Reviewer's report

Title: Homocysteine, Methylene tetrahydrofolate Reductase C677T Polymorphism, and Risk of Retinal Vein Occlusion: An Updated Meta-analysis

Version: 2  Date: 30 September 2014

Reviewer: Shisong Rong

Reviewer's report:

This meta-analysis tested the associations between plasma total homocysteine (tHcy) and C677T of the methylenetetrahydrofolate reductase (MTHFR) and the risk of retinal vein occlusion (RVO). The authors found an association between plasma tHcy with an increased risk of RVO, but not between MTHFR C677T and RVO. The author did a comprehensive search for literatures. However, major issues should be clarified. The current results could be potentially biased.

Major Compulsory Revisions

1. It is unclear what type of studies the author were looking for to be included in the meta-analysis. Clear definitions should be provided in the inclusion and exclusion criteria.

2. It is not clear that which study was included in the association analysis of tHcy and which was eligible for the test of the genetic associations of MTHFR. Table 1 did not provide sufficient information on this point.

3. And could the author give any reasons that why other polymorphisms of the MTHFR gene were not tested? And how comparison was made between cases and controls using genotype information? Why not test for allelic association and other genotypic associations (e.g. Dominant, Recessive, or Co-dominant)?

4. The NOS score of each included paper should be provided. The score of 6–8 indicated that there were studies of low quality according to the authors’ definition. How were these studies deal with?

5. Most of the studies only matched age factor between case and control groups. And there were studies even did not match any factors between case and control groups. This potentially biased the results. Have this been controlled? How?

Moreover, in the control group, studies used ‘Hospital staff/students’, ‘volunteers’, and ‘Clinic patients/friends’ might also potentially bias the results (not providing a clear definition for the controls). How were these study deal with?

6. Table 1: Please assign reference number to each paper listed.

7. Page 4, line 98. Please provide more information about the search strategies to allow replication (e.g. EMBASE). Please detail about ‘The websites of professional associations’. How the databases were searched? The same information should also be provided for the search in ‘Google Scholar’.

8. Page 4, line 118. Please provide more details about how the ‘tHcy and MTHFR data’ were managed? Type of data, genetic data (allele frequency?
allele counts? genotype information?)

9. Page 5, line 122 to 125. Which tool in the Newcastle-Ottawa Scale was used? And Why a score of '>7' was considered to be of high quality?

10. Page 5, line 140. The author should justify (or provide the rationale underlying) the use of the geographical region (European, Non-European), publication year (before 2004 or after 2004) and sample size (#130 or<130) as the factors for stratification (or subgroup analysis).

11. Page 6, line 153. Why were the 168 studies excluded?

12. Page 6, line 154. It is very important to detail about the reasons for exclusion of the 16 studies. ‘Duplicate publications’ should have been excluded in an earlier step? What does it mean by ‘had insufficient data’?

13. Page 5, line 158. How many ‘trials’ were used? What kinds of trials were used? This was not shown in the methodology section.

14. In the forest plot of genetic associations, the genotype counts for cases and controls should be provided.

15. How did the author performed the sensitivity analysis. Please provide more details.

16. The author should further justify the superiority of this meta-analysis over the published ones.

Minor Essential Revisions

1. Page 3, line 86. How can a GWAS be used to “identify the MTHFR C677T genotype as susceptibility loci for RVO”?

2. Page 4, line 96. Please provide the exact duration (date) the literature search covered.

3. Page 4, line 102. If the language filter was not applied, how did the author deal with non-English articles?

4. Page 4, line 110. How much detail is considered ‘detailed’?

5. Page 4, line 111. How was the relevant ‘review article’ managed, e.g. meta-analysis?

6. Page 5, line 126. Please list the initials of ‘a third reviewer’.

7. Table 1. The follow variables are confusing in the table: Age(year), Sex (M/F). In addition, the ‘Source of Controls’ should be the definition of controls?

8. The methods of measuring the tHcy might be of importance to be mention about.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published
**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

No competing interest.