Reviewer’s report

Title: Association of plasma endothelial lipase levels on cognitive impairment

Version: 0 Date: 17 Dec 2018

Reviewer: Katrina Davis

Reviewer's report:

Thank you for asking me to review this paper. This cross-sectional study of 109 subjects looks at dementia diagnosis, symptoms of dementia and cognitive function against the activity of endothelial lipase in order to explore the hypothesis that high-density lipoprotein cholesterol has a role in Alzheimer's dementia. They find that there is no association with pre-existing MCI/dementia diagnosis, but an association with MMSE and one of the clinical ratings assessed for the study.

I take some issue with the title, as the term "cognitive decline" suggests a longitudinal study. At one point you state that an MMSE≤25 is equivalent to cognitive "decline", but I feel the correct term would be cognitive "impairment". So, it would be more appropriate to say that the team looked at cognition, or for cognitive impairment.

Overall, I found the paper quite confusing. More clarity and explanation is needed as to why the different classifications / distinctions had been made. Also, there was a long section in the methods regarding Amyloid PET positivity: this was only mentioned incidentally in the results, so this section would be better in the supplementary material, as it is distracting.

In more detail:

Background:

In the discussion (p11, lines 40-48) you state that "LIPG facilitates the hydrolysis… other lipid parameters". I felt this would be useful information in the introduction.

You make much of the unreliability of HDL testing. Can you say anything about why LIPG better?

Methods:
The recruitment of subjects, the inclusion and exclusion criteria were quite complicated. It would ideally benefit from a flowchart or flowcharts of the recruitment processes that showed the number of people at each stage and how many were excluded for each group of criteria. This would give the reader a better idea of whether this sample was an ideal and very filtered group to test the hypothesis, or a more general group that would generalise well to the population.

Minor point, but, given the described recruitment, it is a shame that there was not an attempt made to match the ages of the control subjects to those with AD.

The remainder of the methods seemed virtually unrelated to the results. The neuropsychological tests that were defined here were not reported, and those that were reported, MMSE and CDR, are not explicitly mentioned in methods. MRI and PET protocols are given, but the results do not appear in the main paper. I got the impression these had been copied and pasted from another paper rather than written for this one.

In particular, this paper needs some justification (which I think is possible) for including diagnosis of dementia/MCI and CDR and MMSE as continuous and MMSE with cut-off, whether in methods or discussion, to avoid it looking like a "fishing expedition" to find a significant result.

Results:

Table 1: Given the findings, it is a real weakness to not have medication given here. If the use of statins and AChEIs is known, it should be included here.

P9 lines 16-23: "Although there were..." consider rephrasing this sentence so that it is clearer what the significant result was.

P9 line 47: Correct typos

P10 line 8-11 and fig 2: Why was the significance for trend only tested on CDR0-1? Unless there is a convincing reason why it should be discontinuous, it should be tested for the whole severity range. Given that these are unadjusted comparisons, it would be useful to set out the differences between the groups (as you did in table 1, but for CDR levels).

Logistic regression: The independent variables to be included should ideally have been justified
For me, the most interesting tables / figures were table 1, figure 2, figure S2 and table S2. The associations between LIPG and lipids you say has been done before, so this would be better in supplementary material, and the original findings can be spotlighted here.

Discussion:

P11 line 33: "Recently, a similar…" While reference 34 is a very relevant study, I would not say it was a similar finding. I found these three sentences quite confusing, and they would benefit from being rewritten.

P12 line 1: "data not shown". Given that you have a supplement, a line about this in results and a figure in the supplement would be much appreciated.

P12 line 33-6: "LIPG levels in late AD might be a prognostic effect of drug treatment…” I don't think you mean 'prognostic effect', just 'effect' would make better sense.

Conclusion:

Not clear from this what the importance is, and what the next steps will be. Do you imagine this to be a biomarker? Or a target for treatment? Or does it suggest something about AD pathology that will be useful?

note to editor - I do not have any experience with which to appraise the PET part of this trial, so if that were to become more prominent, I would recommend a review by someone more familiar with PET methods.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

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I am able to assess the statistics

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