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

Sudarshan Ramachandran\textsuperscript{a,b}, Richard C. Strange\textsuperscript{a,c}, Peter W. Jones\textsuperscript{a,c}, Seema Kalra\textsuperscript{a,c}, Devaki Nayak\textsuperscript{a,c}, Clive P. Hawkins\textsuperscript{a,c,*}

\textsuperscript{a}Keele Multiple Sclerosis Research Group, Department of Neurology, University Hospital of North Staffordshire, Stoke-on-Trent, ST4 7LN Staffordshire, England, United Kingdom
\textsuperscript{b}Department of Biochemistry, Good Hope Hospital, Heart of England Foundation Trust, Sutton Coldfield B75 7RR, England, United Kingdom
\textsuperscript{c}Institute for Science and Technology in Medicine, Keele University Medical School, Hartshill Campus, Stoke-on-Trent ST4 7QB, England, United Kingdom

Received 5 November 2013; received in revised form 14 May 2014; accepted 17 June 2014

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 suggesting 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.

© 2014 Published by Elsevier B.V.
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; Weinschenker 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 measurement 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 categories (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 significantly 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
MSSS with those using the progression model and also considered the relationship in female patients only.

3. Results

3.1. MSSS and onset age

Simple linear regression analysis demonstrated in relapse onset patients (MS onset age 15.0-54.9 years), that MSSS (dependent variable) was significantly associated (p<0.001) with onset age. However, while significant, the association was weak (r=0.3) showing the extent of variability explained by the model was modest.

3.1.1. Does rate of accumulation of disability assessed using MSSS change with onset age?

We grouped patients into 5 year bands of onset age and determined their median MSSS values. Figure 1 shows that within each onset age band the range of MSSS values was large. Median MSSS values in the 4 groups with onset ages 15.0-19.9, 20.0-24.9, 25.0-29.9 and 30.0-34.9 years were similar (range 4.40-5.10) though in the subsequent groups, median MSSS values increased (6.50-7.70). Linear regression analysis showed that MSSS values in patients whose onset ages were 15.0-19.9 (coefficient= -0.06, 95% CI -1.02 to 0.89, p=0.90), 20.0-24.9 (coefficient= -0.03, 95% CI -0.72 to 0.66, p=0.94), and 30.0-34.9 (coefficient= -0.09, 95% CI -0.78 to 0.60, p=0.79) years were not significantly different from that in the reference category (25.0-29.9 year group, chosen because largest patient group). However, in patients with onset ages greater than 35 years, MSSS values were significantly higher than in the reference category; 35.0-39.9 (coefficient=1.21, 95% CI 0.48-1.94, p=0.001), 40.0-44.9 (coefficient=1.46, 95% CI 0.66-2.26, p<0.001), 45.0-49.9 (coefficient=2.41, 95% CI 1.35-3.47, p<0.001), 50.0-54.9 (coefficient=2.21, 95% CI 0.60-3.83, p=0.007). Note the increased values of the coefficients reflecting the increases in values of the slopes of the relationship between onset age and MSSS. The conclusion that the rate of accumulation of disability is greater in patients with later

Figure 1  Median MSSS in MS patients stratified by onset age. MS patients were grouped by 5 year bands of onset age and their median MSSS values determined. Circles show median MSSS and bars show the percentage of patients in that age group with an MSSS value greater than the median for the total case group of 500 patients. Corresponding data for female patients only: median MSSS in the age categories: 5.0 (15.0-19.9 years), 4.3 (20.0-24.9 years), 4.4 (25.0-29.9 years), 4.3 (30.0-34.9 years), 6.5 (35.0-39.9 years), 6.5 (40.0-44.9 years), 7.0 (45.0-49.9 years), 8.1 (50.0-54.9 years). Percentage of female patients with MSSS greater than the median MSSS value for females (5.13): 44.8% (15.0-19.9 years), 37.9% (20.0-24.9 years), 43.4% (25.0-29.9 years), 36.1% (30.0-34.9 years), 67.2% (35.0-39.9 years), 70.7% (40.0-44.9 years), 84.2% (45.0-49.9 years), 75.0% (50.0-54.9 years).

Table 1  Median MSSS, MS duration and EDSS values in patients stratified by 5 year bands of onset age.

