When are we going to take modifiable risk factors more seriously in Multiple Sclerosis?

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Complete List of Authors:	Coetzee, Timothy; National MS Society, National MS Society Thompson, Alan; UCL Institute of Neurology, Brain Repair and rehabilitation
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EDITORIAL

When are we going to take modifiable risk factors more seriously in Multiple Sclerosis?

Tim Coetzee and Alan Thompson

Dr Tim Coetzee
National MS Society
733 Third Avenue, 3rd floor
New York, NY 10017, USA
Timothy.Coetzee@nmssorg

Professor Alan J Thompson
University College London
Faculty of Brain Sciences
Institute of Neurology
Queen Square
London WC1N 3BG, UK
alan.thompson@ucl.ac.uk

Correspondence: alan.thompson@ucl.ac.uk

Identifying and quantifying the role of risk factors with potential to modify multiple sclerosis (MS) disease course from onset to the emergence and evolution of the progressive phase, is of paramount importance for patients and clinicians in the optimum management of the condition[1]. Across online discussion boards and related social media settings, patients engage in ongoing dialog about which diets, exercise and other activities can empower them to live well and effectively manage their disease. These discussions also influence the patient's interaction with their physician as they ask for their provider's perspective on which diet/exercise or other activity they should undertake. Sadly this patient-physician dialogue is often challenging and unfruitful as the majority of studies evaluating areas such as diet, vitamin supplementation or exercise, tend to be either small or lacking in robust methodology. Thus while many factors are frequently cited as having an impact on disease course, few have the necessary evidence-base to support this contention. Furthermore clarity as to the importance of the role of such factors is essential in selecting out those that justify further evaluation in clinical trials, thus focusing effort and avoiding the expense of unnecessary studies.

These issues are comprehensively addressed in the pair of systematic reviews carried out by Hempel and colleagues from RAND Corporation

and United States Veterans Administration[2,3]. They focus specifically on fourteen risk factors in the context of progression or worsening which is particularly relevant, given the paucity of effective treatments for these forms of the disease[4]. In the first paper, the authors review all potential modifiable risk factors applying random meta-analysis models and GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework to assess the quality of evidence in 59 studies. The GRADE framework for prognostic factor research incorporates eight criteria including not only study limitations and cohort size but also inconsistency, indirectness, imprecision and publication bias[5].

The authors found that of fourteen risk factors studied, there was sufficient evidence to make definitive statements about only three of them; Lower Vitamin D levels were associated with higher EDSS scores and cigarette smokers had an increased risk of progression while, on the other side, there was no evidence of an association between disease progression and the use of epidural analgesics during childbirth. For the other eleven risk factors, which included diet, alcohol, exercise and trauma there was insufficient evidence to determine a firm and compelling relationship with progression.

In the second systematic review, 37 trials of the effect of modifiable risk factor interventions on progression were reviewed. No clear beneficial

effect from any risk factor was identified. The most striking and consistent finding was the poor quality of the trials of modifiable risk factors – a feature readily identified by the GRADE framework.

The important and troubling messages from these papers are very clear and highly relevant to our aspiration to provide optimum care for persons with MS. The first and most concerning is the very poor quality of studies in this important area the majority of which were well below what would be regarded as acceptable and what we have come to expect in therapeutic trials. The second message is that there are factors, albeit only two, with a significant association with progression and therefore warrant well designed therapeutic trials. This applies most strongly to Vitamin D and although there are currently two studies underway, there is a case for considering additional trials.

Overall, this is a very valuable body of work and if there are any criticisms to be made, perhaps the use of the term progression may be one. Here it applies to deterioration or worsening as a result of relapse activity or gradual deterioration as is seen in the progressive phase of MS. This use of the term progression runs contrary to the recommendations contained within the recent revision of the clinical course descriptors[6] where we are encouraged to restrict the term progression to the gradual deterioration seen in progressive MS and use

the term worsening when referring to deterioration as a sequelae to a relapse.

Notwithstanding, the MS community would do well to take heed of and be guided by the findings of these systematic reviews. It is time we took the role of potentially modifiable factors more seriously and accorded their study the same rigour and attention that we so readily apply to therapeutic trials of disease modifying agents. While investment in such rigour will require energy, focus and importantly - financial resources, clarifying the role of modifiable factors in progression is essential to generate the evidence which will allow patients and physicians can have productive dialog about actions the patient can take to manage their disease. Such a step change would be welcomed by all parties.

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