Author's response to reviews

Title: Association between periodontal disease and mortality in people with CKD: A meta-analysis of cohort studies

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Author’s response to reviews:

Dear Prof. Girish Nadkarni and reviewers,

Thank you for your letter and for the reviewers’ comments concerning our manuscript entitled “Association between periodontal disease and mortality in people with CKD: A meta-analysis of cohort studies” (BNEP-D-17-00114). Those comments are all valuable and very helpful for revising and improving our paper. We have studied comments carefully and made corrections which we hope meet with approval. Revised portion are marked in red in the paper. The responds to the reviewer’s comments are presented below. If necessary, we will seek help from a professional organization to further improve the language.

Peter Hamar, MD, PhD, Dsc (Reviewer 1):

Question: The expected pathomechanism of PD's influence on CKD mortality is induction of inflammatory processes contributing to CV disease progression. Since the result rule out this mechanism, the reason for elevated all-cause mortality remains unanswered. The paper would be substantially more valuable if the reason for elevated all-cause mortality would be found. Further analysis of the available data would enable searching for other factors for eg. careless personality associated with bad oral hygiene leading to less compliance with therapies or more accidents. Focusing on heart rate and blood-pressure is not a sensitive way of estimating cardiovascular status.

Response: Thank for your kind suggestion. Indeed, the reason for elevated all-cause mortality remains unanswered in our study. As this is a meta-analysis, only limited data can be extracted and analyzed here. By using a systematic literature review, we found many noncardiovascular factors can be used to explain this phenomenon. A large number of meta-analyses reported that periodontal disease was associated with increased risk of various kinds of cancers, such as oral
cancer, pancreatic cancer, colorectal cancer (see Ren et al., Annals of Oncology (2016), 27:1329-1336; Maisonneuve et al., Annals of Oncology (2017), 28: 985-995; Ye et al., J Cancer Res Ther (2016), C237-C240), diabetes mellitus (see Esteves et al., J periodontal (2016),87(1):48-57; Abariga et al., BMC Pregnancy Childbirth (2016)8:16(1):344), and chronic obstructive pulmonary disease (see Zeng et al., Plos One (2012);7 (10)). It was also reported that periodontal treatment could reduce the risks of hospitalization for adverse respiratory events (Shen et al., Eur J Intern Med (2017)). In addition, the study by Ruokonen (one of included study) also revealed that noncardiovascular systemic diseases, such as infection (n=13), and malignant disease (n=10) were the main causes of death among CKD populations, which show significant association with periodontal disease. Accordingly, it is reasonable that periodontal disease was only related to all-cause death, but not cardiovascular mortality. However, we still could not exclude the possibility that the absence of a statistically significant association between periodontal disease and cardiovascular death in adjusted models might be caused by inadequate power to detect their association.

Minor comments:

Response: Thank for your kind suggestion, errors have been revised. Please refer to the revised context.

Maria Haller (Reviewer 2):

Question: Eligibility criteria should be reworded to assure they are clear and unambiguous. As only cohort studies were eligible, it is needless to report that all included studies were cohort studies in the results section. It should also be clearly stated if any (co-)interventions were done/compared in the included studies or whether this was an exclusion criterion.

Answer: Thank for your kind suggestion, eligibility criteria were supplemented and revised. Please refer to the context/methods/Eligibility criteria.

Question: It needs a more extensive and clear description of how outcome data were extracted and pooled, especially bc the methods section states that multivariable adjusted risk estimates were pooled, while pooled estimates for specific adjustment variables are reported in table 3 (e.g. 'adjusted for smoking'...). Also the methods section states that random effects models were used, but there are plenty of fixed effects models in the results section/tables.

Answer: Thank for your kind suggestion. For primary and secondary study outcome, we extracted data from the full statistical model that adjusted for the largest number of potential confounders. As for subgroup analyses, data from full adjusted models which include smoking and diabetes were pooled and analyzed respectively.

In the present study, random effects models were used for the primary and secondary outcome because of the moderate to high heterogeneity. With regard to subgroup analyses, both random and fixed effects models were used, according to the size of heterogeneity.
Question: As for the subgroup analyses, it seems difficult to combine hemodialysis patients with transplant recipients as they have a totally different baseline risk to die.

Answer: Thank for your kind suggestion, subgroup analyses were revised and performed again. Please refer to Table 3.

Question: Evaluating publication bias with a funnel plot usually requires >10 studies and seems not feasible here given the small number of included studies.

Answer: Thank for your kind suggestion, just as written in the Cochrane handbook, the inspection performance of funnel plot was too low to evaluate publication bias when less than 10 studies were included. However, up to now, there is no ideal solution for this situation. Therefore, some researchers took a compromised approach. Funnel plot was used for evaluating publication when no less than 8 studies were included. (see Brunner et al., Diabetologia (2015), 58:2229-2237), and even in less 8 studies (see Maisonneuve et al., Annals of Oncology (2017), 28: 985-995). In our study, Egger’s regression test was primarily adopted to evaluate publication bias, and funnel plot is merely used as a supplementary visual method.