<table>
<thead>
<tr>
<th>Onset age range (years)</th>
<th>Patients (%) (n=500)</th>
<th>Median MSSS</th>
<th>median Years MS duration (median)</th>
<th>EDSS (median)</th>
<th>Females (%) (n=379)</th>
<th>MS duration</th>
<th>Median years MS duration</th>
<th>EDSS (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.0-19.9</td>
<td>34 (6.8)</td>
<td>5.1</td>
<td>18.0</td>
<td>4.5</td>
<td>29 (7.7)</td>
<td>5.0</td>
<td>17.5</td>
<td>4.8</td>
</tr>
<tr>
<td>20.0-24.9</td>
<td>89 (17.8)</td>
<td>4.4</td>
<td>13.5</td>
<td>4.0</td>
<td>66 (17.4)</td>
<td>4.3</td>
<td>14.0</td>
<td>3.8</td>
</tr>
<tr>
<td>25.0-29.9</td>
<td>116 (23.2)</td>
<td>5.0</td>
<td>12.0</td>
<td>3.5</td>
<td>83 (21.9)</td>
<td>4.4</td>
<td>12.0</td>
<td>3.5</td>
</tr>
<tr>
<td>30.0-34.9</td>
<td>89 (17.8)</td>
<td>4.5</td>
<td>8.5</td>
<td>3.5</td>
<td>72 (19.0)</td>
<td>4.2</td>
<td>9.0</td>
<td>3.5</td>
</tr>
<tr>
<td>35.0-39.9</td>
<td>75 (15.0)</td>
<td>6.5</td>
<td>7.0</td>
<td>4.0</td>
<td>61 (16.1)</td>
<td>6.5</td>
<td>7.0</td>
<td>3.5</td>
</tr>
<tr>
<td>40.0-44.9</td>
<td>56 (11.2)</td>
<td>6.5</td>
<td>6.0</td>
<td>4.5</td>
<td>41 (10.8)</td>
<td>6.5</td>
<td>6.0</td>
<td>3.8</td>
</tr>
<tr>
<td>45.0-49.9</td>
<td>26 (5.2)</td>
<td>7.6</td>
<td>4.0</td>
<td>5.5</td>
<td>19 (5.0)</td>
<td>7.0</td>
<td>4.0</td>
<td>5.0</td>
</tr>
<tr>
<td>50.0-54.9</td>
<td>10 (2.0)</td>
<td>7.7</td>
<td>8.0</td>
<td>5.5</td>
<td>4 (1.1)</td>
<td>8.1</td>
<td>4.5</td>
<td>5</td>
</tr>
</tbody>
</table>

MS patients were grouped by 5 year bands of onset age and their median MSSS values determined. Patient numbers, MS duration and median EDSS are shown for the whole case group and females alone.

Please cite this article as: Ramachandran S, et al. Associations between onset age and disability in multiple sclerosis patients studied using MSSS and a progression model. Multiple Sclerosis and Related Disorders (2014), http://dx.doi.org/10.1016/j.msard.2014.06.002
onset is also supported by data in Table 1 showing that while EDSS values were not markedly different in the 8 onset age groups, MS duration progressively fell. Analysis using t-tests showed EDSS values in each of the consecutive pairs of onset age groups were not significantly different (all values, \( p \geq 0.50 \)).

### 3.1.2. Does rate of accumulation of disability assessed using the progression model change with onset age?

To add support to the finding that onset ages 30–40 years define a change in the association between onset age and disability, we re-examined the association described above using the progression model. Patients were categorized as reaching an EDSS in more (slow progression) or equal/less (fast progression) than the median time. Logistic regression analysis showed that onset age was significantly associated (odds ratio = 1.09, 95% CI 1.07, 1.12, \( p < 0.001 \)) with disability assessed using this model (dichotomized dependent variable, fast versus slow progression; reference category, slow progression). Figure 2 shows the proportion of patients classified as fast progressors in each of the onset age groups.

