD increased the risk of  
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22 239 COPD, but only by a ratio of 1.20 (95% CI 1.09 to 1.32,  $p=0.0002$ ,  $I^2=79\%$ ) (**figure 2**).  
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25 240 Further exclusion of any single study did not materially alter the overall pooled OR, with  
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27 241 a range from 1.17 (95% CI 1.06-1.28) to 1.28 (95% CI 1.12-1.46). Sensitivity analysis  
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29 242 limited to studies with larger sample size ( $\geq 500$ )<sup>15 19 20 28-30 34-39 41</sup> revealed similar results  
30  
31 243 (OR 1.24, 95% CI 1.08 to 1.43,  $p=0.003$ ,  $I^2=82\%$ ) (**online supplemental figure 1**).  
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34 244 However, significant publication bias was noted by visual inspections of the funnel plot  
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36 245 (**online supplemental figure 2**) and the Egger' s test for small study effects (bias  
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38 246 coefficient 1.49, 95% CI 0.44 to 2.55,  $p=0.008$ ).  
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44 247 Subgroup analyses indicated that assessment parameters of PD ( $p=0.02$ ), study design  
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46 248 ( $p=0.05$ ) and diagnosis of COPD ( $p=0.05$ ) were the potential main causes of  
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48 249 heterogeneity (**table 2**). Moreover, there were several findings in subgroup analyses.  
49  
50 250 First, after further controlling for smoking intensity, PD did not increase the risk of  
51  
52 251 COPD (OR 1.14, 95% CI 0.86 to 1.51,  $p=0.38$ , 10 studies<sup>15 19 20 29-33 35 37</sup>), similar to the  
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54  
55 252 subgroup applying a GOLD criterion (OR 1.10, 95% CI 1.00 to 1.22,  $p=0.06$ , 12  
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253 studies<sup>15 19 20 31-35 37 39-41</sup>). Second, among the parameters of CAL, ABL and PPD, only  
 254 subgroup using the parameter of ABL showed a significant association between PD and  
 255 the risk of COPD (OR 1.98, 95% CI 1.32 to 2.97,  $p=0.001$ , six studies<sup>15 28 29 31 32 39</sup>).  
 256 Third, in the three geographical locations (Asia, North America and Europe), only the  
 257 subgroup of Europe indicated that PD increased the risk of COPD (OR 2.05, 95% CI  
 258 1.07 to 3.95,  $p=0.03$ , four studies<sup>31 33 36 39</sup>).

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**Table 2** Subgroup analyses regarding the risk of COPD

Subgroups	No. Studies	No. Participants /Cases	OR value (95% CI)	P value	I <sup>2</sup> , %
Adjusted for smoking intensity <sup>a</sup>					
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)	<b>0.0002</b>	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)	<b>0.001</b>	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)	<b>0.03</b>	71

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 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)	<b>0.0007</b>	46
Study design					
Case-control	8	9,911 / 4,472	1.12 (1.01-1.24)	<b>0.03</b>	86
Cross-sectional	9	38,593 / 4,540	1.34 (1.08-1.66)	<b>0.007</b>	45
Cohort	1	878 / 22	3.51 (1.15-10.74)	<b>0.03</b>	-

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261 <sup>a</sup>Duration and dose of smoking.

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

265 **Bold:** subgroups with positive results.

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

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## 272 Secondary outcome

273 Only four studies evaluated the risk of COPD-related AE or mortality.<sup>16 21 42 43</sup> Definition  
 274 of AE was acute deterioration in clinical presentations according to the recommendation  
 275 in GOLD guideline.<sup>21 42 43</sup> Pooled analysis showed that after adjusting for smoking status,  
 276 PD did not increase the risk of COPD-related AE or mortality (OR 1.18, 95% CI 0.71 to  
 277 1.97, p=0.52, I<sup>2</sup>=36%) (**figure 3**).

