

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Association between Periodontitis and Hypertension: Cross-Sectional Survey from the Fourth National Oral Health Survey of China (2015-2016)
AUTHORS	Zhan, Yalin; Jiao, Jian; Jing, Wu-di; Feng, Xiping; Tai, Baojun; Hu, Deyu; Lin, Huan-cai; Wang, Bo; Wang, Chunxiao; Zheng, Shuguo; Liu, Xuenan; Rong, Wensheng; Wang, Weijian; Wang, Xing; Si, Yan; Meng, Huanxin

VERSION 1 – REVIEW

REVIEWER	Tada, Akio Hyogo Univ
REVIEW RETURNED	19-Oct-2022

GENERAL COMMENTS	<p>This study investigated the association between periodontal status and hypertension among Chinese adults. Although it is adequately analyzed, there are some problems.</p> <p>There are sexual differences in the prevalence of periodontitis and hypertension. Moreover, confounding factors for the association between periodontitis and hypertension have different prevalence in both genders (e. g. smoking). The authors should analyze the association between periodontitis and hypertension in men and women, separately.</p> <p>Many studies analyzing the association between periodontitis and hypertension have been published to date. Systematic reviews were published concerning this association (Muñoz et al 2020, Martin-Cabezas et al 2016). The authors should read these articles and highlight feature and attractive points of their study.</p> <p>The explanation for classification from stage 1-4 gives a question. AL and tooth loss are used for parameters but if there is a discrepancy between these parameters, which category the subjects are classified to? For example, a subject with AL=6 and 4 teeth loss. It is necessary to explain to make readers who are not familiar with periodontology understand.</p> <p>In 55-65 years (55-64years?), significant differences in the prevalence of PD\geq4mm and 6mm were seen between HT and normal, but not in the prevalence of AL\geq4mm and 6mm. The authors should discuss this finding.</p> <p>There are problems in Tables. Table 2: It needs improvement on the format. The position of PTA makes us "PTA" applies to BOP+, PD\geq4mm, . . . because</p>
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	<p>“PTA” and periodontal states are in the same column. Similar is in Table 3.</p> <p>Table 3: I cannot understand what “Number of percentage” mean.</p> <p>Table4: The authors should enter the reference in the table.</p> <p>Table 5: This table is difficult to understand. I guess blood pressure is classified into “Hypertension2 and “Normal”.</p> <p>“Percentage of teeth affected” is a continuous variable. What is the cut-off point of this variable? Similar point is applied to Table 6.</p> <p>And the reference is not unclear in these Tables.</p>
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REVIEWER	Cruz-Hervert, Luis Pablo Instituto Nacional de Salud Pública, Centro de Investigaciones Sobre Enfermedades Infecciosas
REVIEW RETURNED	19-Oct-2022

GENERAL COMMENTS	<p>Personally, I appreciate all the effort from the authors to perform all my suggestions. I find the paper perfectly suitable for publication.</p> <p>However, I have a last minor suggestion.</p> <p>As the authors correctly describe, they conducted a cross-sectional study, so it is not possible to assume causality. I strongly recommend substituting the “increase” word for “higher” because increases assume an augmentation from the basal, not a higher prevalence, and that might be interpreted as causation.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

This study investigated the association between periodontal status and hypertension among Chinese adults. Although it is adequately analyzed, there are some problems.

Thank you very much for your kind and professional comments. We have revised the manuscript carefully based on your valuable and professional suggestions.

There are sexual differences in the prevalence of periodontitis and hypertension. Moreover, confounding factors for the association between periodontitis and hypertension have different prevalence in both genders (e. g. smoking). The authors should analyze the association between periodontitis and hypertension in men and women, separately.

Thank you very much for your professional comments. In the revised version, we considered the gender differences in the relation between periodontitis and hypertension. In revised Table 1, we compared the percentage and 95% CI of various periodontal status between hypertensive and normotensive groups by stratified analysis based on gender. At the same time, the sexual differences were also analyzed in the results.

Many studies analyzing the association between periodontitis and hypertension have been published to date. Systematic reviews were published concerning this association (Muñoz et al 2020, Martin-Cabezas et al 2016). The authors should read these articles and highlight feature and attractive points of their study.

