Author's response to reviews

Title: No Effect of Preterm Birth on the Risk of Multiple Sclerosis: A Population Based Study

Authors:

Sreeram Ramagopalan (sramagopalan@gmail.com)
William Valdar (valdar@well.ox.ac.uk)
David Dyment (ddyment@well.ox.ac.uk)
Sarah Orton (ortons@well.ox.ac.uk)
Irene Yee (iyess@well.ox.ac.uk)
Kevin Atkins (fisher@helix.medgen.ubc.ca)
Maria Criscuoli (mcriscuoli@helix.medgen.ubc.ca)
George Ebers (george.ebers@clneuro.ox.ac.uk)
Dessa Sadovnick (dessa.sadovnick@gmail.com)

Version: 2 Date: 15 July 2008

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

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

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

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

We have changed the title to “No Effect of Preterm Birth on the Risk of Multiple Sclerosis: A Population Based Study”.

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.

This is an excellent point, however there were no differences when stratifying by disease course.
Reviewer 2

1. The question is clearly stated in the background section of the abstract. The authors intended to investigate whether preterm birth increased the risk of subsequently developing multiple sclerosis (MS). However, in the last paragraph of the introduction the aim does not occur to be as clearly stated as in the abstract. I believe the main aim should have been stated as clearly as in the abstract.

The introduction now states “Here, in a population-based cohort, we investigate whether preterm birth increases the risk to subsequently develop MS.”

2. The methods section is incomplete and difficult to understand for those of limited knowledge about the CCPGSMS-project. More general description of the collection and questionnaires are essential for the understanding of the paper.

Gestational age data were collected by telephone interview with the mothers of the MS index cases. This may introduce recall bias. It is stated that the validity of the information was corroborated by additional questions asked about birth weight, length of hospital stay, and the use of incubator, nothing is said about the criteria for this additional asked questions. What answers supported that the delivery was a true preterm delivery and what did not? What was done about those who did not remember? I also wonder how many were asked the gestational age questions, and how many that did not answer or were unable to answer properly.

Specific to this study, preterm data was collected by telephone interview with mothers of MS index cases and spouse controls (the term “spouse” is used generically to refer to legal spouse, same-sex partner or common law partner). Each CCPGSMS index case and spouse control (if available) was asked if he/she had a biological mother who could provide information on the individual’s early life. If a positive answer was received the biological mother of the case/control was contacted by a CCPGSMS site research nurse and administered a standardised questionnaire, details of which are described in [16]. CCPGSMS site research nurses have all been trained by personnel from the central CCPGSMS centre at the University of British Columbia. An individual was classed as being born preterm if born at under 37 weeks gestational age. It is well known that maternal recall of birth weight is sufficiently accurate for clinical and epidemiological use [18], but the validity of this information was corroborated by further information asked for on the standardised questionnaire, including data about birth weight (less than 5 pounds), length of hospital stay (average 5 to 7 days between 1940-1965, the peak time of birth for our cases and controls), and the use of an incubator, as these factors are known to be associated with preterm birth [11, 19]. If a mother could not remember exact details and/or the supporting data did not fit criteria for a preterm birth, the offspring was not classed as being born preterm.

The discussion has an ok balance, but I find it a bit awkward that the month of
birth effect is presented (Table 3), when in fact it is underpowered as stated in the discussion section.

We acknowledge the reviewers point and have now removed this table.

6. The possible limitations such as recall problems, the fact that gestational age info is based on interview is not discussed in this paper. A firm discussion of limitations is necessary.

The following is included in the discussion “Our study may be limited in that maternal recall of data may not as accurate as data from clinical records etc. Additionally, as we erred on the side of caution when classifying individuals as preterm, we may have missed those who were born borderline preterm and hence we may be underestimating the number of preterm births in our cohort. However, this will apply equally to cases and controls and maternal recall of preterm birth has been shown to be accurate enough for epidemiological use [18].”

8. The title “population-based” is not well described in the manuscript; in fact it needs to be addressed more firmly. This adds to my criticism above, that the methods section is way to slim to be assessable for a reader that is unfamiliar with this specific topic. Also the methods section in the abstract needs to be sharper. How was the cases and controls defined, how was the information gathered?

The methods section now reads “Cases and controls were identified through the population-based, longitudinal Canadian Collaborative Project on Genetic Susceptibility to Multiple Sclerosis (CCPGSMS), the methodology of which has been previously described [16, 17]. Briefly, specialist MS clinics in 11 cities across Canada use standardised, personally administered questionnaires to screen individuals with MS (MS index cases) and to collect data about themselves and their families. Each participating CCPGSMS site has obtained ethical approval from the relevant institutional review board. The entire project was reviewed and approved by the University of British Columbia. This CCPGSMS combines both genetic epidemiology and molecular genetics to investigate the aetiology of MS. A key strength of the CCPGSMS is that the MS study population is derived from 14 regional clinics that have a patient pool representative of the Canadian MS population. This minimizes ascertainment biases inherent in genetic epidemiological investigations and generates a sufficiently large sample size from which significant results from both molecular and epidemiological studies can be attained. To date over 30,000 MS patients and their families have been screened.”

9. The writing is acceptable, but the authors need to adhere to the journal style and to avoid putting tables in the main body of the text at this stage. Some other
minor errors are evident and disturb the reading experience.

*We have now moved tables to the end of the manuscript.*

We would be grateful if the Journal would reconsider the revised manuscript addressing the reviewers’ comments. We look forward to hearing from you.

Sincerely yours,

[Signature]

A. Dessa Sadovnick  
Professor  
Department of Medical Genetics & Faculty of Medicine, Division of Neurology  
UBC

Sreeram Ramagopalan MA, D. Phil. Candidate  
Oxford University