

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	The association between chronic obstructive pulmonary disease and periodontal disease: a systematic review and meta-analysis
<b>AUTHORS</b>	Yang, Mei; Peng, Ran; Li, Xiaoou; Peng, Junjie; Liu, Lin; Chen, Lei

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Pedro Bullón University of Seville
<b>REVIEW RETURNED</b>	05-Nov-2022

<b>GENERAL COMMENTS</b>	<p>The main issue of this paper is that the authors try to determine the association of PD with the risk of COPD. Therefore, it is essential to define both diseases that were related.</p> <p>At first, they write COPD risk. Perhaps they mean COPD not risk; if they determine risk then they must relate PD with COPD risk factors, and in this paper they relate PD with COPD that was previously diagnosed. We propose to write the association of PD with the risk of COPD. Furthermore, the authors should analyze whether the diagnosis of COPD was the same in all articles. Usually the main criteria are based on the Global Initiative for Chronic Obstructive Lung Disease(GOLD) spirometry guidelines: Global Strategy for the Diagnosis, Management, and Prevention of COPD (update2007) (Rabe et al. 2007)</p> <p>They associate PD and are identified as independent variables, so it is important to diagnose what PD is. The best way to do it is to use the last classification of periodontal disease (Papanou PN et al. Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. J Clin Periodontol. 2018 Jun;45 Suppl 20:S162-S170) a patient is a “periodontitis case” if: Interdental CAL is detectable at <math>\geq 2</math> non-adjacent teeth, or Buccal or oral CAL <math>\geq 3</math> mm with pocketing <math>\geq 3</math> mm is detectable at <math>\geq 2</math> teeth but the observed CAL cannot be ascribed to non-periodontitis-related causes. The article used for the metanalysis shows different diagnoses of periodontitis. For example, the 15th reference shows three mild, moderate, and severe. The 20th reference used mean loss of attachment and mean probing depth, both categorized into five groups. If they used the mean of CAL, ABL, and PPD, they used data from patients who did not suffer PD. The authors conclude: PD was not associated with the risk of COPD and COPD-related events. They should conclude that they do not associate CAL, ABL, and PPD with the risk of COPD, not with PD.</p>
-------------------------	--

<b>REVIEWER</b>	Florence Carrouel Universite Claude Bernard Lyon 1
<b>REVIEW RETURNED</b>	05-Nov-2022

<b>GENERAL COMMENTS</b>	<p>Dear author,  Your systematic review and meta-analysis analyzing the association of periodontal disease with COPD risk and clinical events has been conducted according to PRISMA checklist and the conclusions are supported by the results. The methodology used was good and there is no over interpretation.  However, I have 2 comments:  1. It is difficult to understand why the number of studies included in qualitative and quantitative study is not the same. The manuscript will be more clear if you only included 22 studies. Indeed, it is difficult because in the summary, you only described the 22 included studies whereas p3 lines 181-182 (results section) you wrote "Finally, 24 studies were included in the review."  2. In the conclusion section the sentence "PD was not associated with risk of COPD and COPD-related events was supported by the results" should be less affirmative because as you explained after "future well-designed studies are required to validate the present findings".</p>
-------------------------	--

<b>REVIEWER</b>	Tiago Jacinto CINTESIS, Faculdade de Medicina da Universidade do Porto, Portugal, Centro de Investigação Médica, Faculdade de Medicina da Universidade do Porto
<b>REVIEW RETURNED</b>	29-Dec-2022

<b>GENERAL COMMENTS</b>	<p>The authors present an interesting manuscript, detailing a systematic review that shows the little to no association of PD to COPD, adjusted for smoking habits. The manuscript follows the recommended structure in the PRISMA guidelines.</p> <p>Although it is well-written, I do have some comments that can hopefully contribute to an improvement of the manuscript.</p> <ol style="list-style-type: none"> <li>1) I suggest a slight restructuring of the objective, in the last paragraph of the introduction. The objective should clearly state that the association between PD and COPD was the target, and for that, a systematic review of the literature was used;</li> <li>2) In page 7, line 112, the definition of adults should be detailed;</li> <li>3) In page 7, line 113, the “clear diagnostic or assessment criteria” must be detailed;</li> <li>4) In page 7, line 114, the measures of association should be detailed;</li> <li>5) In page 10, line 184, the sentence is not clear, is this mean COPD prevalence?</li> <li>6) In table 1, and overall, perhaps the appropriate term would be “studies” instead of “articles”?</li> <li>7) The first paragraph of the discussion should be rewritten to better show the main results of the study;</li> <li>8) I feel that it it would be important to have a table with a description of the included studies in the main body of the manuscript;</li> </ol>
-------------------------	---

	9) An overall review of the English language may be needed for additional clarity.
	10) The methods in the abstract could be more detailed.

