Author’s response to reviews

Title: Meta-analysis of associations of vascular endothelial growth factor protein levels and -634G/C polymorphism with systemic lupus erythematosus susceptibility

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Version: 2 Date: 11 Jan 2019

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Response to the reviewers

Dear Ping An, M.D., MPH and reviewers,

We are hereby submitting our revised manuscript entitled “Meta-analysis of associations of vascular endothelial growth factor protein levels and -634G/C polymorphism with systemic lupus erythematosus susceptibility” (Manuscript ID: MGTC-D-18-00492R1). In the past several days, all of the authors participated in revising this manuscript. We have fully addressed the comments of the reviewers. We hereby provide our point-by-point responses to all of the concerns as detailed below.

Editor’s comments:

6a. you should indicate (pg/ml) in the table or table note. Then removing from the text: “In common, the difference of dosage unit was an important source for mean VEGF levels vary so dramatically among studies. However, we checked the included studies and found all the dosage unit for VEGF was pg/ml in all the included studies”, you are expected to perform this QC before meta-analysis.

Response: Thank you very much for your suggestion. We have added the (pg/ml) in the caption of table 1. We also deleted the sentence of “In common, the difference of dosage unit was an important source for mean VEGF levels vary so dramatically among studies. However, we checked the included studies and found all the dosage unit for VEGF was pg/ml in all the included studies” in the text. Thanks again!
6b. “We suspected the VEGF levels vary so dramatically among studies was caused by the different test kits or different test equipment”

Indeed different test kits with various sensitivity were responsible for the vast measurement ranges among studies included in the meta-analysis.

I checked 2 outline measurements in table 1:

a. SLE mean 40 RHO 2008. RHO, et al. (J Rheumatol. 2008 Sep; 35(9): 1789–1794.) uses Lincoplex® Multiplex Immunoassay Kit (Linco Research) This kit may have measured VEGF at a lower concentration than ELISA. E.g. For IL-1β, IL-5, IL-6, IFN γ, and TNF α, the LINCOplex multiplex kit yielded cytokine concentrations that were from 2- to 10-fold lower than the ELISA determinations. (J Reprod Immunol. 2005 Aug; 66(2): 175–191.)

b. Hrycek 2009 et al. SLE mean 3244. Ray-Bio kits were used for the quantitative determination of human VEGF. “The RayBio® Immuno-Quantitative ELISA (IQELISA) kit is an innovative assay platform that combines the specificity and ease of use of a sandwich ELISA test with the sensitivity of real-time PCR. Duplication via PCR enhances sensitivity up to 10 times in comparison to a traditional ELISA test” (https://www.antibodies-online.com/news/2/5311/raybio-immuno-quantitative-elisa-iqelisa-kits/)

On the other hand, Colombo use Quantikine Human VEGF enzyme-linked immunosorbent assay (ELISA) kit (R&D System), which gave reasonable range comparable to more of others.

Those studies and measurements must be comparable to qualify for being combined in the meta-analysis. Non-traditional ELISA with 5-10 fold sensitivity difference should be excluded, unless you can transform their data with the empirical (experimental proven) conversion factors to the traditional ELISA scale. Otherwise the meta-analysis result is artificially affected and not reflective of true biological difference. Add exclusion reasons in the text.

Response: Thank you very much for your care and suggestion. We have added in Inclusion and Exclusion Criteria in the text. “Levels of VEGF should be detected by enzyme-linked immunosorbent assay (ELISA)” in Inclusion Criteria, and “non-traditional ELISA method for the determination of VEGF levels, such as sandwich ELISA test.” in Exclusion Criteria.

You need to check all other studies included with this criterion.

Response: Thank you very much for your suggestion and care. We have checked all the studies and found them right. Thanks again!

8. table 1. kuryliszyn, why only choose active SLE score-2-3
Response: For the reason that the data from active SLE score 2-3 will be much better than data from active SLE with score 0-1. So, we chose these data.

9. define “Active” SLE, compared to “SLE”

Response: We have added the definition for them in the revised manuscript. Thanks again!

10. However, the figures were generated by the software of Cochrane Review Manager Version 5, and we cannot edit the scale. You can use other software, excel to draw the forest plot part.

Response: We have found how to re-set them. We have revised the figures. Thanks again!

11. Table 1: add sex, mean age info. It appears possible. Eg. Colombo 2009 is female only. (female percentage (100%)

Response: We have added them in the revised Table 1. Thank you very much!

In the past weeks, all the authors tried their best to revise this manuscript carefully. BMC Medical Genetics is an outstanding journal. We are grateful for the numerous comments, which have vastly improved our manuscript, and feel that our manuscript now fully meets the reviewer comments and requirements for your journal. We hope that is you will find it acceptable.

Sincerely yours,

Wenzhuang Tang, et al.