Thank you very much for your professional recommendation. Systematic reviews (Muñoz et al 2020, Martin-Cabezas et al 2016) analyzing the association between periodontitis and hypertension have been cited in revised manuscript. We have highlighted feature and attractive points of our study in revised manuscript, described as follows.

In recent systemic reviews analyzing the association between periodontitis and hypertension, the included studies had been conducted in different countries across Asia, Europe, America, and Africa, lacking the large-scale data from China. In this study, we used data from a large-scale national survey in which participants were representative of the Chinese population. Besides, the lack of consistent measures of case definition and severity of periodontitis in the retrieved studies did not allow for a relevant analysis of extent and severity of periodontitis with hypertension. In the present study, periodontitis was diagnosed in accordance with the classification proposed at the 2017 World Workshop.

In most of the studies, periodontal status was clinically evaluated through PD and/or clinical attachment level measurement. Nevertheless, several definitions of periodontal diseases have been used across studies and only a few have distinguished severe forms of periodontitis. In the present study, periodontitis severity was defined using the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. Participants with severe periodontal disease (stages III and IV periodontitis) had a greater risk of hypertension compared with participants who had mild or no periodontal disease.

The explanation for classification from stage 1-4 gives a question. AL and tooth loss are used for parameters but if there is a discrepancy between these parameters, which category the subjects are classified to? For example, a subject with AL=6 and 4 teeth loss. It is necessary to explain to make readers who are not familiar with periodontology understand.

Thank you very much for your kind comments. Stages of periodontitis reflects not only the severity and extent of periodontitis but the complexity of managing the individual patient (Tonetti et al 2018). It is a comprehensive indicator. However, periodontal clinical parameters (such as AL, BOP, PD) are indicators reflecting specific periodontal problems: for example, AL reflects the destruction of periodontal attachment, while BOP and PD focus more on the indicators of existing inflammation. In the clinical study of periodontology, we often refer to both the severity of the disease (the stages for example) and specific periodontal parameters to support our conclusions through different indexes. As the reviewer put it, a subject with AL=6 and 4 teeth loss is likely to be classified as periodontitis Stage III (Of course, we need more clinical and radiographic parameters to make a more accurate diagnosis). According to the suggestions of the reviewer, the corresponding explanations have been added to the materials and methods section of the revised version.

In 55-65 years (55-64years?), significant differences in the prevalence of $PD \geq 4\text{mm}$ and 6mm were seen between HT and normal, but not in the prevalence of $AL \geq 4\text{mm}$ and 6mm . The authors should discuss this finding.

Thank you very much for the professional recommendation. According to your professional suggestion, the corresponding discussion has been supplemented in the revised version. Compared with AL, PD seems to be more closely related to hypertension. For example, significant differences of the percentages/numbers of $PD \geq 4\text{mm}$ and 6mm in 55-64 years were seen between hypertensive and normotensive individuals, but not in the percentages/numbers of $AL \geq 4\text{mm}$ and 6mm (Table 2 and 3). This is because AL is more related to periodontal attachment damage, while PD is more related to the existing periodontal inflammation. This also indicates that the correlation between periodontitis and hypertension may be related to the increase of systemic inflammation.

There are problems in Tables.

Table 2: It needs improvement on the format. The position of PTA makes us "PTA" applies to BOP+, $PD \geq 4\text{mm}$, . . . because "PTA" and periodontal states are in the same column. Similar is in Table 3.

Thank you very much for your kind comments. According to the suggestions, Table 2 and 3 has been revised.

Table 3: I cannot understand what "Number of percentage" mean.

Thank you very much for your kind comment. The title of the table should be “Table 3. Number of teeth affected by age groups and smoking status.” and were corrected in the revised manuscript.

Table 4: The authors should enter the reference in the table.

Thank you for the valuable suggestion. The reference has been added in the revised manuscript.

Table 5: This table is difficult to understand. I guess blood pressure is classified into “Hypertension and “Normal”. “Percentage of teeth affected” is a continuous variable. What is the cut-off point of this variable? Similar point is applied to Table 6. And the reference is not unclear in these Tables.

