Author's response to reviews

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

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Version: 3 Date: 30 September 2013

Author's response to reviews: see over
September 30, 2013

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

Dear Colleagues:

Enclosed is the revised version of our manuscript “Relating relapse and T2 lesion changes to disability progression in multiple sclerosis: A systematic literature review and regression analysis.” After careful review and consideration we have addressed and responded to all reviewer comments within the manuscript to produce the revised draft. We have highlighted the changes we made in the response document following this letter.

We look forward to your receiving your feedback on the revised manuscript.

For questions, please send all correspondence to Dr. Fahrbach:

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Sincerely,

Kyle Fahrbach, PhD
Comments from Robert Zivadinov

Dear Robert,

Thank you for reviewing our manuscript, we appreciate your feedback and have responded to each point following each comment below.

1. Would it be possible to search the literature and add studies that eventually meet the criteria for years 2011 and 2012?

   We have updated our literature search and analysis to reflect a June 2013 search cut-off date to include more recently published evidence in our review. Seven new studies were identified by the expanded search period and included the addition of citations 40-46 (Edan *Journal of Neurology, Neurosurgery and Psychiatry* 2011, Freedman *Neurology* 2011, Cohen 2012 *The Lancet*, Coles 2012 *The Lancet*, Comi 2012 *N Engl J Med*, Fox 2012 *N Engl J Med*, and Gold 2012 *N Engl J Med*) to the reference list. Based on the inclusion of these additional studies we have updated the study attrition counts and analysis results appropriately.

2. The results of the study are important and expand upon our understanding of the impact of T2 lesion variables in relation to disability progression. The Discussion should compare the results of this study and other similar studies, especially those using meta-analysis.

   We have added a statement at the end of the first paragraph of the discussion section to highlight how are findings compare to the results of a similar analysis (Sormani 2010). To our knowledge the Sormani publications are the only other analyses using study-level data in an MS population to evaluate surrogate endpoints of disability progression.

3. In that sense, can authors comment on the methodological differences in studies using meta-analysis vs. the systematic review analysis techniques. If this Reviewer understood correctly, the authors did not have access to the raw data, which was the case in some previous meta-analysis studies. How could these affect study findings?

   Almost all meta-analyses we have found in the literature are limited to use of published data. Access to raw data can help examine individual-level surrogacy as opposed to aggregate-level surrogacy; we do point out this limitation in our conclusion. However, we do not believe that the lack of patient-level data adversely impacts our study-level findings.

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Comments from Hanneke Hulst

Dear Hanneke,

Thank you for reviewing our manuscript, we appreciate your feedback and have responded to each point in red text following each comment below.

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.
We have added additional references to support the use of relapse rate (Hirst *J Neurol* 2002) and T2 lesion volume (Rio *Mult Scler* 2008) as appropriate outcomes measures for disease progression but felt the study rationale was described in a clear and concise manner and did not warrant further additions.

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).

This point was also suggested by the other reviewer so we have updated our literature search and analysis to reflect a June 2013 search cut-off date to include more recently published evidence in our review. Seven new studies were identified by the expanded search period and included the addition of citations 40-46 (Edan *Journal of Neurology, Neurosurgery and Psychiatry* 2011, Freedman *Neurology* 2011, Cohen 2012 *The Lancet*, Coles 2012 *The Lancet*, Comi 2012 *N Engl J Med*, Fox 2012 *N Engl J Med*, and Gold 2012 *N Engl J Med*) to the reference list. Based on the inclusion of these additional studies we have updated the study attrition counts and analysis results appropriately.

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).

We believe our approach to be methodologically superior as we don’t think the assumption of a nonzero intercept can be justified scientifically. However, we did find substantively the same relationship as Sormani did; our main difference is the addition of a new outcome, plus an update of additional studies from the literature.

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

We’ve changed the abstract’s conclusions to make it more clear what the direction of effect is with the addition of the following sentence to the last paragraph of the discussion section:

Specifically, studies with lower relative differences in relapse rate had lower relative differences in EDSS progression: the stronger the treatment effect on reducing ARR, the stronger for reducing disease progression.

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

We prefer to keep the title as it is, as one can have a systematic literature review without any quantitative component (e.g., a meta-analysis).

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.
We agree to remove this text and have expanded on the description of the methods in the related section of the body text as you suggested.

6. Can the authors please provide a definition for disability progression in the abstract?

We have added text the background and methods to note that disease progression was defined as measured by the Expanded Disability Status Scale (EDSS). We also added text to the methods section within the body text to specify that definitions for relapse and disease progression were captured as part of extraction to ensure similar methods were used for these disease measures across studies.

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?).

We have revised the text of the abstract to address to make the conclusions clearer by replacing the word significantly with positively so the sentence now reads as follows:

Treatment differences in relapse reduction and T2 lesions are positively related to differences in disease progression over the first two years of treatment.

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)?

The non-zero intercept does not necessarily lead to either an overestimate or underestimate of the relationship. The problem is that it can lead to results that are nonsensical; a non-zero intercept implies that if there were a study conducted where the two treatment arms were literally identical, a zero difference in the predictor would lead to a non-zero difference on the outcome, which is obviously impossible.

There is also the problem of deciding how to code studies which pit active treatments against one another; the estimated regression slope will change depending on which treatment one uses as the control. This problem does not arise when the intercept is taken out of the equation.