<b>REVIEWER</b>	Josep Roca Institut d'Investigacions Biomediques August Pi i Sunyer, Hospital Clinic de Barcelona (ICR)
<b>REVIEW RETURNED</b>	08-Jan-2023

<b>GENERAL COMMENTS</b>	<p>The authors have done a good systematic review of the relationships between PD and COPD (prevalence and undesirable events). As expected, they showed negative results after correction for tobacco smoking. The research work is technically acceptable, the document is properly written and the intrinsic study limitations were well identified and described.</p> <p>It is well known that patients with COPD show high prevalence of co-morbid conditions likely due to underlying disturbances in relevant biological pathways at systemic level (i.e. nitroso-redox disequilibrium, inflammation, etc...) that may have significant impact on clinical events and patients' prognosis. However, I have doubts regarding the added value of the question raised in the current research, as well as the appropriateness of a systematic review of the literature to address the targeted question.</p>
-------------------------	--

### VERSION 1 – AUTHOR RESPONSE

#### Reviewer 1

**Comment 1:** *At first, they write COPD risk. Perhaps they mean COPD not risk; if they determine risk then they must relate PD with COPD risk factors, and in this paper they relate PD with COPD that was previously diagnosed. We propose to write the association of PD with the risk of COPD.*

**Reply:** We have corrected “COPD risk” to “the risk of COPD”.

**Comment 2:** *Furthermore, the authors should analyze whether the diagnosis of COPD was the same in all articles. Usually the main criteria are based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometry guidelines: Global Strategy for the Diagnosis, Management, and Prevention of COPD (update2007) (Rabe et al. 2007).*

**Reply:** The diagnosis of COPD of all included studies were presented in the Results section (Page 11-12, Line 219-221). In subgroup analyses, we further analyzed the subgroup applying the GOLD 2023 spirometry guidelines ( $FEV_1/FVC < 0.7$ ), as shown in the Table 2.

Ref: Global Initiative for Chronic Obstructive Pulmonary Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2023 report).

<https://goldcopd.org/2023-gold-report-2/>

**Comment 3:** *They associate PD and are identified as independent variables, so it is important to diagnose what PD is. The best way to do it is to use the last classification of periodontal disease (Papanou PN et al. Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. J Clin Periodontol. 2018 Jun;45 Suppl 20:S162-S170) a patient is a “periodontitis case” if: Interdental CAL is detectable at  $\geq 2$  non-adjacent teeth, or Buccal or oral CAL  $\geq 3$  mm with pocketing  $\geq 3$  mm is detectable at  $\geq 2$  teeth but the observed CAL cannot be ascribed to non-periodontitis-related causes.*

**Reply:** The term of periodontal disease (PD) used in this meta-analysis refers to a wide variety of periodontal abnormalities according to clinical and radiographic assessments, which is not just periodontitis (Ref 1). This can be seen in many relevant studies (Ref 2-4). Besides, across almost all studies included in this meta-analysis, assessment of PD was conducted by experienced or trained dentists.

Ref: 1. Kinane DF, Stathopoulou PG, Papapanou PN. Periodontal diseases. Nat Rev Dis Primers. 2017;3:17038.

2. Ding L, You Q, Jiang Q, et al. Meta-analysis of the association between periodontal disease, periodontal treatment and carotid intima-media thickness. J Periodontol Res. 2022;57(4):690-697.

3. Moraschini V, Calasans-Maia JA, Calasans-Maia MD. Association between asthma and periodontal disease: A systematic review and meta-analysis. J Periodontol. 2018;89(4):440-455.

4. Molina A, Huck O, Herrera D, Montero E. The association between respiratory diseases and periodontitis: A systematic review and meta-analysis [published online ahead of print, 2023 Jan 6]. J Clin Periodontol. 2023;10.1111/jcpe.13767.

**Comment 4:** *The article used for the metanalysis shows different diagnoses of periodontitis. For example, the 15th reference shows three mild, moderate, and severe. The 20th reference used mean loss of attachment and mean probing depth, both categorized into five groups. If they used the mean of CAL, ABL, and PPD, they used data from patients who did not suffer PD. The authors conclude: PD was not associated with the risk of COPD and COPD-related events. They should conclude that they do not associate CAL, ABL, and PPD with the risk of COPD, not with PD.*

**Reply:** Similar to most relevant studies, periodontal disease in this study refers to a wide variety of periodontal abnormalities, not just periodontitis. Currently, the diagnostic criteria of PD vary across studies, and there are very limited studies applying unified diagnostic criteria. This induces heterogeneity and has been an unavoidable limitation in relevant studies, which we also explained in the Limitations section. According to current evidence, CAL, ABL and PPD have been regarded as the primary variables for assessing PD (Ref 1 and 2), thus if more than one adjusted estimate was shown in the paper (such as the 20th reference), we preferentially used the estimate regarding these parameters (CAL > ABL > PPD), or the estimate being better adjusted for tobacco smoking (never

smokers > adjusting for smoking intensity [duration and dose] > adjusting for smoking status), or the estimate regarding more severe PD (such as the 15th reference). This can be seen in other studies (Ref 3). Meanwhile, we also conducted subgroup and stratified analyses concerning these variables, such as CAL, ABL, PPD and smoking status (Table 2 and Figure 2,3).