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279 **DISCUSSION**

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

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

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5 299 adjustment for smoking, OR value for the risk of COPD ranged from 1.28 to 2.08.<sup>45-48</sup>  
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8 300 However, our findings were similar to studies conducted in never smokers,<sup>15 19 20 29 32 35</sup>  
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10 301 which showed that PD conferred no risk for COPD. Additionally, pooled analyses  
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12 302 regarding parameters of CAL, ABL and PPD revealed that PD also did not increase the  
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14 303 risk of COPD-related AE or mortality. These findings demonstrate that previously  
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16 304 reported correlation between PD and COPD may be results of flawed study design,  
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18 305 confounding by smoking and even other factors, such as age and living condition.  
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23 306 As a momentous inducer for inflammation-related pathological processes, tobacco is  
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25 307 known to correlate with a variety of systemic disorders.<sup>49</sup> It is also one of the foremost  
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27 308 risk factors for both COPD and PD.<sup>5 10</sup> From the epidemiological perspective, tobacco  
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29 309 smoking is a confounder with spuriously inflated effect on the relationship between PD  
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31 310 and systemic diseases.<sup>49</sup> To investigate the true association between PD and COPD, it is  
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33 311 of great importance to rigorously control the confounding effect of smoking, which  
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35 312 means initiating research in never smokers. However, the majority of former studies  
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37 313 failed to do that. After a wide search, only six studies focusing on never smokers were  
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39 314 found, which unanimously indicated PD was not related with the risk of COPD. We also  
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41 315 observed a decreased intensity of the association between both diseases with the increase  
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43 316 of control for smoking. Therefore, it could be too early to make a certain conclusion on  
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45 317 the COPD-PD relationship. Although interventional studies revealed that periodontal  
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47 318 treatment reduced the risk of AE, a number of problems existed, including small sample  
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49 319 size, limited study quality and unclear history of smoking or medication during the  
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5 320 follow-up.<sup>17 18</sup> For example, compared with control subjects, patients in treatment groups  
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7 321 may reduce smoking intentionally, which could spuriously enhance the positive effect  
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10 322 of periodontal treatment. Consequently, future researches need to take these problems  
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13 323 into account.

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15 324 It is worth noting that, another possibility that smoking acts as an effect modifier in  
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18 325 the COPD-PD relationship should not be ignored. Two observational studies performing  
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21 326 stratified analyses concerning smoking status found that the strong correlation of PD  
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23 327 with the risk of COPD was restricted to smokers.<sup>15 20</sup> However, this was not revealed in  
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26 328 the present study, thus more investigations in smokers and never smokers respectively  
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29 329 are required.

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31 330 Besides, current evidence has demonstrated several issues to be addressed in future  
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34 331 study, comprising inconsistent diagnostic criteria of COPD and PD, the lack of  
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37 332 prospective study design and differing adjustments for covariates. These contribute to  
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40 333 substantial heterogeneity among studies.<sup>45 46</sup> The present study indicated the  
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43 334 heterogeneity was partly explained by study design, diagnostic criteria of COPD and PD.  
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46 335 Significant association concerning PD and risk of COPD was only identified in  
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49 336 subgroups lacking well designs, applying non-GOLD criteria or utilizing ABL as the  
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52 337 measure of PD. For one thing, this demonstrated that, as sources of bias, observational  
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55 338 study design and nonstandard diagnostic method for COPD could induce apparent  
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58 339 deviations, confusing the true relationship between COPD and PD. For another, given  
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60 340 undetermined diagnostic criteria for PD, discrepancies between ABL and other indexes

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5 341 cannot fully support the COPD-PD association. Notably, as a radiographic measure,  
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8 342 although ABL has been widely considered to reflect cumulative effects of periodontal  
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10 343 attachment loss over time by chronic inflammation,<sup>28</sup> it does not only exist in PD. Non-  
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13 344 periodontal diseases such as liver disorders, cancer and osteoporosis<sup>50</sup> could also result  
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15 345 in ABL. As mentioned previously,<sup>28</sup> the observed correlation between ABL and risk of  
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18 346 COPD may relate to those non-periodontal diseases.