Logistic regression analysis shows that in patients whose onset ages were 15.0–19.9 (odds ratio = 0.56, 95% CI 0.24, 1.31; \( p = 0.18 \)), 20.0–24.9 (odds ratio = 0.91, 95% CI 0.52, 1.61; \( p = 0.76 \)), and 30.0–34.9 (odds ratio = 1.12, 95% CI 0.64, 1.99; \( p = 0.68 \)) years were not significantly different from that in the reference category (25.0–29.9 years). However, in patients with onset ages greater than 35 years, disability levels were significantly higher than in the reference category; 35.0–39.9 (odds ratio = 2.47, 95% CI 1.34, 4.54; \( p = 0.004 \)), 40.0–44.9 (odds ratio = 5.23, 95% CI 2.50, 10.9; \( p < 0.001 \)), 45.0–49.9 (odds ratio = 7.84, 95% CI 2.54, 24.2; \( p < 0.001 \)), and 50.0–54.9 (odds ratio = 12.8, 95% CI 1.57, 104.7; \( p = 0.017 \)). In these analyses, fast progressors were the outcome (compared with slow progressors) and stratified age groups (factorized) were the independent variables (age range 25.0–29.9 years as reference category).

For comparison, the proportions of patients with MSSS greater than the median value are also shown. The two methods of assessing disability give similar results; the proportion of fast progressors increases in patients with MS onset ages above 35 years.

### 3.2. MS onset age and change in MSSS

Data obtained using two methods to assess the rate of accumulation of disability indicate onset ages between 30 and 40 years define a change in the association between the two variables. To better define these associations three possible relationships between onset age and MSSS were tested; firstly, that values of the slopes (\( \beta_1 \) and \( \beta_2 \)) defining the association of MSSS with onset age in the \(<\) onset age and \(\geq\) onset age groups are not significantly different but the intercept points (\(C_1, C_2\)) of the two lines on the vertical axis (MSSS) are different. This would suggest a step change in the association described by two parallel lines (both with slopes = 0 or a higher number) implying that at a certain onset age(s), the extent of disability worsened but thereafter its rate of change was similar. Secondly, that values of the slopes and possibly intercept points in the \(<\) onset age and \(\geq\) onset age groups are significantly different but values of MSSS defining the slope (\( \beta_1 \)) in the \(<\) onset age group are not significantly different from 0 suggesting there is no association between MSSS and onset age below the cut-off age in contrast with patients above the cut-off age (see Figure 2). This would suggest the association between onset age and MSSS does not change in the \(<\) onset age group but does change in the \(\geq\) onset age group. Thirdly, both the values of the slopes (significantly greater than 0) and possibly intercept points in the \(<\) onset age and \(\geq\) onset age groups are significantly different and values of MSSS defining the slope (\( \beta_1 \)) in the \(<\) onset age group are significantly different indicating the association changes differently in the two groups. Accordingly, to determine the nature of the association between onset age and disability before and after the putative change point, we dichotomized, for each onset age between 25 and 37 years, patients into groups defined by \(<\) onset age and \(\geq\) onset age and determined if the values of the slopes and intercept points describing the relationship between onset age and disability in the \(<\) onset age
(;1, C1) and corresponding \( \geq \) onset age \((;2, C2)\) were significantly different.

We used linear regression analysis to compare regression slopes of the relationship between each onset age and MSSS in the < onset age and \( \geq \) onset age groups. Table 2 shows for each onset age, patient numbers, values of the slopes and intercepts for < onset age \((;1, C1)\) and \( \geq \) onset age \((;2, C2)\) and \( p \) values identifying significant differences in the values of the slopes. The data show that the relationship between onset age and MSSS changes at 30 years of age. Thus, the slope of the regression line in the 242 patients with onset ages <30 years was significantly different from that in patients aged \( \geq 30 \) years \((t(\beta)=2.08, p<0.05)\). Similarly, the regression slopes were significantly different in patients dichotomized by onset ages 31, 32, 33, 34 and 35 years (Table 2). Data in Table 2 indicates, on the basis of the \( t(\beta) \) value (2.56), that 31 years was the best discriminator. Thereafter, in patients with onset ages between 36 and 39 years no such significance was observed and \( r \) values were small.

### 3.3. MSSS and onset age in female patients

Though the proportions of female/male patients did not appear to change with increasing age, we repeated the analyses in females only to determine if the observed association between onset age and disability was similar in this more homogeneous group (Table 1). There were too few male patients to allow a corresponding analysis. Figure 1 shows the association between median MSSS and onset age in females was similar to that in the total group. The data indicate onset ages between 30 and 35 years define a change in the association between this variable and MSSS; before this range, increasing age is not associated with a change in MSSS while during and after these ages, MSSS is significantly higher. Further, the proportion of female patients classed as fast progressors was similar to that in the total case group (Figure 2).