Ref: 1. Papapanou PN, Sanz M, Buduneli N, et al. Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. J Clin Periodontol. 2018;45 Suppl 20:S162-S170.

2. Kinane DF, Stathopoulou PG, Papapanou PN. Periodontal diseases. Nat Rev Dis Primers. 2017;3:17038.

3. Zeng XT, Tu ML, Liu DY, et al. Periodontal disease and risk of chronic obstructive pulmonary disease: a meta-analysis of observational studies. PLoS One. 2012;7(10):e46508.

## **Reviewer 2**

**Comment 1:** *It is difficult to understand why the number of studies included in qualitative and quantitative study is not the same. The manuscript will be more clear if you only included 22 studies. Indeed, it is difficult because in the summary, you only described the 22 included studies whereas p3 lines 181-182 (results section) you wrote "Finally, 24 studies were included in the review."*

**Reply:** We have made corresponding modifications. A total of 22 studies were included for meta-analysis.

**Comment 2:** *In the conclusion section the sentence "PD was not associated with risk of COPD and COPD-related events was supported by the results" should be less affirmative because as you explained after "future well-designed studies are required to validate the present findings"*

**Reply:** We have made corresponding modifications (Page 19, Line 368-372).

## **Reviewer 3**

**Comment 1:** *I suggest a slight restructuring of the objective, in the last paragraph of the introduction. The objective should clearly state that the association between PD and COPD was the target, and for that, a systematic review of the literature was used.*

**Reply:** We have made corresponding modifications (Page 5, Line 103-107).

**Comment 2:** *In page 7, line 112, the definition of adults should be detailed.*

**Reply:** We have made corresponding modification (Page 6, Line 119).

**Comment 3:** *In page 7, line 113, the “clear diagnostic or assessment criteria” must be detailed.*

**Reply:** To provide more comprehensive evidence, we did not limit the diagnostic or assessment criteria of COPD and periodontal disease when conducting the literature search and inclusion. However, we did subgroup analyses on different assessment criteria of both diseases (Table 2).

**Comment 4:** *In page 7, line 114, the measures of association should be detailed.*

**Reply:** We have made corresponding modifications (Page 6, Line 121-124).

**Comment 5:** *In page 10, line 184, the sentence is not clear, is this mean COPD prevalence?*

**Reply:** We have made corresponding modification (Page 9, Line 190).

**Comment 6:** *In table 1, and overall, perhaps the appropriate term would be “studies” instead of “articles”?*

**Reply:** We have made corresponding modification (Table 2).

**Comment 7:** *The first paragraph of the discussion should be rewritten to better show the main results of the study.*

**Reply:** We have made corresponding modifications (Page 15, Line 277-281).

**Comment 8:** *I feel that it would be important to have a table with a description of the included studies in the main body of the manuscript.*

**Reply:** We have added a table with descriptions of the included studies (Table 1).

**Comment 9:** *An overall review of the English language may be needed for additional clarity.*

**Reply:** We have reviewed the English language and made some modifications to ensure clarity.

**Comment 10:** *The methods in the abstract could be more detailed.*

**Reply:** We have made corresponding modifications.

**Reviewer 4**

**Comment:** *However, I have doubts regarding the added value of the question raised in the current research, as well as the appropriateness of a systematic review of the literature to address the targeted question.*

**Reply:** The association between respiratory disease and periodontal disease (PD) has always been paid much attention. By 2023, a number of systematic review and meta-analysis have indicated that PD could increase the risk of COPD, but failed to fully adjust for confounding by smoking (Ref 1-3). In this context, it is reasonable and valuable to conduct this study. Firstly, this study answered the controversial question that whether PD was associated with the risk of COPD when adjusting for confounding by smoking, which was also the primary objective. Secondly, patients with COPD often have PD, thus it is important and necessary to understand the effect of PD on COPD-related events. Although included studies were limited, we also tried to answer this question. Thirdly, the results of this study demonstrated the non-negligible effects of smoking on the association between respiratory disease and PD, and underscored the importance of study on non-smokers.