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### 22 23 348 **Limitations**

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26 349 Several potential limitations should be taken into consideration when interpreting the  
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29 350 present results. First, all included studies are observational, which are highly subject to  
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32 351 selection bias and confounding by indication. Second, substantial heterogeneity was  
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35 352 identified in current study, though we conducted subgroup and stratified analyses to  
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38 353 partly explain and reduce it. As stated above, several problems leading to heterogeneity  
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41 354 need to be addressed in future researches. Third, the number of studies on risk of COPD-  
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44 355 related events was limited, thus the result needs to be carefully understood. Limited  
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47 356 number of studies in subgroup and stratified analyses suggested more relevant studies  
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50 357 with larger sample size are required. Fourth, although confounding effects of age and  
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53 358 smoking were controlled by stratified analysis and statistical adjustment, other potential  
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56 359 confounders such as gender, living condition and socioeconomic status<sup>10</sup> could also  
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59 360 reduce reliability of the results. Fifth, obvious publication bias was noted in relevant  
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361 meta-analyses,<sup>45 46</sup> including the present study. For the purpose of rapid review,<sup>23</sup> we

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5 362 only included articles in English. There could exist non-English publications and  
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8 363 unpublished evidence, although we searched English-language studies as much as  
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10 364 possible. Finally, although smoking status and intensity were considered in subgroup  
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13 365 analysis, information regarding tobacco content and chemical composition were not  
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15 366 collected. This information is difficult to obtain, especially from self-reported smoking,  
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18 367 leaving a residual smoking-related bias. Consequently, it is advisable to explore  
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21 368 relationship between COPD and PD in never smokers.  
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## 26 370 **CONCLUSION**

28 371 In summary, this systematic review and meta-analysis suggests that PD is not associated  
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31 372 with the risk of COPD and COPD-related events after strict adjustment for smoking,  
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34 373 although the positive relationship between COPD and PD was previously reported.  
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36 374 Large-scale prospective cohort studies with control of potential confounding factors are  
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39 375 warranted to validate the present findings.  
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## 44 377 **Abbreviations**

46 378 ABL: Alveolar bone loss; AE: Acute exacerbation; BI: Bleeding index; CAL: Clinical  
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49 379 attachment level; CI: Confident interval; COPD: Chronic obstructive pulmonary disease;  
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52 380 GB: Gingival bleeding; GOLD: Global Initiative for Chronic Obstructive Lung Diseases;  
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55 381 HR: Hazard ratio; OHI: Oral health index; OR: Odds ratio; PD: Periodontal disease; PLI:  
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57 382 Plaque index; PPD: Probing pocket depth; RR: Relative risk.  
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8 384 **Contributors** LC and LL designed the study. MY and XL screened and selected relevant  
9  
10 385 studies. MY, RP and XL rated the study quality and extracted the data. MY, RP, XL and  
11  
12 386 JP analyzed the data. All authors interpreted the data, and MY, RP, XL, JP drafted the  
13  
14 387 paper. LC and LL critically revised the paper. All authors acknowledged and agreed with  
15  
16 388 the format and content of the paper before submission for publication. LC and LL are  
17  
18 389 the guarantors and responsible for the overall contents of this study.  
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26 391 **Funding** This study was supported in part by grant 2016YFC0901100 from the National  
27  
28 392 Key Research and Development Program of China.  
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34 394 **Competing interests** None declared.  
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40 396 **Patient and public involvement** No patients or other individuals are involved in the  
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42 397 design, conduct, reporting or dissemination of this research.  
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48 399 **Patient consent for publication** Not applicable.  
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54 401 **Ethics approval** Not applicable.  
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60 403 **Data availability statement** All data relevant to the study are included in the article or

404 uploaded as supplementary information.

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53 **Figure legends**

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55 548 **Figure 1** PRISMA flow diagram of study selection.

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58 549 **Figure 2** Forest plot of the risk of COPD by periodontal disease, subgroup analysis based  
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550 on adjusted by smoking status and intensity versus by smoking status only. Values more  
551 than one indicate a higher risk in patients with periodontal disease.  
552 **Figure 3** Forest plot of the risk of COPD-related events by periodontal disease. Values  
553 more than one indicate a higher risk in patients with periodontal disease.

