Author's response to reviews

Title:Chlamydia pneumoniae infection and cerebrovascular disease:A systematic review and meta-analysis

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Author's response to reviews: see over
Dear editor Josef,

On behalf of my co-authors, we thank you very much for giving us an opportunity to revise our manuscript, we appreciate editor and reviewers very much for your efficient work in processing our manuscript entitled “Chlamydia pneumoniae infection and cerebrovascular disease: A systematic review and meta-analysis” (MS: 611173399086405).

I have to say the reviewers are very professional and kind. I appreciate all the precious and constructive suggestions by the reviewers, which help us a lot. We have revised the manuscript and highlight the amendment in red in the paper, according to the comments and suggestions of reviewers and editor, and responded, to the comments point by point as listed below this letter.

Responses to the editor


Answer: Yes, we completed this meta-analysis following the recommendations of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) and the statement of “MOOSE” has been added in revised version (page 4, paragraph 2, line 1). Although most published meta-analysis of observational studies did not follow any explicit or authoritative guideline, we reported the background, search strategy, methods and results according to the proposal of MOOSE to improve the usefulness of the meta-analysis for readers.

2. Copy editing: We advise you to seek the assistance of a fluent English speaking
colleague, or to have a professional editing service correct your language. Please ensure that particular attention is paid to the abstract.

Answer: We have asked a fluent English speaking colleague to correct our language and reedited the manuscript including the abstract to make it easier to understand.

Besides, I wish to make a change in the author affiliations because I did this Meta-analysis before graduation, and now I and a coauthor have been working at the internal medicine departments of different hospitals for half a year. We hope that this change is acceptable. However, please advise if you have any question about this change.

Point-by-point responses to the reviewers’ comments

Reviewer #1: minor mistake: page 2 INTRODUCTION and no INTRODUCTION.

Answer: According to the journal style, we have replaced the word “introduction” with “background” in the revised version (page 2, paragraph 2, headline).

Reviewer #2:

1. The paper need to be improved grammatically. It had better consult an English speaking person and modify the text.

   Answer: We have asked a fluent English speaking colleague to correct our language and reedited the manuscript including the abstract to make it easier to understand.

2. An upper date limit of literature search was September 2012, it is preferred to search
the database again and add the latest studies if any. The latest reference can also be added.

Answer:

During the “under review” period, we did research the databases in May 10th 2013, and obtained more relevant studies. But all the new studies were ineligible because they didn’t meet the inclusion criteria. Most of the studies retrieved were reviews, animal experiments or cardiovascular research, and without an eligible new case-control or prospective cohort study researching the relationship between Chlamydia pneumoniae infection and cerebrovascular disease. Therefore, new research(May 2013) did not alter the original contents and conclusions of our manuscript submitted. If you think it is necessary, we can update the manuscript search date May 2013, and added some new necessary references. But if so, it would be incompatible with the date of submission. I sincerely hope that you can give us some advice.

3. In page 9, the author mentioned that "IgG antibody does not reach high title untile 6 weeks after the onset of illness”, which was in contradiction with the following sentence”an especially high level of IgG represents a current infection”, and they are hard to comprehend.

Answer:

(1) Serum IgG is secreted by plasma cells, accounting for 75% -80% of the total serum immunoglobin, and the half-life is about 20 ~ 23 days. IgG is the only antibody that can cross the placenta and it is the most important antibody involved in the
second immune response. The majority of anti-bacterial, anti-viral, anti-toxin antibodies, certain autoantibodies, II and III type hypersensitivity-type antibodies are IgG. Thus, IgG play an important role in body's resistance to infection and toxins.

(2) Patients with previous infection may have IgG levels approaching the cutoff titer for several years. Preexisting antibodies are indicated by IgG titers greater than 16 and less than 512 and this is suggestive of past infection.

(3) IgG antibody may not reach high titer until 6-8 weeks after the onset of illness. But in case of reinfection, the level of IgG antibody titer increases quickly to a high titer (≥512) with 1-2 weeks, suggesting possible acute infection.

4. It is noted that there were two kinds of specialized methods, MIF and ELISA, to detect serum antibodies to the C. pneumonia, it is prefered to simply introduce the difference between them and the possible effects on the final conclusion, for the specificity and sensitivity may be different between the two methods.

Answer: The most used serological assay formats include the microimmunofluorescence(MIF) test, and ELISA. MIF was developed by Wang and Grayston in the early 1970s, it’s still considered the established serological standard of determining C. pneumoniae infection, according to Centers for Disease control and Prevention recommendations. (Almudena Burillo, 2010) This assay uses formalin-fixed purified C. pneumoniae elementary bodies in a specific pattern on glass slide scan detect a species response and shows a sensitivity of 50% to 90% using paired sera. The MIF assay format is technically demanding, time consuming, and less useful for higher volume testing.
Enzyme-linked immunosorbent assay (ELISAs), used in the current and other recent studies, has been shown to have an overall high correction with the MIF test in terms of sensitivity and specificity, is considered less subjective and data interpretation is less operator dependent. (David Tanne, 2003) In some studies, the sensitivity and specificity of ELISA is 98% and 97% for detecting specific IgA and antibody, and 95% and 97% for specific IgG. (S. Karger AG, 2003)

In all the studies enrolled in our meta-analysis, about half used MIF and the other used ELISA as the detecting methods. In fact, we did the subgroup analysis based on the different detecting methods. When IgA was considered as a diagnostic method, the results showed the OR was 2.28 by MIF and 2.28 by ELISA. Meanwhile, the ORs were 1.46 vs 1.79 (MIF vs ELISA) by IgG. Therefore, different detecting methods did not cause significant impact on the final conclusion, and did not influence the conclusion about the relation between C.pneumoniae infection and cerebrovascular disease, so we did a pooled analysis to incorporate more studies.

Reviewer #3:

1. ABSTRACT: Results and Conclusion:

   (1) “No significant association was found in serum IgM or in-situ-detection of arterial biopsies.” What did the serum IgM or in-situ-detection of arterial biopsies have no significant association with? The authors should note that clearly.

   Answer: The association means the relation between C.pneumoniae infection and CV disease. And we have added the interpretation in the revised version.

   (2) “subgroup analysis by available studies showed that the association was
strongest in patients with stroke of large artery atherosclerosis, but less significant in patients with a stroke due to cardioembolism or other etiologies.” Does it mean that the significant association was found in the patients with atherosclerotic stroke but not in those with other etiology? The description of strongest, higher, or less association may bring confused. It is enough to clarify whether significant association was found or not.

Answer: Thank you for your careful review, we would like to express the meaning” C.pneumoniae is strongest associated with patients with strokes of large artery atherosclerosis, but less frequent in patients with a stroke due to cardioembolism and irrelevant with stroke of other etiology.” The correction has been made in the revised version.

2. INTRODUCTION:

(1) What’s the meaning of “premature morbidity and mortality”.

Answer: The sentence has been changed in revised version to present the meaning more clearly.

(2) “infection burden”should be explained clearly.

Answer: The statement of “infection burden” has been added in the revised version.(page 2, paragraph 3, line 9)

(3)minor essential revisions:

There are several spelling mistakes in the manuscript, for instance. “INTRODUCTION” in page. “size (odd ration)nd” in the part of “statistical analysis” in page 4, and “DISSCUSSION” in page 8.
Answer: According to the journal style, we have replaced the word “introduction” with “background” in the revised version (page 2, paragraph 2, headline). All the other corrections have been made in the revised version.

We would like to express our sincere thanks to the reviewers for the constructive and positive comments.

With kind regards,

Yours Sincerely,

Meijia Zhu