### 4. Discussion

The mechanisms that determine how gender and onset age influence the rate of accumulation of disability in MS patients are poorly understood. Indeed, studying the pathological processes that determine this phenotype is not helped by difficulties in quantitatively assessing disability; its relationship with EDSS is ordinal and strongly determined by duration (Confavreux et al., 2003). Thus, irreversible disability levels of 4, 6 and 7 (EDSS) are reached after median MS durations of 8, 20 and 30 years respectively. Accordingly, we used MSSS to assess disability as the relationship between disability and duration is addressed by this score (Roxburgh et al., 2005). We compared these results with those obtained using the slow/fast progression model which also attempts to allow for the impact of duration on EDSS and demonstrates good agreement between patients classified as slow/fast progressors and MSSS (Ramachandran et al., 2012). Using these two approaches, we found a significant change in the relationship between onset age and disability in patients after 31 years suggesting that MS onset age can help define patient subgroups with differing rates of accumulation of disability.

Our previously described MS group comprises both more recently recruited patients (usually lower EDSS) and those recruited some years ago (usually higher EDSS) (Ramachandran et al., 2012). Since revisions of the McDonald criteria allow earlier diagnosis (Murray, 2006), our group is historical but allows study of untreated patients with long-standing disease. We recruited few patients with an EDSS >8 reflecting the population attending our neurology clinics for routine care. Even though we selected patients with relapse onset MS in an attempt to decrease group heterogeneity, the range of MSSS values in each onset age group was large making more differences in slope values.

<table>
<thead>
<tr>
<th>Onset age (years)</th>
<th>Patients (&lt; onset age)</th>
<th>( \beta )1</th>
<th>C1</th>
<th>Patients (( \geq ) onset age)</th>
<th>( \beta )2</th>
<th>C2</th>
<th>( t(\beta) )</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td>151</td>
<td>0.121</td>
<td>2.208</td>
<td>349</td>
<td>0.133</td>
<td>0.843</td>
<td>0.168</td>
<td>0.87</td>
</tr>
<tr>
<td>27</td>
<td>178</td>
<td>0.046</td>
<td>3.692</td>
<td>322</td>
<td>0.128</td>
<td>1.045</td>
<td>1.29</td>
<td>0.20</td>
</tr>
<tr>
<td>28</td>
<td>200</td>
<td>0.040</td>
<td>3.803</td>
<td>300</td>
<td>0.132</td>
<td>0.861</td>
<td>1.58</td>
<td>0.11</td>
</tr>
<tr>
<td>29</td>
<td>215</td>
<td>0.045</td>
<td>3.700</td>
<td>285</td>
<td>0.139</td>
<td>0.581</td>
<td>1.71</td>
<td>0.09</td>
</tr>
<tr>
<td>30</td>
<td>242</td>
<td>0.048</td>
<td>3.651</td>
<td>258</td>
<td>0.151</td>
<td>0.096</td>
<td>2.08</td>
<td>0.04</td>
</tr>
<tr>
<td>31</td>
<td>263</td>
<td>0.006</td>
<td>4.556</td>
<td>237</td>
<td>0.128</td>
<td>1.046</td>
<td>2.56</td>
<td>0.01</td>
</tr>
<tr>
<td>32</td>
<td>280</td>
<td>0.024</td>
<td>4.150</td>
<td>220</td>
<td>0.139</td>
<td>0.607</td>
<td>2.49</td>
<td>0.01</td>
</tr>
<tr>
<td>33</td>
<td>299</td>
<td>0.043</td>
<td>3.720</td>
<td>201</td>
<td>0.156</td>
<td>0.154</td>
<td>2.46</td>
<td>0.01</td>
</tr>
<tr>
<td>34</td>
<td>313</td>
<td>0.024</td>
<td>4.167</td>
<td>187</td>
<td>0.131</td>
<td>0.956</td>
<td>2.35</td>
<td>0.02</td>
</tr>
<tr>
<td>35</td>
<td>331</td>
<td>0.022</td>
<td>4.204</td>
<td>169</td>
<td>0.113</td>
<td>1.764</td>
<td>1.96</td>
<td>0.05</td>
</tr>
<tr>
<td>36</td>
<td>350</td>
<td>0.029</td>
<td>4.024</td>
<td>150</td>
<td>0.096</td>
<td>2.515</td>
<td>1.38</td>
<td>0.17</td>
</tr>
<tr>
<td>37</td>
<td>371</td>
<td>0.049</td>
<td>3.565</td>
<td>129</td>
<td>0.107</td>
<td>2.019</td>
<td>1.12</td>
<td>0.26</td>
</tr>
<tr>
<td>38</td>
<td>383</td>
<td>0.047</td>
<td>3.595</td>
<td>117</td>
<td>0.081</td>
<td>3.227</td>
<td>0.61</td>
<td>0.54</td>
</tr>
<tr>
<td>39</td>
<td>391</td>
<td>0.058</td>
<td>3.335</td>
<td>109</td>
<td>0.097</td>
<td>2.461</td>
<td>0.68</td>
<td>0.50</td>
</tr>
</tbody>
</table>