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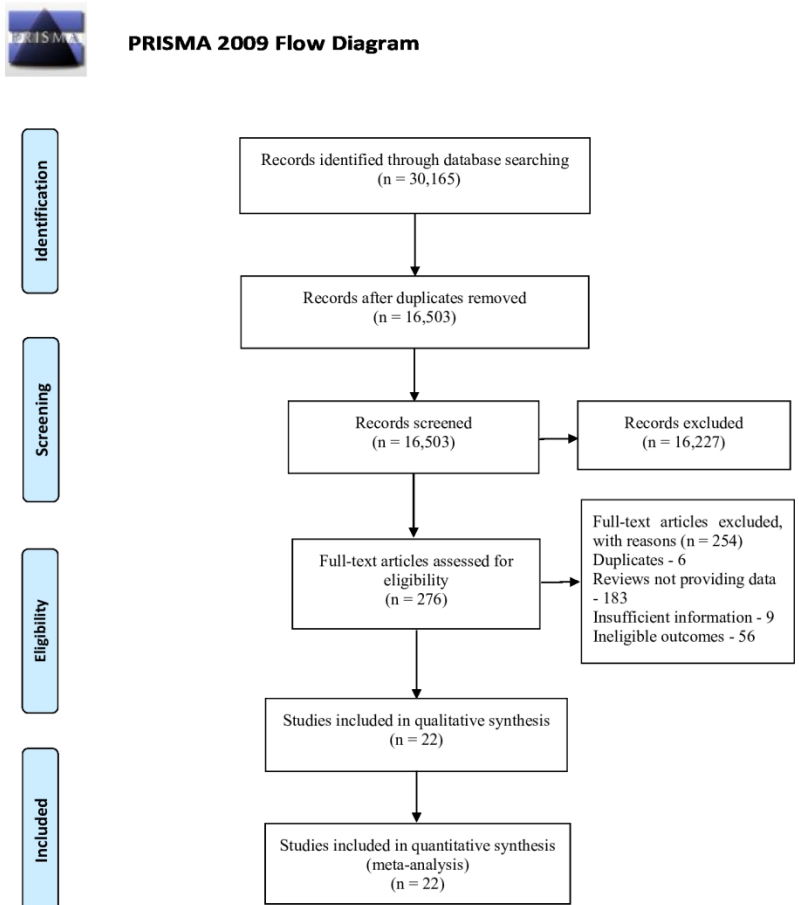


Figure 1 PRISMA flow diagram of study selection.

215x279mm (200 x 200 DPI)

