Reviewer's report

Title: Preterm Birth and the Risk of Multiple Sclerosis: A Population Based Study

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Reviewer: stefano sotgiu

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By taking the advantage of their unique Canadian Collaborative Project and through a population-based study, the authors verified a new hypothesis: the increasingly important maternal effect in MS susceptibility may result from environmental factors which act during pregnancy and, therefore, can also increase the rate of preterm birth in MS. This is to my knowledge the first such study, conducted on a very large dataset composed of 6585 MS probands and 2509 controls from their genetically unrelated spouses, conducted by examining clinical records and by interviewing patients and controls.

As compared to spouses, and even after sex-adjustment, it turned out that preterm birth is not imbalanced in MS. As a logical implication, the existence of common susceptibility factor between preterm-birth and MS susceptibility can be ruled out.

The finding of the Sadovnick’s group is methodologically indubitable and conceptually important. Its relevance relies on the strong genetic-epidemiological sample power and the originality of the working hypothesis and control selection. Despite previous studies have demonstrated otherwise, they could not show a month-of-birth effect for preterm birth. However, possible limitations leading to different results are convincingly stated in the Discussion section.

Overall, the working hypothesis is well described and based on solid literature as well as personal data, both published and unpublished. Methods are appropriate and well described, as are the data. Discussion is well balanced and conclusions adequately supported by the data. Writing is acceptable as well.

The paper is acceptable for publication, however, I have two minor, though essential concerns:

1. The paper’s title is too generic. It should clearly state the result that preterm birth does not contribute to MS aetiology/susceptibility.

2. The topic is an important one, if not for susceptibility, at least for the prognostic implication of the premature birth. It is certainly beyond the scope of this article and perhaps the subject of another publication but, given the detrimental brain consequences of preterm birth, it is extremely intriguing to know whether preterm MS patients develop a worse or earlier neurological disability or MRI lesion load. As 67.9% of the whole MS cohort are RR-MS and likely 32% progressive (SP and PP), authors should indicate on a new table the possible differences in terms
of RR/SP/PP proportion or in the mean age at progression onset in preterm MS patients as relative to the rest of the dataset.

**Level of interest:** An article of importance in its field

**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