PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The burden of chronic diseases associated with periodontal diseases: A retrospective cohort study using UK primary care data
AUTHORS	Zemedikun, Dawit; Chandan, Joht; Raindi, Devan; Rajgor, Amarkumar; Gokhale, Krishna; Thomas, Tom; Falahee, Marie; DE PABLO, Paola; Lord, Janet; Raza, Karim; Nirantharakumar, Krishnarajah

VERSION 1 – REVIEW

REVIEWER	Rathod, Surekha VSPM Dental College and Research Centre, Periodontics and Implant Dentistry
REVIEW RETURNED	06-Mar-2021

GENERAL COMMENTS	check reference no. 8

REVIEWER	Goel, Khushboo BP Koirala Institute of Health Sciences
REVIEW RETURNED	09-Mar-2021

GENERAL COMMENTS	**Please leave your comments for the authors below:** The authors have provided an elaborated retrospective aspect in linking chronic diseases to periodontal disease. **1.** Is the abstract accurate, balanced and complete? - The methods section may be elaborated. Briefly, summarize the statistical method employed in the study - The final conclusion of the study is not mentioned (e.g: whether periodontal disease was significantly associated with the chronic diseases mentioned?) - Suggestions in the conclusion may be edited or provided at the end of manuscript. - Key words: not arranged alphabetically. I am not confirmed for the MeSH terminology. **2.** Are the methods described sufficiently to allow the study to be repeated? - There is a lot of information in a single manuscript with statistical inputs that when disseminated in scientific literature may not be very easy to understand and repeat the methodology to all periodontists and general readers. This could be edited or sliced.

	- The authors may elaborate more on how the diagnosis of periodontal disease was done by general practitioner (gingivitis and periodontitis). The classification and definition apart from the red codes mentioned, that was taken into consideration? (though severity has been mentioned in the limitation). - Most of the chronic diseases have shown a significant odds ratio >1, however, can the authors mention what is the association/effect size (weak or strong?), as the result of this manuscript needs to further strengthen the available literature in the scientific world. - Significance of categorizing age, BMI, smoking, ethnicity only in the descriptive analysis, when only total exposed and unexposed patients are taken into consideration into regression and sensitivity analysis? **3.** Are the outcomes clearly defined? - Outcome has been mentioned by the authors. As it is a retrospective cohort, incidence and prevalence will also be taken into consideration. However, if the authors could have mentioned it an edited manner, it would be much clear. **4.** Are the discussion and conclusions justified by the results? - Extensive literature has shown an association between severe periodontitis and chronic disease, if the coding is the limitation, the strength of the manuscript seems compromised. Periodontitis and gingivitis are now to be defined as per the 2017 classification to reduce the heterogenicity while classifying. - It is not straightforward to measure the end effects of reduction of oral bacteria/inflammation directly on disease outcomes (Chronic, multicausal, and complex nature of the systemic diseases, Variability of case definitions for periodontitis and many chronic diseases, Inability to identify many of the microbes involved). What clinically relevant effects does this study suggest after availability of abundant literature in relation to association of periodontal disease to chronic diseases? (Wenche S. Borgnakke, Does Treatment of Periodontal Disease Influence Systemic Disease? Dent Clin N Am 59 (2015) 885–917). - **“**increased risk of developing Sjogren’s syndrome with periodontal diseases in general”- the authors may elaborate more the mechanism as only these chronic diseases have shown a higher odds ratio of 2.51. - **“**In conclusion, this study demonstrates that periodontal diseases (including gingivitis and periodontitis) are associated with an increased risk of developing cardiovascular…” – to what extent, what effect size (low, moderate, high), is it statistically significant? The authors may mention that.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1
Comment 1: check reference no. 8
Response 1:
We thank the reviewer for their comment. The reviewer was correct as the reference referring to the book “measuring oral health and quality of life” by GD Slade was neither complete nor correctly formatted as per the journal’s style. We have now edited it as below:
“8 Slade GD. Measuring Oral Health and Quality of Life. Chapel Hill, 1997; 3: 385.”