Thank you for the kind comments. Hypertension is a binary variable, that is, hypertension versus normotension. And “Percentage of teeth affected” is a continuous variable whose unit was the percentage (That is one percent). In the calculation, we do not regard it as a classified variable but as a continuous variable. Therefore, there was no cut-off point for this variable. The OR in the table 5 (Take “PD ≥ 4mm” as an example) means the risk of hypertension increases by 1.73 times with the increase of 1% of the percentage of PD ≥ 4mm. And the reference has been explained in Table 5 and 6.

Reviewer 2:

Personally, I appreciate all the effort from the authors to perform all my suggestions. I find the paper perfectly suitable for publication.

However, I have a last minor suggestion.

As the authors correctly describe, they conducted a cross-sectional study, so it is not possible to assume causality. I strongly recommend substituting the “increase” word for “higher” because increases assume an augmentation from the basal, not a higher prevalence, and that might be interpreted as causation.

Thank you very much for your kind comment and professional recommendation. We have revised the manuscript substituting the “increase” word for “higher” according to your professional recommendation.

VERSION 2 – REVIEW

REVIEWER	Tada, Akio Hyogo Univ
REVIEW RETURNED	20-Nov-2022

GENERAL COMMENTS	<p>Authors have made efforts to improve the manuscript and some improvement is confirmed. However, some problems remain and these problems make it difficult to be understood and deteriorate the quality of the study.</p> <p>Table 1 exhibits only percentage of subjects with each periodontal status. However, the title of Table1 includes “Comparison” and in the text, p value is described. Authors should describe the evaluation of statistical significance.</p> <p>Authors should take care for the use of term “periodontal status”. In Table 1, the percentage of subjects with each periodontal status and in Table 2, the percentage of teeth with each periodontal status. Consideration for avoiding confusion is necessary.</p> <p>Table 2: Most of studies have compared percentage of subjects with each periodontal status that exhibits the grade (severity) of periodontitis. On the other hand, this study exhibits the percentage of teeth with each periodontal status that means extension of</p>
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	<p>periodontal pathology in the oral cavity. This is a unique point and authors should highlight this point in the discussion or strength of the study. The assessment of extent of pathological condition for periodontal disease is thought to be important, however, the most severe pathological condition in the oral cavity is assessed in many cases. Authors should notice this feature. Being diagnosed in accordance with the classification proposed at the 2017 World Workshop and surveyed in China are not thought to be so academically important. Other large-scale studies have already published before.</p> <p>Table 2, 3: Authors should make comparisons between genders as well as age groups and smoking status.</p> <p>Table 2: The title of Table 2 should be “Comparison of percentage of teeth affected (PTA) by age group and smoking status”. And delete “PTA” in Table. The same is for Table 3.</p> <p>PTA and NTA are almost parallel. The meaning of using PTA and NTA is unclear.</p> <p>In table 5 and 6, it is difficult to find that OR increases with the increase of 1% of the percentage. Authors should explain it in the Material and Methods section or below Tables. Should refer other articles with similar data (i.e. OR increases with the increase of 1 of any measure value).</p> <p>In general, numerical value is described to first decimal place. For example, 49.83%→49.8%</p>
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VERSION 2 – AUTHOR RESPONSE

Reviewer 1:

Comments to the Author:

Authors have made efforts to improve the manuscript and some improvement is confirmed. However, some problems remain and these problems make it difficult to be understood and deteriorate the quality of the study.

Thank you very much for your kind and professional comments. We have revised the manuscript carefully based on your valuable and professional suggestions.

Table 1 exhibits only percentage of subjects with each periodontal status. However, the title of Table 1 includes “Comparison” and in the text, p value is described. Authors should describe the evaluation of statistical significance.

Thank you very much for your valuable and professional suggestions. In the revised version, the results by Chi square test have been supplemented including differences of distribution proportion of periodontitis (Stage I-IV) and non-periodontitis (health and gingivitis), severe periodontitis (Stage III and IV) and non-severe-periodontitis (health, gingivitis, stage I and stage II) between hypertensive and normotensive subjects in different age/gender groups. The corresponding description has been supplemented in the footnote of Table 1. The p value has been added in Table 1. The evaluation of statistical significance has also been described in the text.

Authors should take care for the use of term “periodontal status”. In Table 1, the percentage of

subjects with each periodontal status and in Table 2, the percentage of teeth with each periodontal status. Consideration for avoiding confusion is necessary.

