Author's response to reviews

Title: Risk of fractures in patients with multiple sclerosis: record-linkage study.

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Author's response to reviews: see over
Dear Editor,

Thank you for your e-mail, detailing the comments from the reviewers. We thank the reviewers for their helpful and constructive comments and respond to their comments in turn (our responses are italicized).

Reviewer 1
Introduction, first paragraph: 'On the basis of strong......disease”, I suggest to delete it since it is not relative to the manuscript findings.

This has been deleted.

Introduction, second paragraph: "Osteoporosis....disability". I recommend to tone down the evidence for the etiology of osteoporosis in MS patients since it appears a complex issue. I suggest change it to "Osteoporosis occurs more frequently among patients with MS, possibly as a result of immobility, imbalance, progressive disability or other undetermined yet factors". If you like you could mention in a few sentences evidence for contribution or not of vitamin D metabolism and steroids in this condition.

We have changed the sentence to the one suggested.

Discussion, first paragraph. You may need to discuss a little more the immobility and osteoporosis, and relation of disability scores in other studies and osteoporosis. In addition, according to the present study the increased risk of fractures before and after the first year following MS admission may indicate that not only steroids are unlikely a major contributor but that also degree of disability since during the early stages of the disease disability is usually limited. Similar results have been noted in other studies that degree of disability scale scores may not be a major factor for osteoporosis.

We have included the following in the discussion “Studies consistently show that bone mineral density (BMD) at the femoral neck decreases with increasing MS-related disability 11. However, lower than expected BMD has recently been reported in individuals newly diagnosed with MS or clinically isolated syndromes as compared to controls 12 questioning a predominant role for disability. Our finding of an increased risk of fracture within the first year of admission and also years afterwards may support this but we do not have data on disability at admission to appropriately address this.”
Reviewer 2
There are some major methodological considerations. The patients included are
those admitted to hospital in a defined period, and constitutes a selection of the
MS-population. The age distribution indicated that older patients are
overrepresented and thus one would expect more disability and an increased risk
of fractures compared to the general MS-population. At least these aspects
should have been discussed.

The discussion now states “The dataset is limited to people who were admitted to
hospital, or who received day case specialist care. We lack treatment and disability
data for MS; these can themselves influence the risk of fracture. There is very limited
information on potential confounding factors such as detailed socioeconomic
characteristics and ethnicity. Thus the generalisability of our findings to the entire
MS patient population therefore is unclear.”

Furthermore the control group is not matched as this group mainly consists of
people under the age of 15. The actual number of patients in the older age
groups is very limited. Thus the validity of the findings may be questioned.

The control cohort is fairly evenly age-distributed. For example, in the age group 15-
24, there are 992,362 control people (511 controls for each of the 1942 people with
MS in that age group). In the age group 45-54 there are 806,328 controls (36 controls
for each of the 22398 people with MS in that age group). Since we have a fairly
evenly age-distributed reference cohort, we would expect the matching ratio to be
higher amongst the young than amongst the old, because relatively few young people
have MS. In the older age bands, where MS is more common, the cases of MS are still
matched to a very high degree, as the above indicates. We have expanded the first
paragraph of Results to explain this; and have now given a footnote to table 1, with
example calculations, which we hope will make this wholly clear. In particular, we
hope that this will make it clear that the number of controls within each age stratum,
including the elderly, is very large indeed.

Several fracture sites are registered, but a statistical correction for multiple
comparisons has not been performed and should be included.

We had not included multiple testing corrections, as we tend to take the view that it is
more informative to give the exact p-values for each site (which we did). The readers
can then decide for themselves what they would wish to take as the significance
threshold. However, we are very pleased to explain this approach and to show what a
full Bonferroni would give. We have now explained this in the Method and have
added symbols to indicate significant findings after full Bonferroni correction on
Table 2.

The discussion on possible etiological factors is very limited – probably because
the study does not provide valuable information on this aspect due to the above
mentioned limitations. As this article only confirms earlier findings one would
require an update on relevant literature and especially articles in this field
published in 2011 and 2012 are missing.
We agree with the reviewer that our data do not provide information on reasons behind the association, however we have referenced excellent recent reviews. We have updated the reference list.

Reference 5 should be updated.

*This has been done.*

The statistical soft-ware used should be given.

*The following sentence has been added to the Methods section: “The analysis was run using a suite of programs developed ‘in house’ using SAS 9 software (SAS Institute, Cary, NC, USA).”*

Abbreviations should be written in full the first time they appear in the text.

*This has now been done.*

We hope the journal will now reconsider our manuscript.

Sreeram Ramagopalan on behalf of all co-authors