Author’s response to reviews

Title: IL-13 -1112 Polymorphism and Periodontitis Susceptibility: A Meta-analysis

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Author’s response to reviews:

Reply to Hermann Agis, PhD (Reviewer 2):

We would like to thank the Hermann Agis’s great efforts in reading our manuscript and for your constructive comments and suggestions. Our responses to the comments and suggestions are listed as follows:

Major Issues:

1) It is unclear how many studies were included 4 or 5? The authors should clearly this. E.G.: See figure 1 and table 1

Reply: We collected a total of four articles that were included in the study, all of which were case-control studies. Additionally, 1 of these studies also investigated AgP and CP and thus could be regarded as two independent case-control study. Therefore, the total number of studies included in this manuscript is five (Results section, Line 153-155). The possible ambiguity caused by the error in explanation has been modified and rewritten in the article.

2) Indeed the authors explained that studies on the role of IL-13-1112 polymorphism come to different conclusions. However, it remains unclear how this meta-analysis based on 4-5 studies can resolve this issue. The authors conclude that the IL-13-1112 polymorphism may have a
differential impact on chronic and aggressive periodontitis. However, only two studies were included which investigated the effect of aggressive periodontitis and three studies which investigated the effect of chronic periodontitis. What benefit does this meta-analysis have compared to the original studies? The authors should speculate on this.

Reply: A meta-analysis is a combination of multiple studies with the same purpose collected by reviewing the literature. The purpose is to collect a number of studies related to a particular problem and perform a statistical analysis of the results of these studies using a quantitative synthesis method to provide a quantified average effect or contact strength and answer the question. The goal is to combine homogeneous research results to achieve a higher sample size and higher test performance, resulting in more accurate results. In this study, five related databases were searched for studies investigating the IL-13-1112 gene polymorphism published before November 30, 2016, and rigorously screened, and only five studies were selected. This small number is a shortcoming of this article. However, our articles were evaluated for quality. The results suggested that the articles included in this paper were high quality. Additionally, sensitivity analysis testing in which each study was excluded individually was performed to validate the meta-analysis results. The indicated direction of the effect did not change, suggesting that the results of this study were realistic and reliable. Therefore, although the number of articles included in this study is small, the results are relatively robust and reliable, all of these are described in the discussion section (Discussion section, Line 243-291). Of course, we look forward to more research on the IL-13-1112 gene polymorphism and periodontitis in future studies. Relevant studies have emerged and have the possibility of offering more precise and reliable conclusions.

Compared with the original study, gene polymorphism and periodontitis research currently mostly consists of case-control studies. Case-control studies are often flawed and contain issues such as the absence of a sufficient sample size, neglect of control for confounding factors and multiple statistical measurements; thus, case-control studies themselves can provide weak evidence. A meta-analysis can provide more credible conclusions than a single study. Therefore, we used a meta-analysis of published studies to search for more accurate results and to elucidate the association between the IL-13-1112C/T gene polymorphism and periodontitis susceptibility. This issue has been revised in the discussion and summary sections of the article (Discussion section, Line 243-259).

3) The authors included one study from Germany and three studies from China. For which populations can the authors make conclusions based on their study? Have there been reports of differences in the effect of the IL-13-1112 polymorphism in the German population and the Chinese population?
Reply: Because few studies investigating IL-13-1112 are available, this study uses a collection of articles from the databases. However, only five studies were found, and only one study included a German Caucasian population. This lack of diversity is a deficiency of this study, which is intended to analyze the susceptibility of this gene for periodontitis in different populations. We look forward to more studies on the association of the IL-13-1112 gene polymorphism with periodontitis in different populations, regions and races in the future to ensure that we can obtain more reliable conclusions.

In our study of the correlation between the IL-13-1112 gene polymorphism and periodontitis, Gonzales et al. found that the IL-13-1112 genotype and the C and T allele frequencies were not associated with AgP susceptibility. Studies by Wu and others found that the IL-13-1112 CC genotype but not the CT/TT genotypes was a risk factor for AgP. The results of the two studies are not the same (Discussion section, Line 263-266). Therefore, we speculated that the IL-13-1112 gene polymorphism differs between the German and Chinese populations suffering from periodontitis. In other studies of diseases, such as asthma gene polymorphism studies, Nie and others have shown that the IL-13-1112 gene polymorphism is associated with asthma susceptibility in Caucasian populations but not Asian and African American populations (Discussion section, Line 235). Therefore, we inferred that the IL-13-1112 gene polymorphism differed between the German and Chinese populations.