Thank you very much for your kind and professional suggestions. In the revised version, two different terms have been used in Table 1 and 2 to avoid confusion for readers. In Table 1, periodontal status (health, gingivitis, and periodontitis stage I to IV according to the 2017 World Workshop on the Classification of Periodontal and Per-Implant Diseases and Conditions) were used to compare the percentage of subjects with each periodontal status between hypertensive and normotensive subjects. In Table 2, periodontal parameters (BOP, PD \geq 4 or 6 mm and AL \geq 4 or 6 mm) were used to compare the percentage of teeth with each periodontal parameter between hypertensive and normotensive subjects.

Table 2: Most of studies have compared percentage of subjects with each periodontal status that exhibits the grade (severity) of periodontitis. On the other hand, this study exhibits the percentage of teeth with each periodontal status that means extension of periodontal pathology in the oral cavity. This is a unique point and authors should highlight this point in the discussion or strength of the study. The assessment of extent of pathological condition for periodontal disease is thought to be important, however, the most severe pathological condition in the oral cavity is assessed in many cases. Authors should notice this feature. Being diagnosed in accordance with the classification proposed at the 2017 World Workshop and surveyed in China are not thought to be so academically important. Other large-scale studies have already published before.

Thank you for your kind and valuable suggestions. Thank you very much for pointing the unique point of this study. We have highlighted the feature of this study in the discussion according to your suggestion that the extent of pathological condition for periodontal disease in the oral cavity was assessed the percentage of teeth with each periodontal status.

The classification of periodontal diseases and conditions proposed at the 2017 World Workshop has been adopted and further characterized based on a multi-dimensional staging and grading system. Staging is largely dependent upon the severity of disease at presentation as well as on the complexity of disease management. This study exhibited participants with different periodontitis stages that means severity, complexity and extent and distribution of periodontal pathology in the oral cavity. This study evaluated the relationship between hypertension and age stratified periodontitis stages, after adjustments for sex, smoking status, region, duration of education, and annual family income (Table 4). Compared with participants who did not have periodontitis, participants with stages III and IV periodontitis had a significant increased risk of hypertension. However, the difference between participants with stages I and II periodontitis and participants without periodontitis was not statistically significant. It indicated that hypertension prevalence increased with periodontitis severity.

Table 2, 3: Authors should make comparisons between genders as well as age groups and smoking status.

Thank you very much for the professional recommendation. In the revised Table 2 and 3, comparisons of the percentage (Table 2) and number (Table 3) of teeth with each periodontal parameter between hypertensive and normotensive subjects by gender, age groups and smoking status were supplemented.

Table 2: The title of Table 2 should be "Comparison of percentage of teeth affected (PTA) by age group and smoking status". And delete "PTA" in Table. The same is for Table 3. PTA and NTA are almost parallel. The meaning of using PTA and NTA is unclear.

Thank you very much for your kind and valuable suggestions. The title of Table 2 has been revised as "Comparison of the percentage of teeth with each periodontal parameter between hypertensive and

normotensive subjects by gender, age groups and smoking status". The title of Table 3 has been revised as "Comparison of the number of teeth with each periodontal parameter between hypertensive and normotensive subjects by gender, age groups and smoking status". PTA and NTA were easily misunderstood. According to your suggestions, "PTA" and "NTA" has been deleted and revised as "Periodontal parameter" in Table 2 and 3.

In table 5 and 6, it is difficult to find that OR increases with the increase of 1% of the percentage. Authors should explain it in the Material and Methods section or below Tables. Should refer other articles with similar data (i.e. OR increases with the increase of 1 of any measure value).

Thank you very much for your kind comments and professional recommendations. In Table 5 and 6, the corresponding footnotes have been added below Tables so that readers can understand the meaning of OR values. We have referred other articles with similar data and added relevant references in Table 5 and 6.

In general, numerical value is described to first decimal place. For example, 49.83%→49.8%.

Thank you for the valuable suggestion. In the revised manuscript and Tables, numerical value has been described to first decimal place, except for OR values which were described to second decimal place.