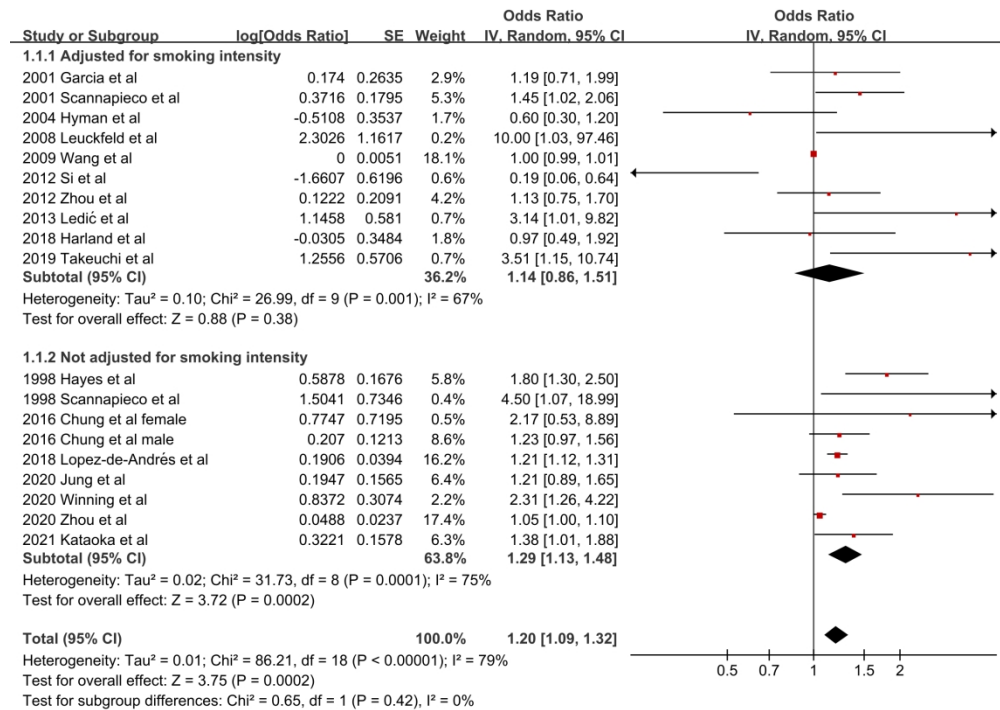


Figure 2 Forest plot of the risk of COPD by periodontal disease, subgroup analysis based on adjusted by smoking status and intensity versus by smoking status only. Values more than one indicate a higher risk in patients with periodontal disease.

536x384mm (118 x 118 DPI)

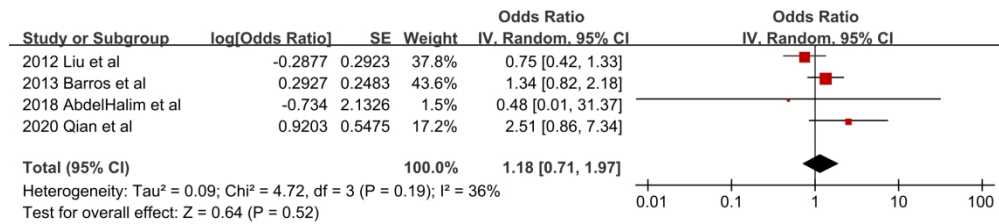


Figure 3 Forest plot of the risk of COPD-related events by periodontal disease. Values more than one indicate a higher risk in patients with periodontal disease.

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  
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 "ambulatory care facilities"[All Fields] OR "clinic"[All Fields] OR "clinic s"[All  
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 Fields] OR "clinics"[All Fields]) AND ("attach"[All Fields] OR "attachable"[All  
 Fields] OR "attached"[All Fields] OR "attachement"[All Fields] OR "attaches"[All  
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 "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 <i>et al</i> <sup>1</sup>	Age, smoking, education, height
Scannapieco <i>et al</i> <sup>2</sup>	Smoking
Garcia <i>et al</i> <sup>3</sup>	Age, height, alcohol, education ( <b>with stratified analysis on smoking</b> )
Leuckfeld <i>et al</i> <sup>4</sup>	Age, female gender, <b>pack years of smoking</b>
Liu <i>et al</i> <sup>5</sup>	Age, gender, BMI and smoking
Wang <i>et al</i> <sup>6</sup>	Age, gender, BMI ( <b>with stratified analysis on smoking</b> )
Si <i>et al</i> <sup>7</sup>	Age, gender, occupation, educational level ( <b>with stratified analysis on smoking</b> )
Zhou <i>et al</i> <sup>8</sup>	Age, gender, smoking, BMI, season ( <b>with stratified analysis on smoking</b> )
Ledić <i>et al</i> <sup>9</sup>	Age, gender, <b>pack years of smoking</b> , BMI
Lopez-de-Andrés <i>et al</i> <sup>10</sup>	Age, gender, smoking, educational level, DM, obesity
Zhou <i>et al</i> <sup>11</sup>	Age, gender, smoking, BMI
Kataoka <i>et al</i> <sup>12</sup>	Age, smoking
Qian <i>et al</i> <sup>13</sup>	Age, sex, education levels, BMI, smoking, drinking, hypertension, DM
Barros <i>et al</i> <sup>14</sup>	Age, gender, Race, BMI, education, <b>pack years of smoking</b> , hypertension
Scannapieco <i>et al</i> <sup>15</sup>	Age, gender, <b>pack years of smoking</b> , Race, education, income, dental visits, alcohol, DM
Hyman <i>et al</i> <sup>16</sup>	Age, gender, Race, history of hypertension and heart attack, dental visit within 1 year, BMI, family income ( <b>with stratified analysis on smoking</b> )
Chung <i>et al</i> <sup>17</sup>	Age, smoking, family income, education, alcohol, exercise, BMI, tooth brushing frequency, DM, number of natural teeth
Harland <i>et al</i> <sup>18</sup>	Age, number of present teeth, BMI, alcohol consumption, occupation, hypertension, DM ( <b>with stratified analysis on smoking</b> )
Takeuchi <i>et al</i> <sup>19</sup>	Age, gender, <b>pack years of smoking</b> , occupation, DM, BMI, physical activity, alcohol intake, number of present teeth

