



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

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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, 3<sup>rd</sup> floor

New York, NY 10017, USA

[Timothy.Coetzee@nmss.org](mailto:Timothy.Coetzee@nmss.org)

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](mailto:alan.thompson@ucl.ac.uk)Correspondence: [alan.thompson@ucl.ac.uk](mailto:alan.thompson@ucl.ac.uk)

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5 Identifying and quantifying the role of risk factors with potential to modify  
6 multiple sclerosis (MS) disease course from onset to the emergence and  
7 evolution of the progressive phase, is of paramount importance for  
8 patients and clinicians in the optimum management of the condition<sup>1</sup>.  
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11 Across online discussion boards and related social media settings,  
12 patients engage in ongoing dialog about which diets, exercise and other  
13 activities can empower them to live well and effectively manage their  
14 disease. These discussions also influence the patient's interaction with  
15 their physician as they ask for their provider's perspective on which  
16 diet/exercise or other activity they should undertake. Sadly this patient-  
17 physician dialogue is often challenging and unfruitful as the majority of  
18 studies evaluating areas such as diet, vitamin supplementation or  
19 exercise, tend to be either small or lacking in robust methodology. Thus  
20 while many factors are frequently cited as having an impact on disease  
21 course, few have the necessary evidence-base to support this  
22 contention. Furthermore clarity as to the importance of the role of such  
23 factors is essential in selecting out those that justify further evaluation in  
24 clinical trials, thus focusing effort and avoiding the expense of  
25 unnecessary studies.  
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55 These issues are comprehensively addressed in the pair of systematic  
56 reviews carried out by Hempel and colleagues from RAND Corporation  
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3 and United States Veterans Administration<sup>2,3</sup>. They focus specifically on  
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5 fourteen risk factors in the context of progression or worsening which is  
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7 particularly relevant, given the paucity of effective treatments for these  
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9 forms of the disease<sup>4</sup>. In the first paper, the authors review all potential  
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11 modifiable risk factors applying random meta-analysis models and  
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13 GRADE (Grading of Recommendations Assessment, Development and  
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15 Evaluation) framework to assess the quality of evidence in 59 studies.  
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17 The GRADE framework for prognostic factor research incorporates eight  
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19 criteria including not only study limitations and cohort size but also  
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21 inconsistency, indirectness, imprecision and publication bias<sup>5</sup>.  
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29 The authors found that of fourteen risk factors studied, there was  
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31 sufficient evidence to make definitive statements about only three of  
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33 them; Lower Vitamin D levels were associated with higher EDSS scores  
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35 and cigarette smokers had an increased risk of progression while, on the  
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37 other side, there was no evidence of an association between disease  
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39 progression and the use of epidural analgesics during childbirth. For the  
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41 other eleven risk factors, which included diet, alcohol, exercise and  
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43 trauma there was insufficient evidence to determine a firm and  
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45 compelling relationship with progression.  
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53 In the second systematic review, 37 trials of the effect of modifiable risk  
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55 factor interventions on progression were reviewed. No clear beneficial  
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3 effect from any risk factor was identified. The most striking and  
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5 consistent finding was the poor quality of the trials of modifiable risk  
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7 factors – a feature readily identified by the GRADE framework.  
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11 The important and troubling messages from these papers are very clear  
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13 and highly relevant to our aspiration to provide optimum care for persons  
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15 with MS. The first and most concerning is the very poor quality of studies  
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17 in this important area the majority of which were well below what would  
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19 be regarded as acceptable and what we have come to expect in  
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21 therapeutic trials. The second message is that there are factors, albeit  
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23 only two, with a significant association with progression and therefore  
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25 warrant well designed therapeutic trials. This applies most strongly to  
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27 Vitamin D and although there are currently two studies underway, there  
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29 is a case for considering additional trials.  
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38 Overall, this is a very valuable body of work and if there are any  
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40 criticisms to be made, perhaps the use of the term progression may be  
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42 one. Here it applies to deterioration or worsening as a result of relapse  
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44 activity or gradual deterioration as is seen in the progressive phase of  
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46 MS. This use of the term progression runs contrary to the  
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48 recommendations contained within the recent revision of the clinical  
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50 course descriptors<sup>6</sup> where we are encouraged to restrict the term  
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52 progression to the gradual deterioration seen in progressive MS and use  
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3 the term worsening when referring to deterioration as a sequelae to a  
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5 relapse.  
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9 Notwithstanding, the MS community would do well to take heed of and  
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11 be guided by the findings of these systematic reviews. It is time we took  
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13 the role of potentially modifiable factors more seriously and accorded  
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15 their study the same rigour and attention that we so readily apply to  
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17 therapeutic trials of disease modifying agents. While investment in such  
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19 rigour will require energy, focus and importantly - financial resources,  
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21 clarifying the role of modifiable factors in progression is essential to  
22  
23 generate the evidence which will allow patients and physicians can have  
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25 productive dialog about actions the patient can take to manage their  
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27 disease. Such a step change would be welcomed by all parties.  
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