**VERSION 2 – REVIEW**

<b>REVIEWER</b>	Pedro Bullón University of Seville
<b>REVIEW RETURNED</b>	27-Feb-2023

<b>GENERAL COMMENTS</b>	<p>I would appreciate a letter with the answer of my requeriments</p> <p>The main issue of this paper is that the authors try to determine the association of PD with the risk of COPD. Therefore, it is essential to define both diseases that were related.</p> <p>At first, they write COPD risk. Perhaps they mean COPD not risk; if they determine risk then they must relate PD with COPD risk factors, and in this paper they relate PD with COPD that was previously diagnosed. We propose to write the association of PD with the risk of COPD. Furthermore, the authors should analyze whether the diagnosis of COPD was the same in all articles. Usually the main criteria are based on the Global Initiative for Chronic Obstructive Lung Disease(GOLD) spirometry guidelines: Global Strategy for the Diagnosis, Management, and Prevention of COPD (update2007) (Rabe et al. 2007)</p> <p>They associate PD and are identified as independent variables, so it is important to diagnose what PD is. The best way to do it is to use the last classification of periodontal disease (Papanou PN et al. Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant</p>
-------------------------	--

	Diseases and Conditions. J Clin Periodontol. 2018 Jun;45 Suppl 20:S162-S170) a patient is a “periodontitis case” if: Interdental CAL is detectable at $\geq 2$ non-adjacent teeth, or Buccal or oral CAL $\geq 3$ mm with pocketing $\geq 3$ mm is detectable at $\geq 2$ teeth but the observed CAL cannot be ascribed to non-periodontitis-related causes. The article used for the metanalysis shows different diagnoses of periodontitis. For example, the 15th reference shows three mild, moderate, and severe. The 20th reference used mean loss of attachment and mean probing depth, both categorized into five groups. If they used the mean of CAL, ABL, and PPD, they used data from patients who did not suffer PD. The authors conclude: PD was not associated with the risk of COPD and COPD-related events. They should conclude that they do not associate CAL, ABL, and PPD with the risk of COPD, not with PD.
--	---

<b>REVIEWER</b>	Tiago Jacinto CINTESIS, Faculdade de Medicina da Universidade do Porto, Portugal, Centro de Investigação Médica, Faculdade de Medicina da Universidade do Porto
<b>REVIEW RETURNED</b>	16-Mar-2023

<b>GENERAL COMMENTS</b>	Thank you for responses, the comments I've made have been adequately addressed.
-------------------------	---

## VERSION 2 – AUTHOR RESPONSE

### Reviewer 1

#### Dr. Pedro Bullón, University of Seville

**Comments:** *The main issue of this paper is that the authors try to determine the association of PD with the risk of COPD. Therefore, it is essential to define both diseases that were related.*

*At first, they write COPD risk. Perhaps they mean COPD not risk; if they determine risk then they must relate PD with COPD risk factors, and in this paper they relate PD with COPD that was previously diagnosed. We propose to write the association of PD with the risk of COPD. Furthermore, the authors should analyze whether the diagnosis of COPD was the same in all articles. Usually the main criteria are based on the Global Initiative for Chronic Obstructive Lung Disease(GOLD) spirometry guidelines: Global Strategy for the Diagnosis, Management, and Prevention of COPD (update2007) (Rabe et al. 2007)*

*They associate PD and are identified as independent variables, so it is important to diagnose what PD is. The best way to do it is to use the last classification of periodontal disease (Papanou PN et al. Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. J Clin Periodontol. 2018 Jun;45 Suppl 20:S162-S170) a patient is a “periodontitis case” if: Interdental CAL is detectable at  $\geq 2$  non-adjacent teeth, or Buccal or oral CAL  $\geq 3$  mm with pocketing  $\geq 3$  mm is detectable at  $\geq 2$  teeth but the observed CAL cannot be ascribed to non-periodontitis-related causes. The article used for the metanalysis shows different diagnoses of periodontitis. For example, the 15th reference shows three mild, moderate, and severe. The 20th reference used mean loss of attachment and mean probing depth, both categorized into five groups. If they used the mean of CAL, ABL, and PPD, they used data from*



*patients who did not suffer PD. The authors conclude: PD was not associated with the risk of COPD and COPD-related events. They should conclude that they do not associate CAL, ABL, and PPD with the risk of COPD, not with PD.*

**Reply:** We have provided responses to these questions and made corresponding revisions in the first revision of this manuscript (ID: bmjopen-2022-067432.R1), which was submitted via online system on February 25, 2023.

### **Reviewer 3**

**Dr. Tiago Jacinto, CINTESIS, Faculdade de Medicina da Universidade do Porto, Portugal**

**Comment:** Thank you for responses, the comments I've made have been adequately addressed.

**Reply:** Thank you for suggestions.