Jung <i>et al</i> <sup>20</sup>	Age, gender, smoking, educational level, household income, alcohol consumption, periodontal status, number of missing teeth, oral health factors
Winning <i>et al</i> <sup>21</sup>	Age, gender, smoking, height, BMI, exercise, DM, hypertension, MI, education level, living condition
AbdelHalim <i>et al</i> <sup>22</sup>	Age, BMI, low-level of education, <b>pack years of smoking</b> , 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**

<b>Study Author</b>	<b>Diagnostic parameter/criteria</b>	<b>Measurement/Calculation</b>
Hayes <i>et al</i> <sup>1</sup>	<b>Worst alveolar bone loss (ABL) quintile vs all others</b>	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 <i>et al</i> <sup>2</sup>	<b>Simplified oral hygiene index=6</b>	Calculated by adding together the simplified debris index and the simplified calculus index scores.
Garcia <i>et al</i> <sup>3</sup>	<b>ABL</b>	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 <i>et al</i> <sup>15</sup>	<b>Mean attachment loss (AL) ≥ 3mm</b>	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 <i>et al</i> <sup>16</sup>	<b>Mean AL ≥ 4mm</b>	AL was calculated based on the probe distance in millimeters from the FGM to the CEJ and the base of the sulcus.
Leuckfeld <i>et al</i> <sup>4</sup>	<b>Mean marginal bone level ≥ 4mm</b>	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 <i>et al</i> <sup>6</sup>	<b>Clinical attachment level (CAL) ≥ 4mm</b>	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 <i>et al</i> <sup>5</sup>	<b>CAL &gt; 4mm</b>	Consistent with the study by Wang <i>et al</i> <sup>6</sup> .
Si <i>et al</i> <sup>7</sup>	<b>Probing depth ≥ 5mm and CAL ≥ 4mm</b>	The two indices were recorded on six sites of each tooth.
Zhou <i>et al</i> <sup>8</sup>	<b>CAL</b>	Consistent with the study by Wang <i>et al</i> <sup>6</sup> .
Barros <i>et al</i> <sup>14</sup>	<b>≥ 2 interproximal sites with CAL ≥ 6mm (not on same tooth) and ≥ 1 interproximal site with probing depth ≥ 5mm</b>	Using the consensus definitions published by the joint Center for Disease Control/American Association of Periodontology working group.
Ledić <i>et al</i> <sup>9</sup>	<b>CAL ≥ 4mm at at least 60% of the measured sites</b>	CAL was determined as the distance from the CEJ to the bottom of the pocket. The aforementioned value