4) The search strategy is unclear. Please present the search algorithm and the decision tree. Ensure that you followed the guidelines for presentation of Meta-Analysis.

Reply: The search algorithm and the decision tree have been presented in the text according to the revised opinions (Materials and Methods, search strategy section, Line 103).

Minor Issues:

1) Abstract: Please clarify the search strategy in the materials and methods of the abstract. Also the conclusion is very weak. What did the study show? What was the mayor finding? This is in particular of high importance as a meta-analysis was provided which should extend our knowledge beyond the findings of the included original articles.

Reply: The changes have been made in accordance with the above amendments in the summary of the materials and methods to clarify the search strategy and modify the conclusions (Abstract section, Line 58-60).
2) Background & Discussion: The authors should provide an in detailed analysis of the current knowledge on IL-13, IL-13-1112 polymorphism including the different types, and the role in other inflammatory diseases. This should also be discussed in the discussion section.

Reply: The changes have been made in accordance with the revised comments in the discussion section regarding the increased IL-13 and IL-13-1112 gene polymorphism knowledge and the roles of the gene in the development of other diseases (Discussion section, Line 211-242).

3) Background: The authors should present why this study is required and what the benefit of this meta-analysis is in addition to providing a summary of the available literature studies.

Reply: Currently, gene polymorphism and periodontitis research mostly consists of case-control studies. Case-control studies are often flawed and include issues such as an insufficient sample size, neglect of control for confounding factors and multiple statistical measurements. Additionally, case-control research itself may be weak. A meta-analysis can offer more credible conclusions than a single study. A meta-analysis is a quantitative analysis method for the synthesis of multiple similar studies. The advantage of this approach is that it can achieve the purpose of increasing the sample content from the statistical perspective and improve the performance of the test, especially when many of the research results are statistical analyses or present inconsistent conclusions. The meta-analysis method can offer results that are closer to the real situation of the system analysis results. The results provide the best evidence for health decision-making and clinical practice.

Whether the IL-13 -1112 gene polymorphism is associated with susceptibility to periodontitis has been studied at home and abroad in recent years, but there are inconsistencies in the findings due to the limited sample sizes and the possible differences in design between different studies. The IL-13 -1112 gene polymorphism and the possible association with periodontitis need to be analyzed from the perspective of evidence-based medicine. Therefore, we performed a meta-analysis of published studies to elucidate the association between the IL-13 -1112C/T gene polymorphism and periodontitis susceptibility. All of these are described in the discussion section (Discussion section, Line 220-259).

4) Background & Discussion: The authors state that different conclusions on the role of IL-13-1112 polymorphism have been published. What are divergent results are found in the literature? The authors should present those divergent conclusions and also discuss them in the discussion section.
Reply: The different conclusions concerning the IL-13-1112 gene polymorphism and the susceptibility to periodontitis have been incorporated and revised based on the comments and have been modified in the discussion section of the article (Discussion section, Line 260-291).

5) Discussion: The authors should present future perspectives. What is the clinical relevance of their findings and how can they be translated into the clinical practice. What are their suggestions for the future and what should be the focus of future research?

Reply: This issue has been added based on the revised views. We increased the Implications for future research section and put forward recommendations for the future concerning the focus of research and the need to translate basic research into clinical practice (Implications for future research section, Line 328-346).

6) Raw data: The authors state that the datasets are available on reasonable requests. What is a reasonable request? BMC strongly encourages the authors to provide the raw data. This would be of importance for future meta-analysis that can build on the data which was collected by the authors.

Reply: The original data here include the full text of the collected literature and the STATA software results that can be provided by the author. The use of "reasonable request" is a language misunderstanding, and the author expresses regret for the confusion (Availability of data and material section, Line 363).

7) Acknowledgements: As reviewer I appreciate to be acknowledged. However, this is the first time that I have seen that authors put this into their acknowledgement section of a manuscript. Personally I would find it more important to acknowledge the work of the authors who published the original articles on which this meta-analysis is based on than on my input as reviewer.

Reply: The acknowledgments section has been modified according to the reviewers' suggestions (Acknowledgments section, Line383).

8) The manuscript should be revised with the support of a scientifically trained native speaker.

Reply: We have requested special English grammar experts to modify the English grammar in the article.
Reply to Mojtaba Dorri (Reviewer 3):

We would like to thank the Mojtaba Dorri’s great efforts in reading our manuscript and for your constructive comments and suggestions. Our responses to the comments and suggestions are listed as follows:

L28: you need to also mention that pubmed is an interface for Medline database.