Reviewer 2
Comment 1: Is the abstract accurate, balanced and complete?
- The methods section may be elaborated. Briefly, summarize the statistical method employed in the study.
Response 1:
We thank the reviewer for highlighting these points to clarify the abstract. We have now elaborated the methods in the abstract by adding the following:
“Logistic regression models accounting for covariates of clinical importance were undertaken to estimate the adjusted odds ratio (aOR) of having chronic diseases at baseline in the exposed compared to the unexposed group. Incidence rates for each outcome of interest were then provided followed by the calculation of adjusted hazard ratios (aHR) using cox regression modelling to describe the risk of outcome development in each group.”
Comment 2: The final conclusion of the study is not mentioned (e.g: whether periodontal disease was significantly associated with the chronic diseases mentioned?)
Response 2:
We have now amended the abstract accordingly:
“In this cohort, periodontal diseases appeared to be associated with an increased risk of developing cardiovascular, cardiometabolic, autoimmune diseases and mental ill health.”
Comment 3: Suggestions in the conclusion may be edited or provided at the end of manuscript.
Response 3:
As recommended by the reviewer we have now moved the following sentences from the conclusion section of the abstract to the end of the main manuscript: “It is imperative that preventative approaches, including those aimed at preventing and detecting gingival inflammation and its associated consequences, and improved communication between medical and dental teams, are implemented to reduce the risk of ill health.”
Comment 4: Key words: not arranged alphabetically. I am not confirmed for the MeSH terminology.
Response 4:
We have now arranged the key words in alphabetical order.
Comment 5: Are the methods described sufficiently to allow the study to be repeated?
- There is a lot of information in a single manuscript with statistical inputs that when disseminated in scientific literature may not be very easy to understand and repeat the methodology to all periodontists and general readers. This could be edited or sliced.
Response 5:
We thank the reviewer for this point. Upon internal review of the manuscript, we are sufficiently confident that the detail provided is sufficient for the study to be repeated by another team and the format of the manuscript is in line with research published using primary care data. In the manuscript we provide information on; database characteristics, study design, coding selection (with code lists attached in the supplementary information) and statistical analysis. Additionally, we provide referenced documents for readers to explore further to enhance their interpretation. If we remove any of these sections, it may affect the reader’s ability to appropriately appraise the methods.

However, we do agree that as this is one of the first occasions whereby primary care data has been used in such a manner to explore dental outcomes, general dental readers may be unfamiliar with the dataset or methods used. To support the interpretation, we have ensured two things: 1) a clear data access statement providing details on how readers can contact the study team to gain access to the dataset, analysis code or address any queries and 2) clarified any technical jargon which may be unfamiliar to general readers in the manuscript, for example:
"To improve data quality and reduce under-recording of events, general practices were included 12 months following instalment of electronic practice records or from the practice's acceptable mortality recording date. The acceptable mortality reporting date for each practice is when the practice publishes mortality rates similar to the expected rate for their population outlined by the Office for National Statistics (ONS).1"
"The data extraction and cohort selection was facilitated using the data extraction for epidemiological research (DExtER) tool.40 DExtER utilises an extract, transform and load mechanism to extract study specific data with demonstrated reliability and validity.40"
"The Townsend score is a measure of material deprivation within a locality, incorporating information on unemployment, household overcrowding and car/home ownership;53 a higher score indicates a greater level of socioeconomic deprivation."
"To mitigate immortality time bias,54 the same index date was assigned to the corresponding unexposed patient. Immortality time bias refers to a period of follow up where death or the study outcome cannot occur."

Comment 6: The authors may elaborate more on how the diagnosis of periodontal disease was done by general practitioner (gingivitis and periodontitis). The classification and definition apart from the red codes mentioned, that was taken into consideration? (though severity has been mentioned in the limitation).
Response 6:
As mentioned currently in the manuscript, the Read code system has not yet been validated for periodontal diseases, therefore it is not possible to ensure the codes accurately reflect the classification of disease. Additionally, there is no published literature describing the rationale for general practitioners choosing to code for periodontal disease.
Despite these limitations our team of authors have experience of working in general practice, with general practitioners or in dental practice and noted that most commonly such clinical codes appear in the medical record through one of three mechanisms: 1) the patient's registered general dentist/specialist provides a formal communication with the GP informing them of the diagnosis, 2) the patient reports their diagnosis to the GP following independent consultant with a general dentist/specialist or 3) particularly for gingivitis, the GP may make the diagnosis themselves based on clinical features.
To clarify this point for the reader we have expanded on this in our limitations section:
"Periodontal Read codes are thus likely to be inputted following receipt of clinical letters from dental healthcare professional, though GP diagnosis (more likely for gingivitis) and self-report are also possibilities."

Comment 7: Most of the chronic diseases have shown a significant odds ratio >1, however, can the authors mention what is the association/effect size (weak or strong?), as the result of this manuscript needs to further strengthen the available literature in the scientific world.
Response 7:
Following the reviewer's important recommendations, we have now indicated the strength of the associations in the manuscript. As many of the findings had an increased risk profile ranging from aHR 1.10 - 1.40 we most commonly referred to a "moderate" association. We have now added such statements in the 'Summary of results' section of the discussion and in the conclusion sections of the manuscript.

