Reviewer’s report

Title: Aspirin and Multiple Sclerosis

Version: 1 Date: 8 March 2015

Reviewer: Friedemann Paul

Reviewer’s report:

In general, this is a well-written and comprehensive review on an interesting and important topic. I have a few suggestions for a revised paper.

Minor essential revisions

1. A figure could be added to illustrate the MOA of aspirin
2. Introduction: "A substantial percentage..." This reads rather speculative, any concrete data on that?
3. Introduction: "Vascular changes include..." Please add ref. PMID:17382348
4. p6 "...their physical activity may contribute to the higher prevalence..." This is not entirely true for the MS population as a whole given that many patients are diagnosed earlier and have little or no disability so one would not expect reduced physical activity in EDSS ranges 0-1, perhaps 2. So the authors should add whether there are data on an association of vascular events with disease duration and/or EDSS and not just a diagnosis of MS
5. p6. "Additionally, a positive association..." It is not entirely clear what the authors mean, please describe this in more detail and comment on the robustness of the original data underlying this assumption. As the therapeutic landscape is changing rapidly the author should add if available data on newer compounds such as fingolimod (cardiac side effects!), dimethylfumarate and teriflunomide, as there are probably no through analyses on this issue the authors could have a look at published side effects from the pivotal trials
6. p7 "Increased risk of dying from cardiovascular disease" The authors should add some more ideas what the underlying cause could be. They nicely summarize animal data on platelet activation in EAE etc., however, the association in human disease remains blurry. For example, see recent data on an association of metabolic alterations/obesity in MS as a possible link PMID:24048545, PMID:24347183, PMID:25182290, PMID:22952735.
7. p9. on vessel congestion/perfusion of cerebral structure, please add PMID:22736752 as relevant paper in this context
8. p13. on suggested causes of fatigue: please add recent data on impaired functional connectivity associated with/ as a cause of fatigue, see PMID 24347184, PMID:25392321
9. p13 on treatment of fatigue: please add treatment of sleep disorders and vitamin d as possible therapeutic approaches: PMID:25344375, PMID:23764040,
10. p14 on ASA studies in fatigue: risk of bleeding as side effect should be mentioned and undiagnosed sleep disorders as underlying fatigue cause should be mentioned as this may have a relevant confounder and could explain inconsistent results resp. lack of a clear effect of ASA on fatigue, see also PMID: 24360534.

**Quality of written English:** Acceptable

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

**Declaration of competing interests:**

No competing interests