Reply: This statement has been modified in the text based on the comment (Materials and methods, search strategy section, Line 96).

L35: What do you mean by 4 studies? what type of studies are they?

Reply: The four studies referenced are the four articles included in this study. However, the four articles contain a total of five studies, all of which were case-controlled studies. One of these studies also examined AgP and CP and thus could be regarded as two independent case-controlled studies. This description has been modified in the article (Results section, Line 152-L155).

L65: authors need to cite the refs for their statement here and also the findings of those other studies and why the findings are not consistent - what are you going to do differently to ensure more reliable results.

Reply: This issue has been modified according to the amendment (Background section, Line 78-89).

L78: reports published from when to Nov 2016 were assessed for inclusion?

Reply: The analysis contains literature published before November 30, 2016; this explanation has been modified in the article (Materials and methods, search strategy section, Line 102).

L 81: authors need to elaborate on characteristics of case and control groups.

Reply: The characteristics of the case and control groups have been described and modified in the article (Materials and Methods, Conditions for study inclusion section, Line 106-115).
L84: authors need to be more specific about what data should be presented in the included studies?

Reply: The specific data that should be provided in the included article have been specifically described and added to the inclusion and exclusion criteria (Materials and methods, Conditions for study inclusion section, Line 106-115).

L86: what if the largest study is not the most recent one, or the opposite?

Reply: When multiple documents are identical or overlapping, the most recently published study was selected. This section has been modified in the article (Materials and methods, Conditions for study inclusion section, Line 106-115).

L90: please provide more info re the researchers, e.g. their education, experience, etc.

Reply: We added the following information on the Title page as follows:

Author information:

First Author: Wenbo Zhang: doctoral student in reading, residency

Corresponding author: XuPu, PhD, chief physician

Other authors: Zhuogeng Chen: Master’s, resident

Yannan Cheng, PhD, in reading, attending physician

Xiaoni Li: doctoral student, resident

Qiuhua Mao: Master, attending physician (Title page, Line 10-15).

L93: add reference.

Reply: A reference has been added based on the revised comments (Materials and methods, Data extraction Section, Line 126).

L106: please add the date of release and company name for the version of STATA used in the present study.
Reply: This information has been added as required (Materials and methods, Data analysis section, Line 143).

L113: what do you mean by "papers" and how they are different from studies?

Reply: The term “papers” here refers to the total number of documents included in this study, which is 4, of which 1 paper reported on AgP and CP and thus could be regarded as two independent case-control studies. The other three studies represented only single case-control studies. Therefore, we included five case-control studies in this study.

L117: which test was used and what was the result?

Reply: The NOS scale for document quality assessment was used. The results have been added and described in the text (Results, Study selection and characteristics section, Line 157-162).

L148: What about other sources of bias

Reply: In this study, the NOS scale was used to evaluate the quality of the included literature, and the bias in each study was evaluated (Results, Study selection and characteristics section, Line 157-162). This study also included the gene detection method in the data table of the literature. One study used the MALDI-TOF-MS method, whereas the others used PCR-RFLP. The sensitivity of the two methods is somewhat inconsistent. Additionally, a control group in one study did not meet the HWE balance; thus, the control group subjects might exhibit population bias (Discussion section, Line 292-299). Due to the limitations of including only articles published in English and Chinese, there may be relevant literature published in other languages, which may have contributed to selection bias (Discussion section, Line 299-303). The above section was added in the discussion section of the article.

L151: not fully convincing!

Reply: The commonly used methods to detect publication bias are Egger's regression method, the funnel regression method, Begg's rank method and the trim and fill method. Some scholars have noted that at least five or more independent studies (the point of the funnel map >5) are needed for the funnel regression method to be persuasive. At the same time, some scholars believe that Begg's rank method and Egger's regression method are less sensitive for the identification of publication bias when they are included in the study. The clipping method for the identification of bias also has a certain degree of risk when incorporated into a study that is
too small because it may result in overestimation; therefore, this method should be used with caution. Since the number of studies included is small, there is likely to be bias in this study given that several commonly used publication bias detection methods are limited in this case. This issue has been discussed in the discussion section in the revision (Discussion section, Line 303-317).

L158: some of info here about the IL, should be presented in the Introduction

Reply: The information concerning IL-13 has been added in the discussion section based on the changes (Discussion section, Line 211-259).

Finally, we would like to thank the reviewers and editors again for the careful reading of our paper. In addition, we have revised the manuscript carefully and believe that the new version is much better than the old one. Hope the revised version is acceptable.