		was recorded on the nearest millimeter by one calibrated examiner on six places per tooth (mesiobuccally, buccally, distobuccally, mesiolingually, lingually and distolingually).
Chung <i>et al</i> <sup>17</sup>	<b>Community periodontal index (CPI) &gt;5.5mm pocket (deep periodontal pocket)</b>	WHO criteria (Oral health surveys: basic methods- 5th edition).
AbdelHalim <i>et al</i> <sup>22</sup>	<b>CAL ≥5mm</b>	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 <i>et al</i> <sup>18</sup>	<b>CPI score ≥3 (at least one sextant with a pocket depth ≥4 mm)</b>	WHO criteria.
Lopez-de-Andrés <i>et al</i> <sup>10</sup>	<b>Teeth bleeding spontaneously or while brushing, or/and teeth moving</b>	Questionnaire investigation.
Takeuchi <i>et al</i> <sup>19</sup>	<b>Severe periodontitis (2 or more interproximal sites with ≥6mm CAL [not on same tooth] and 1 or more interproximal sites with ≥5mm PPD)</b>	According to the suggested Centers for Disease Control and American Academy of Periodontology case definitions for periodontitis surveillance.
Jung <i>et al</i> <sup>20</sup>	<b>CPI=3-4 (periodontal pockets ≥4mm)</b>	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 <i>et al</i> <sup>13</sup>	<b>Proportion of remaining bone height of the teeth (calculated from total root length and total bone height)</b>	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 <i>et al</i> <sup>21</sup>	<b>A distance between the alveolar bone level and CEJ based on a threshold of ≥4mm found at ≥30% of teeth.</b>	The extent of ABL was measured at the mesial and distal aspects of all teeth excluding third molars.
Zhou <i>et al</i> <sup>11</sup>	<b>CAL ≥5mm</b>	Consistent with the study by Wang <i>et al</i> <sup>6</sup>
Kataoka <i>et al</i> <sup>12</sup>	<b>PPD ≥4mm</b>	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.

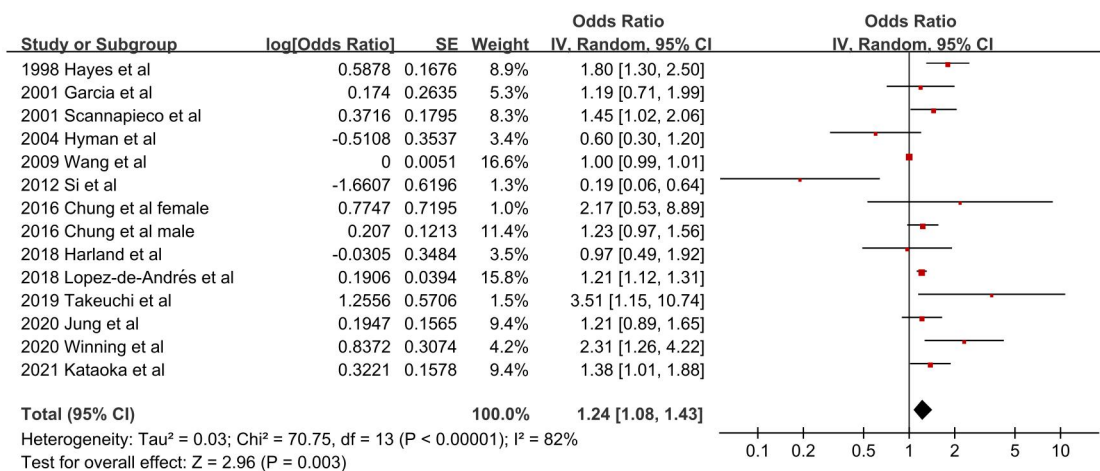
Table 4 Quality assessment based on the Newcastle-Ottawa Scale

## (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 <i>et al</i> <sup>14</sup>	*	*	*	...	...	*	*	*	6
Takeuchi <i>et al</i> <sup>19</sup>	*	*	*	*	...	*	*	*	7
Gian <i>et al</i> <sup>13</sup>	...	*	*	...	...	*	*	...	4

