Reviewer's report

Title: Association between Paraoxonase gene and stroke in the Han Chinese Population

Version: 4 Date: 19 July 2012

Reviewer: Tom Trikalinos

Reviewer's report:

Thank you for your revisions in response to my comments and the comments of my colleagues. I do find that this has become a much clearer manuscript. A few of my comments remain, and I deem that they should be addressed.

I organize the comments into major compulsory revisions and other comments, as per journal instructions

/* MAJOR COMPULSORY REVISIONS */

1. Specifically, please revisit my previous comment 3.A, on your choice to perform adjusted analyses. In general, we should be very clear in why we are adjusting for some factors, and what the adjusted estimates mean. According to standard epidemiological thinking, we should not be adjusting indiscriminately. For example, it is not a good strategy to adjust for any factor that was significantly different in the two groups, without some additional rationale and clarification (and this the strategy you state in the methods). In your reply to my comment, you give a very different justification for your adjustments, namely that several factors are associated with stroke. This is getting closer to a better explanation, but it is not sufficient.

To address my question, you have to describe how you think that the major factors are causally related.

For example, in your reply to my comment in your cover letter, you indicate that you believe that the following directed acyclic graph (DAG) is correct:

GENE ----> LDL ----> Stroke

Then you should *not* adjust for LDL - you do not adjust for intermediates in the path.

If you believe that the GENEs affect Stroke not only through intermediaries but also directly (there is an arrow from GENE to Stroke), again to get the total effect of the GENE you would *not* adjust for LDL (the intermediate factor). If you adjust for the intermediate factor in the second case, you are attempting to do a mediation analysis, and you should do a lot more explaining, and perhaps use more advanced methods that what you did here.
So, if you opt to keep the adjusted analyses, please show the DAG you operate under, and explain what the adjusted results mean.

2. I meant that you could just discuss the findings in the context of the previous meta-analyses, but you went a step further. That is fine, and I commend you for this extra work. I would think that you should add in the methods section that you used 2 previous meta-analyses and added your study to them to contextualize your findings. Acknowledge that this is not a real meta-analysis update (you have not searched for additional studies that may have appeared in the meanwhile, nor performed real analyses, not even analysed other genetic models). I would use only the random effects model.

3. Note that in the haplotype analyses, the OR for each haplotype refers to a reference haplotype. Usually, this is the most common haplotype. Please mention the reference haplotype in the table (or its footnote). As you know, the choice of the reference haplotype is arbitrary. For example, I could ask you to use any haplotype as a reference. All the ORs would change, but the omnibus test will remain exactly the same. Therefore, the interpretation of the ORs is very much unique to the reference haplotype. The way that you describe the haplotypes' ORs as protective or predisposing in the Discussion is not clear -- you have to say with respect to the reference haplotype XYZ.

MINOR:

4. Remove the term cohort from the Abstract.
5. Drop the fixed effects meta-analysis graph.
6. Some attention to language is needed. The edits have introduced some syntax and grammar errors.

Thank you very very much for the opportunity to comment.

Cordially,

TA Trikalinos

**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:**

'I declare that I have no competing interests'