Author's response to reviews

Title: No sex-specific difference in disease trajectory in multiple sclerosis patients of pre- and post-menopausal ages.

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Author's response to reviews: see over
Response to Reviews

Title: No sex-specific difference in disease trajectory in multiple sclerosis patients of pre- and post-menopausal ages.

Version: 1 Date: 7 December 2012

Reviewer: Jacqueline Bernard

This is an important question, and thus needs to be more completely studied and defined.

Response:
Thank you.

This paper has four major limitations:
1. No clear definition of menopause (see J Clin Endocrinol Metab; April 2012, 97(4):1159-1168 for typical definitions).

Response:
A definition of menopause has been added, thank you. We agree that the STRAW+10 is an essential reference.

2. The two groups C1 and C2 seem arbitrary (i.e. 38-46 and 54-62, because mean age in Western societies is 49-52)

Response:
Thank you for requesting this clarification. A more specific rationale for the cohort selection has been provided, recognizing that one limitation is that we did not know individual ages at menopause.
Thus, recognizing the marked endocrine variations occurring surrounding the time of menopause, as well as variability in age at natural menopause, we sought to identify cohorts who broadly reflected either the reproductive/early perimenopause STRAW+10 stages, or a later stage of postmenopause, i.e. at least 2 years after the final menstrual period.

3. Duration of study of two years is too short to comment on disease course around a hormonal event that typically has a duration of more than one year

Response:
The duration of the study was designed to assess longitudinal trajectories that occurred within the same menopause exposure category (pre-, i.e. C1 or post, i.e. C2 menopause). In other words, we wanted to see whether 2Y changes in the post-menopause group are different from 2Y changes in the pre-menopause group. Therefore, we intended to limit this timeframe in order to limit potential chronological overlap with the time of menopause.

Separately, we do agree that this menopausal transition occurs over more than 2 years in most cases, and we intend to follow individuals over this
entire transition in more detail in the future.

4. Patient reported outcomes (PROs) are by definition non-objective and therefore should not be used as objective evidence in primary analysis. Perimenopausal women did report lower physical functioning than men (p=0.002), so that could be looked at in a quality of life study, for example.

Response:
Thank you for this clarification.
Recognizing that PROs are not objective, but also that these PROs may provide complementary information, we have chosen to keep these data in the paper but to change the manuscript to reflect the reviewer’s comment. Specifically, we describe the objective (clinical, MRI) as primary and the PRO analyses as secondary in the revised manuscript.

Minor revisions: BPF might be better evaluated on DTI

Response:
We were unable to perform this analysis with existing data.

Other medical conditions and co-morbidities were not discussed i.e: osteoporosis, OCP use, HRT use etc.

Response:
We agree with this point, and have included this in our discussion of our limitations.

At least one non-sequitur sentence....."the age at symptom onset was greater with increasing age..."

Response:
This has been modified.

Overall, very important topic that could be made into a more powerful and convincing article with the above revisions. Would be worth the time and effort.

Response:
Thank you for these constructive comments.
Reviewer: Judith Greer

Reviewer's report:
In this manuscript, the authors start to address the question of whether there is an acceleration in the trajectory of decline in female multiple sclerosis (MS) patients during the post-menopausal years. This is an important question and one worth studying. As acknowledged by the authors, a major limitation of the study is the use of defined age cohorts of females who are likely to be pre- or post-menopausal, rather than following a cohort of women through individual menopausal transition.

The data for the female groups appears to be relatively robust; however, another limitation of the study is that the number of males in the older age group is very low; this may affect some of the conclusions drawn from the data in Tables 2 and 3, and contribute to the lack of concordance between the trajectories of decline (based on MRI and clinical measures) and the patient-reported outcomes.

Major Compulsory Revisions
1. The number of males in the older age group is rather low and the standard deviations for this group for many measures are large. What is the power of the study to actually detect a difference, if one exists? This should be stated.

   Response:
   The reviewer is certainly correct that we might be underpowered to observe small to moderate differences between groups, especially in the models focused on the interaction between age and gender. To clarify this limitation of the study, we have added the following information to the limitations section of the paper.

   “Second, given the exploratory nature of this study, we included all available patients in each age cohort, leading to limited older males in particular. Given our sample sizes (258 females in C1, 153 females in C2, 93 males in C1 and 47 males in C2), we had 80% power to detect interaction effects of at least 0.575 standard deviations for any of the measures. Since this is a moderate effect size, our results demonstrate that the difference between men and women in the two age groups is not large, but to detect a mild to moderate effect size larger sample sizes would be required.”

Minor Essential Revisions
2. What proportion of the “progressive” patients in each group are PPMS? It would be useful to include SPMS and PPMS as separate rows in Table 1. It would also be helpful to split up the “age at disease onset” row by disease course.

   Response:
This information has been added to the paper in Table 1.

3. The second sentence in the results section (“Most notably, in both men and women, the age at symptom onset was greater with increasing age”) needs to be reworded.

   Response:
   This has been reworded, thank you.

Also, the analysis of age at symptom onset should take into account the disease course.

   Response:
   This information has been added to the paper. In particular, we have reported the information from the entire cohort as before and added analyses stratified by disease course.