## (B) Case-control / cross-sectional study

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

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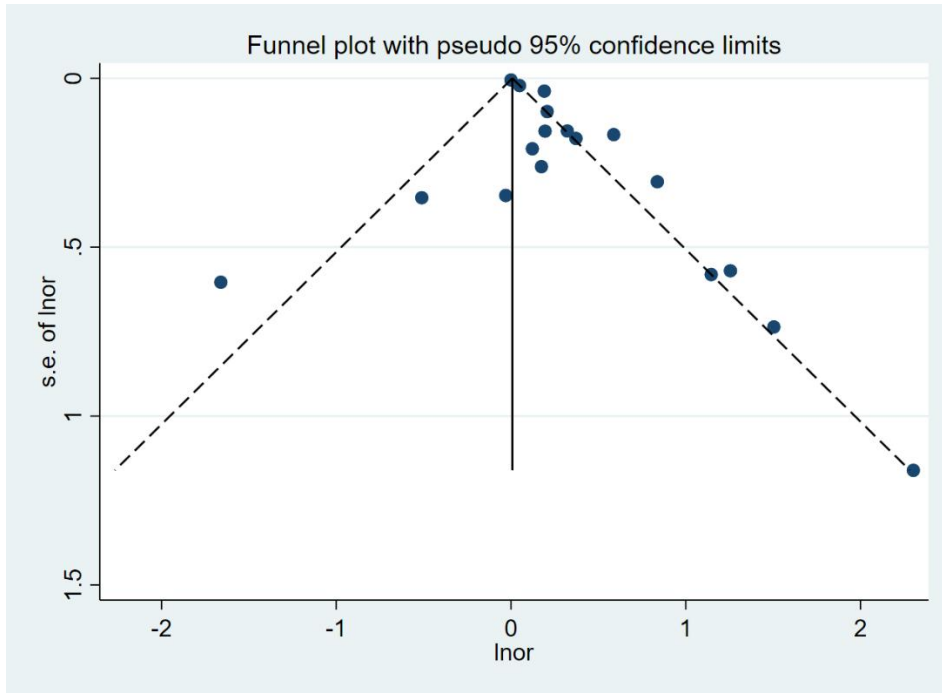
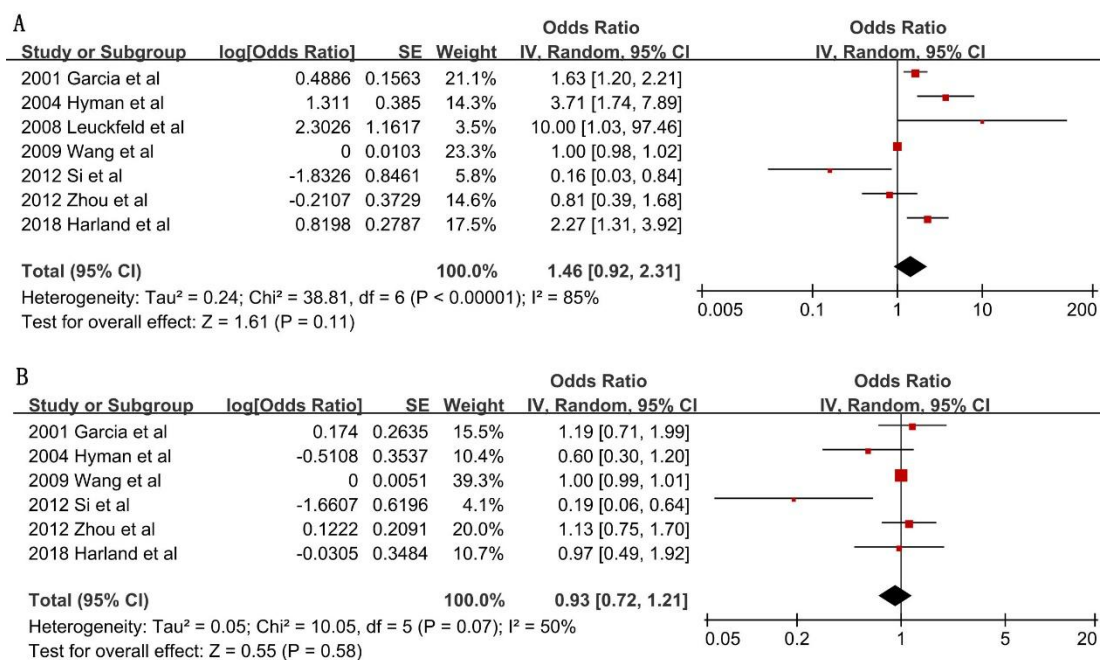


Figure 2 Funnel plot for the risk of COPD, with pseudo 95% confidence limits.

Peer review only



**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
<b>TITLE</b>				
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1 / Line 2,3	Title page
<b>ABSTRACT</b>				
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
<b>INTRODUCTION</b>				
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
<b>METHODS</b>				
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 <sup>2</sup> ) 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
<b>RESULTS</b>				
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
<b>DISCUSSION</b>				
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

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<b>FUNDING</b>				
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

**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

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