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# Associations between onset age and disability in multiple sclerosis patients studied using MSSS and a progression model

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**KEYWORDS**
Multiple sclerosis;
EDSS;
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**Abstract**
*Background:* While many factors have been examined, male gender and older age at multiple sclerosis onset are among few variables consistently associated with increased disability. Interestingly, the association between onset age and disability may not be linear with some data suggesting a faster rate of accumulation of disability in patients aged more than 30 years at onset.
*Objective:* Explore the relationship between onset age and disability.
*Methods:* We studied 500 MS patients grouped by cut-offs in onset age. Disability was assessed using Multiple Sclerosis Severity Scale (MSSS) and, a model based on time to reach an Extended Disability Severity Score (EDSS) (progression model). Data were analyzed using linear and logistic regression.
*Results:* The association between disability (assessed by both MSSS and the progression model) and onset age was different in patients whose MS onset occurred after an age band of 30–35 years. Before this age range, changing age was not associated with changes in disability while during and after this age range, disability was increased.
*Conclusion:* We found a significant change in the relationship between disability and onset age after about 31 years supporting the idea that while onset age does not define a sharp cut-off, it can help define subgroups of patients with differing rates of accumulation of disability.


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## 1. Introduction

The mechanisms that determine the variable rate of accumulation of disability in multiple sclerosis (MS) patients remain unclear (Dean and Kurtzke, 1971; Kurtzke, 1975, 1983; Weinshenker et al., 1989; Confavreux et al., 2003; Hensiek et al., 2003). While many factors have been examined, male gender and older age at MS onset are among few variables consistently associated with increased disability. Interestingly, the association between onset age and disability may not be linear (Confavreux and Vukusic, 2006). Thus, in patients with onset ages less than 30 years (up to 19 years and 20–29 years) an Extended Disability Severity Scale (EDSS) score of 7 was reached after a median duration of 33 years in both groups. However, in those with onset ages of 30–39, 40–49 and over 50 years, the corresponding times progressively fell (25 years, 22 years and 17 years respectively) suggesting two relationships between onset age and disability; a younger group in whom increasing age is not associated with more disability and an older onset group in whom age is linked with more disability (Confavreux and Vukusic, 2006). However, because of the relatively large age spans it is unclear at which interval of onset ages this apparent change occurs.

We now further explore the relationship between onset age and disability. Such studies require a reliable measure of disability and as EDSS is based on an ordinal scale and related to MS duration, models such as Multiple Sclerosis Severity Scale (MSSS) have been developed (Roxburgh et al., 2005). This score is derived from an algorithm relating EDSS to the distribution of disability in patients with similar durations. Importantly, the algorithm is based on data from one patient group (Roxburgh et al., 2005). We described recently, an alternative, cross-sectional EDSS-based approach (progression model) in patients recruited in north west England before disease-modifying therapy (Ramachandran et al., 2012). This model uses time from symptoms onset until a single measure of EDSS to define outcome; patients taking more than the median time to reach an EDSS are slow progressors (implying better outcome) and those taking the median or less are fast progressors (implying worse outcome). Our present aim was firstly to determine if the relationship between disability and onset age was linear throughout the range of ages found in our patients, secondly, if the relationship was not linear, define onset ages associated with a change in the relationship and thirdly, because gender determines disability, identify whether the relationship between onset age and disability in the total group were similar in female patients only. We used MSSS and the progression model to assess disability; the continuous variable MSSS allowed comparison of median values in groups defined by different onset ages while the progression model allowed comparison of proportions of fast and slow progressors in these groups.

## 2. Materials and methods

### 2.1. Patients

We studied 500 unrelated Northern European Caucasians with relapse onset MS (Poser criteria) recruited in Neurology clinics in Stoke-on-Trent and Liverpool with written informed consent and Ethics Committee approval. This cross-sectional study is based on cases recruited between 1995 and 2009 (Partridge et al., 2004; Ramachandran et al., 2012). A single EDSS was determined during the first available stable period at least 1 month from the previous relapse and before use of disease modifying therapy. The time interval between the previous relapse and EDSS measurement was not recorded but the research registrars performing the examination ensured scores were only obtained while patients were in remission. Only this EDSS was used in the study. Clinical onset was defined as date of onset of symptoms reported by patients. We recognize initial symptoms may not be dramatic in cases with mild sensory symptom onset and it may be difficult to precisely define onset.

### 2.2. Statistical analysis

MSSS was derived from an algorithm (Roxburgh et al., 2005; http://www-gene.cimr.cam.ac.uk/MSgenetics/GAMES/MSSS/) and, the median time from MS onset until EDSS measure ment was determined using the progression model described by Ramachandran et al. (2012). This classifies patients by time taken to develop disability (assessed by EDSS) and so provides an alternative way of allowing for the impact of MS duration on EDSS. Thus, for each EDSS value, we determined for each patient with that value, the time from onset until EDSS measurement. We then determined the median time for each EDSS and created, in the 500 patients, a dichotomized variable based on slow (longer than median time to EDSS) and fast (reached EDSS in median or less time) progression. The slow progression group therefore, comprised all the patients who took longer than the median time across the range of EDSS values. The fast progression group comprised patients who took the median time or less. Dichotomizing a continuous variable is problematic since patients with minimal differences may be assigned to polarized cate gories (i.e. fast and slow progression) reducing the sensitivity of the analysis. However, while using more categories would reduce this problem it would result in smaller patient groups with a reduction in the reliability of the statistical analysis. As expected, linear regression analysis showed a significant association ($p<0.0001$) between EDSS and median time to reach EDSS (Ramachandran et al., 2012). Further, mean MSSS signifi cantly increased ($p<0.001$) with each quartile of slow/fast progression (3.54, 4.77, 6.17, 7.32). Associations between onset age and disability were assessed using linear (MSSS) and logistic (progression model) regression analysis (Stata release 8, Stata Corporation, College Station, TX). To more fully describe the data, we present both $p$ and 95% CI values. Significant $p$ values are obtained if the 95% CI interval did not include 1 (logistic regression) and 0 (linear regression).

Our strategy was to firstly, establish that there was a relationship between MSSS and onset age in our patients, secondly, group patients into 5 year bands of onset age and determine if their median MSSS changed with increasing age and thirdly, attempt to define the onset age(s) at which the relationship changed. We compared results obtained using