Comment 8: Significance of categorizing age, BMI, smoking, ethnicity only in the descriptive analysis, when only total exposed and unexposed patients are taken into consideration into regression and sensitivity analysis?
Response 8:
We thank the reviewer for this query. All adjusted regression models were adjusted for categorised age, BMI, smoking, and ethnicity variables as described in the descriptive analysis table. We have now clarified this in the statistical analysis section:
“To describe the prevalence of chronic disease at baseline, we used logistic regression to estimate unadjusted odds ratio (OR) and adjusted OR (aOR), following adjustment for key covariates (age categories, sex, body mass index categories, Townsend deprivation index, smoking status categories and ethnicity categories)”

Comment 9: Are the outcomes clearly defined?
- Outcome has been mentioned by the authors. As it is a retrospective cohort, incidence and prevalence will also be taken into consideration. However, if the authors could have mentioned it an edited manner, it would be much clear.
Response 9:
We thank the reviewer for this comment. The reviewer is correct that due to the retrospective nature of the dataset we were able to include incident and prevalent cases of periodontal disease and then subsequently calculate the risk of the incident (no previous history of the outcome) chronic conditions. However, in order to enhance the rigour of the findings we did undertake a sensitivity analysis limiting to only incident exposed cases, i.e. those who developed the exposure (with no previous of periodontal disease) whilst being eligible for the study and during the study period. We have edited our statistical analysis section to make this clearer:
“An initial sensitivity analysis was conducted, isolating incident only cases (where the exposure occurred during the study period) compared to their respective controls. The purpose of this analysis was to exclude patients who may have had the exposure recorded prior to their study eligibility or study start date, leading to unaccounted period where time dependent confounding factors may not have been sufficiently recorded in the patient’s medical records.”
Comment 10: Are the discussion and conclusions justified by the results?
- Extensive literature has shown an association between severe periodontitis and chronic disease, if the coding is the limitation, the strength of the manuscript seems compromised. Periodontitis and gingivitis are now to be defined as per the 2017 classification to reduce the heterogenicity while classifying.
Response 10:
We thank the reviewer for highlighting this point. We agree that coding accuracy is likely to be a limitation in our methods which has been extensively highlighted in the discussion section of the manuscript. However, the findings are promising for two reasons:
1) We did undertake a sensitivity analysis isolating only those with periodontitis codes which we believe would have a more severe form of disease compared to the gingivitis cohort and ultimately a greater chronic disease burden. The findings did indeed suggest that when restricting to a cohort to those with codes describing a more severe form of periodontal disease the associated chronic disease burden for cardiovascular disease and mental ill health was greater.
2) It is more likely that the misclassification bias would have affected the unexposed group. This may in fact under-estimate the final effect size. Despite this, the associations we describe appear in line with the published literature in terms of both direction and magnitude of risk.
However, in light of the reviewers comment we have now recommended that coding is improved in General Practice in line with the 2017 classification for periodontal disease:
“We also stress the importance of improving dental coding as per the 2017 periodontal classification system in general practice settings to support holistic patient care and oral epidemiological research.73”

Comment 11- It is not straightforward to measure the end effects of reduction of oral bacteria/inflammation directly on disease outcomes (Chronic, multicausal, and complex nature of the systemic diseases, Variability of case definitions for periodontitis and many chronic diseases, Inability to identify many of the microbes involved). What clinically relevant effects does this study suggest after availability of abundant literature in relation to association of periodontal disease to chronic diseases? (Wenche S. Borgnakke, Does Treatment of Periodontal Disease Influence Systemic Disease? Dent Clin N Am 59 (2015) 885-917).

Response 11:

We agree with the important comments here posed by the reviewer. As the reviewer has mentioned in a previous comment, our findings are in agreement with the abundance of literature exploring the association between periodontal disease and chronic disease progression. However, in the original version of the manuscript we only commented on the clinically relevant effects of periodontal treatment on glycaemic control. Therefore, we thank the reviewer for highlighting this review article summarising the treatment effects of periodontal disease on systemic disease outcomes. We have edited our discussion accordingly to refer to this piece:

“In addition to the known relationship between successful periodontal treatment and glycaemic management, there is an emerging field of literature identifying that periodontal treatment can lower levels of oral bacteria and circulating inflammatory markers.72 Although, the relevance on how this relationship may translate into clinical endpoints such as the reduced incidence of chronic conditions is still unclear and requires further research.”

Comment 12- “increased risk of developing Sjogren’s syndrome with periodontal diseases in general”- the authors may elaborate more the mechanism as only these chronic diseases have shown a higher odds ratio of 2.51.

Response 12:

We thank the reviewer for this comment and have added the following text to the discussion:

“Our study also demonstrates the most substantial increased risk ratio was seen in the development of Sjogren’s syndrome in those with periodontal diseases (HR 2.51; CI 1.87-3.38), with the periodontitis only cohort showing a substantial increased hazard ratio; however, the low number of outcomes means that the results must be interpreted with caution (aHR 6.67; CI 1.66-26.86). Despite these significant findings, the pathophysiology explaining this relationship is not well understood. It is apparent that both conditions may present with xerostomia leading to bacterial overgrowth in the oral cavity and over expression of pro-inflammatory cytokines which may in turn act as risk factors for either periodontal disease or Sjogren’s syndrome progression.32”

Comment 13-: - “In conclusion, this study demonstrates that periodontal diseases (including gingivitis and periodontitis) are associated with an increased risk of developing cardiovascular…” - to what extent, what effect size (low, moderate, high), is it statistically significant? The authors may mention that.

Response 13-: We thank the reviewer for this important recommendation. We have now amended this section to indicate moderate association which was statistically significant.