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

In the current text included on page 5 we explain the information we are adding as well as ways we planned to improve upon a previous analysis, which includes the identification of new trials to consider, analysis on SPMS patients, and analysis of an additional MRI outcomes on T2 lesion volume. Additionally, we felt the study was necessary as we did not agree with the statistical approach used by Sormani.

In this quantitative meta-analysis, we have extended the Sormani et al. analyses by including data from DMTs involving secondary progressive MS (SPMS) patients. In addition, we have expanded the MRI predictors to include T2 lesion volume, a potentially better predictor of disability progression than new and enlarging T2 lesions. Finally, our statistical approach, which excludes the use of an intercept in the regression analyses, should provide a more meaningful
prediction of the relative risk of EDSS progression from treatment differences in the surrogate endpoints of interest (relapse rate and T2 lesions).

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.

   Given manuscript length considerations we felt we did not have the space to cover this in depth. We did run an analysis limited to placebo-controlled studies and A+B vs A studies (i.e., studies in which it is obvious which the control arm should be) and found an intercept that was close to zero.

Methods:

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

   We feel algorithm is the appropriate terms as we provide step by step instructions on how are searches were conducted and are hesitant to replace the word algorithm with keywords as our search strategy included both MeSH (Medical Subject Headings) terms and keywords.

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

   We created our search algorithm to cast the broadest net of studies reporting on relapse and disability progression or changes in T2 lesion volume. Studies were required to report relapse so we chose to combine that term with keywords for the MS indication and screen out any studies that did not report both relapse and disease progression or relapse and T2 lesion changes.

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).

   The literature search has been updated through June of 2013 and results have been updated to reflect the inclusion of the newly identified studies.

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).

   Further detail has been added to specify the reasons for rejection for full text articles on page 9 in the result’s section text:

   The primary reason for exclusion following full text review was study duration less than 22 months (n=23), followed by no extractable outcomes of interest (n=20).

   This information is also available in Figure 1.

Figure 1 seems to be lacking?

   It appears the figure 1 we uploaded as part of the submission is showing as blank so we have updated the manuscript to ensure Figure 1 is visible.
15. Page 7 ‘Discrepancies were reviewed…by a third investigator.’ Can the authors please describe what discrepancies are meant exactly?

Text has been edited to clarify the discrepancies are related to data extraction. For instance if an investigator extracted a value that the second investigator either feels is incorrect or that they cannot locate within the paper and the two investigators cannot reach agreement on which data was correct they would consult a third investigator for resolution. The following new text begins in the second sentence on page 7 of the data extraction section:

Discrepancies in data extraction were reviewed by the two investigators and, and when necessary, any unresolved discrepancies were resolved by a third investigator.

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.

We did not feel as though length of study was as important as the number of patients evaluated, and in such a weighted analysis, they count equally. As most of the studies have a 2-3 year follow-up, though, if we had weighted by follow-up duration, the results would be quite similar to those we found with the unweighted analysis.

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

Yes, CIS studies did not end up meeting the criteria to be included for analysis as they did not report changes in EDSS; rather they reported the number of patients who progressed to definite MS.

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

We prefer to include this text in the manuscript so we are transparent about the fact that we tried this as part of our review.

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?)

Studies with three arms supplied two comparisons to the analysis (i.e., each of the non-control treatments vs the control treatment). The effective sample size of the control treatment was cut in half in these studies in order to reduce giving the study undue weight; luckily, as most studies had only two treatment arms, this was generally not an issue.

20. Page 9, please provide better descriptions for tables 1 and 2.
The variables in tables 1 and 2 have been revised to provide further detail. The title of table 1 has been updated to reflect better verb tense: Table 1. Study summaries in trials reporting relapse and disability progression

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).

We think that this information may be redundant, as one can simply take the predictor value (i.e., an ARR difference) and find that study in the scatterplot provided and determine the predicted value of log-EDSS progression.

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

We mention T2 lesion volume in the sentence proceeding, so we think this is okay with the current content.

This is perhaps unsurprising, given the wide confidence interval for the slope (0.43–3.48); while we see a significant relationship between median T2 percentage volume and EDSS progression, it is not one that is precisely estimated. Given the large difference in estimated slope between RRMS, approved DMTs, and RRMS overall, sensitivity analyses were conducted to explore the difference.

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

Currently the manuscript text says:

There was no conclusive evidence that the relationships had different strengths between approved and non-approved DMTs in RRMS patients or between types of MS (RRMS and SPMS) patients, but the sparseness of data and the presence of outliers in some analyses prohibit generalizations. In particular, the analysis limited to non-approved DMTs suggested that some treatments may impact disease progression much more than lesion volume. It remains possible that differences in the mechanism of action between newer DMTs and older DMTs may result in different relapse/EDSS relationships.

Discussion:


We have added further detail to specify T2 lesion counts and volume in this sentence at the bottom of page 14:

This literature review and analysis demonstrates significant links between the therapeutic impact of DMTs on EDSS progression and changes on surrogate markers of disability, namely annualized relapse rates and T2 lesion counts and volumes.

We do not wish to be impolite to Sormani, but we think that an analysis technique which may allow one to predict large differences in disease progression from zero differences in the predictor (i.e., relapse rate) is inherently flawed.