Reviewer's report

**Title**: Relating relapse and T2 lesion changes to disability progression in multiple sclerosis: A systematic literature review and regression analysis

**Version**: 2 **Date**: 1 April 2013

**Reviewer**: Hanneke Hulst

**Reviewer's report:**

Dear authors,

The manuscript is written well. It confirms the results from previous studies, which is always helpful for readers who are particularly interested in this topic. However, I do have some questions, which I will explain below.

**Major compulsory revisions:**

1. Can the authors please expand on the background and rationale for this study and cite important references in the field that used ARR and T2 lesion volumes as outcome measures for disease progression.

Also, I understand that the literature search has been done a while ago, however, can the authors please perform a quick literature search for the last 2 years to see if some important papers on this topic have been published (and mention this in the discussion as a potential limitation since this literature is lacking in the analyses).

2. Is it possible for the authors to omit/weaken the comparison between the Sormani paper and the current study since it are actually two different approaches. However, for the discussion it would be highly interesting to describe the differences found between the current study and the Sormani paper and to speculate about the causes for the differences and similarities found (for example the inclusion of a non-zero intercept).

3) Please sharpen the conclusion about what we have learned from this study.

Additionally, I do have some minor essential revisions, which I will provide below:

**Title:**

4. Can the authors please change the title to: ‘Relating relapse rate and T2 lesion changes to disability progression in multiple sclerosis: A systematic literature review

**Abstract:**

5. In the methods section of the abstract (page 2) it is unclear what the following sentence means: ‘Data were collected into an... by consulting with a third investigator’. I would propose to omit this here, however, describe it in more detail in the methods section of the paper.
6. Can the authors please provide a definition for disability progression in the abstract?

7. Please rephrase the main conclusion of the abstract into a conclusion that really tells something to the reader (for example: treatments with little effect on relapse reduction and T2 lesion volume were associated with a higher disease progression?).

Introduction:

8. Page 4: Can the authors please elaborate a little bit more on the non-zero intercept, especially how this will effect the outcome (over or underestimating the relationship?)

9. Page 5: Can the authors please provide more background information on why this study is necessary? What information does it add?

10. I would like to suggest to the authors to run the analyses with and without non-zero intercept to investigate the difference between the two types of analyses.

Methods:

11. Page 5: Please replace the word ‘algorithm’ by keywords

12. Page 5: can the authors please comment on why they did not include T2 lesion volume as a key word?

13. I understand that the literature search has been done a while ago, however, can the authors please perform a quick literature search for the last 2 years to see if some important papers on this topic have been published (and mention this in the discussion as a potential limitation since this literature is lacking in the analyses).

14. Page 6 ‘Of the 965 abstracts reviewed…and 897 were excluded.’ The authors need to provide information in the text on the main reasons for exclusion of papers (to small study sample, duration of follow up not long enough etc).

15. Page 7 ‘Discrepancies were reviewed…by a third investigator.’ Can the authors please describe what discrepancies are meant exactly?

16. Page 7 ‘…we did not weight by duration of follow up…’ Why did the authors decide not to take follow up duration into account in the analyses? This might be a possible limitation which than needs to be discussed in the discussion part.

17. Page 8 ‘CIS studies were not…of data available’. Were all studies on CIS patients excluded from the analyses totally?’

18. Page 8, please remove from the manuscript the paragraph ‘One other analysis…of EDSS increase).

Results:

19. Can the authors please provide the definitive numbers of papers included in the relapse analysis versus the T2 lesion volume analysis? Also, reasons why
some studies in the end were excluded (for example 24 studies included RRMS patients, in figure 1 25 observations are reported, how is this possible?)

20. Page 9, please provide better descriptions for tables 1 and 2.

21. Page 10/11, the example calculations on the realistic difference in ARR and in T2 lesion volumes are clear, however, only provided for one study for each example. Is it possible to add the realistic difference to an already existing table for all the different studies? As a result, one calculation example in the text would be sufficient (instead of three for the three different analyses).

22. Page 12, ‘Given the large difference…and RRMS overall’ please add in relation to T2 lesion volume.

23. Page 12, please move ‘The high slope…the wide confidence interval.’ to the discussion part.

Discussion:


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

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.