VERSION 3 – REVIEW

REVIEWER	Tada, Akio Hyogo Univ
REVIEW RETURNED	08-Jan-2023

GENERAL COMMENTS	<p>Manuscript is significantly improved. There remains some problems.</p> <p>Discussion P 23 "This association between periodontitis and hypertension has considerable importance." Author should refer to "Why this association is considerably important". This association between periodontitis and hypertension has considerable importance since (because)</p> <p>P24 line 2-16 The authors should organize this part. Similar sentences are written repetitively. It's insistent, "In the present study, periodontitis was diagnosed in accordance with the classification proposed at the 2017 World Workshop." "In the present study, periodontitis severity was defined using the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions."</p> <p>P28 line 13-15 "To our knowledge, the present study is one of few concerning the association between periodontal disease and hypertension in a large sample of Chinese adults, after adjustments for potential confounders ". This fact does not seem to be so important.</p> <p>P28 line 15-21 "The assessment of extent of pathological condition for periodontal disease is thought to be important, however, the most severe</p>
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	<p>pathological condition in the oral cavity is assessed in many studies. In this study, the extent of pathological condition for periodontal disease in the oral cavity was assessed the percentage of teeth with each periodontal status.</p> <p>In addition, we evaluated several clinical measures of periodontal disease that allowed analysis of the relationships between various aspects of periodontal disease and hypertension. We found consistent associations between PD and hypertension. PD may be indicative of poor oral health and periodontal inflammation. It was positively associated with hypertension, suggesting a link between inflammation and hypertension.”</p> <p>Merits of the assessment of extent of pathological condition for periodontal disease must be more appealed.</p>
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VERSION 3 – AUTHOR RESPONSE

Reviewer 1:

Comments to the Author:

Manuscript is significantly improved. There remains some problems.

Thank you very much for your help in improving the quality of the article. We have revised the manuscript carefully based on your valuable and professional suggestions.

Discussion

P 23 “This association between periodontitis and hypertension has considerable importance.”
 Author should refer to “Why this association is considerably important”.
 This association between periodontitis and hypertension has considerable importance since (because)

Thank you very much for your valuable and professional suggestions. The importance of assessing the relationship between periodontitis and hypertension has been added to the article. This sentence has been revised to “This association between periodontitis and hypertension has considerable importance since the high prevalence of both in the population and the serious impact on oral health and general health.22”

P24 line 2-16

The authors should organize this part. Similar sentences are written repetitively. It’s insistent, “In the present study, periodontitis was diagnosed in accordance with the classification proposed at the 2017 World Workshop.”
 “In the present study, periodontitis severity was defined using the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions.”

Thank you very much for your kind and professional suggestion. As suggested, the repetitive text has been simplified.

P28 line 13-15

“To our knowledge, the present study is one of few concerning the association between periodontal disease and hypertension in a large sample of Chinese adults, after adjustments for potential confounders “.
 This fact does not seem to be so important.

Thank you for your valuable suggestion. We have revised this sentence to “To assess the association between the two diseases accurately, several potential confounders were adjusted for, and the associations were evaluated in multiple ways, including not only periodontal severity but also several clinical parameters.”

P28 line 15-21

“The assessment of extent of pathological condition for periodontal disease is thought to be important, however, the most severe pathological condition in the oral cavity is assessed in many studies. In this study, the extent of pathological condition for periodontal disease in the oral cavity was assessed the percentage of teeth with each periodontal status.

In addition, we evaluated several clinical measures of periodontal disease that allowed analysis of the relationships between various aspects of periodontal disease and hypertension. We found consistent associations between PD and hypertension. PD may be indicative of poor oral health and periodontal inflammation. It was positively associated with hypertension, suggesting a link between inflammation and hypertension.”

Merits of the assessment of extent of pathological condition for periodontal disease must be more appealed.

Thank you very much for the professional recommendation. More discussion of the assessment of extent of pathological condition for periodontal disease has been added to the revised version. “When the periodontal tissues are inflamed, the PD increases, allowing more bacteria to accumulate and exacerbating the inflammation.⁴⁴ The total surface area of the pocket epithelium in contact with subgingival bacteria and their products in patients with generalised moderate periodontitis is estimated to be approximately the size of an adult hand palm, with even larger exposure areas in cases with more advanced periodontal destruction.⁴⁵ Therefore, the PD can be used as an indicator of the severity of periodontitis. It was positively associated with hypertension, suggesting a link between inflammation and hypertension.”