To study the association between onset age and disability before and after the putative change point, we dichotomized, for each onset age between 25 and 39 years, patients into groups by < onset age and \( \geq \) onset age and determined if slope values and intercept points describing the relationship between onset age and disability in the < onset age \((;1, C1)\) and corresponding \( \geq \) onset age \((;2, C2)\) were different. We used linear regression analysis to compare regression slopes of the relationship between each onset age and MSSS in the < and \( \geq \) onset age groups. The table shows for each onset age, patient numbers, values of slopes and intercepts for < and \( \geq \) onset age and \( p \) values identifying significant differences in slope values.

Please cite this article as: Ramachandran S, et al. Associations between onset age and disability in multiple sclerosis patients studied using MSSS and a progression model. Multiple Sclerosis and Related Disorders (2014), http://dx.doi.org/10.1016/j.msard.2014.06.002
detailed modeling of the association between disability and age problematic. Presumably this variation reflects the imprecision in determining EDSS, using the MSSS algorithm and the use of only a single EDSS to define outcome.

In the first analysis, we used linear regression analysis to confirm that MSSS was significantly associated with disease onset age. We then grouped patients into 5 year onset age bands and showed that MSSS in those with onset ages 15.0–19.9, 20.0–24.9, 25.0–29.9 and 30.0–34.9 years were not significantly different (range 4.75–4.84) though in the subsequent groups, MSSS increased (6.05–7.05) and was significantly higher than in the reference category (25.0–29.9 years). Further, while EDSS was not markedly different in the age groups, MS duration progressively fell supporting the conclusion that disability is worse in patients with later onset.

To further define the onset age(s) associated with change in MSSS, we dichotomized, using each onset age between 25 and 39 years, patients by < and ≥ that onset age. We compared the slope obtained for the < onset age and ≥ onset age groups and found the relationship between onset age and MSSS changed at age 30 years. Thus, the slope of the regression line in the 242 patients with onset ages <30 years was significantly different from that in patients aged ≥30 years. Similarly, the regression slopes were significantly different in patients dichotomized by onset ages 31, 32, 33, 34 and 35 years. No such significance was observed in patients with onset ages between 36 and 39 years.

We recognize that this study has weaknesses. Importantly, the key variable onset age at first symptoms, is somewhat subjective and our patient categories cannot therefore, be precisely defined. Further, the creation of subgroups reduces patient numbers leading to significant p values but wide 95% CI values. EDSS was used as the basic measure of disability and to derive MSSS and progression score. However, its use is problematic (Ramachandran et al., 2012) not least because it is based on an often imprecise subjective evaluation. A further issue is that of relapse contamination. Thus, while the research registrars determining EDSS ensured patients were in remission, we acknowledge that incomplete recovery from the relapse is possible in some patients. In hindsight we accept that it would have been useful to record the time gap between recovery from relapse and the EDSS measurement as there is a possibility that in some patients, EDSS values were falsely high because the measurement was made during a period of incomplete recovery. However, as most MS patients (80–90%) recover from relapse over a few months (Trojano et al., 1995; Confavreux et al., 2003; Confavreux and Vukusic, 2014), we believe that because all our patients underwent careful EDSS assessment after a minimum period of one month from the end of their relapse, this risk was minimized. Finally, the MS population studied comprised an essentially adult group who reported that their onset of symptoms occurred after their 15th birthday. No pediatric patients were studied because the condition is uncommon (1.7–5.6% of the MS population is younger than 18 years) (Pena and Lotze, 2013) and our clinical service was established for adult cases. Given the apparent differences between adult and pediatric MS, it would be interesting to more carefully define the relationship between onset age and disability in a case group that included younger patients.

Data presented by Confavreux and Vukusic (2006) suggest the relationship between onset age and rate of accumulation of disability changes after 30 years of age. Our analysis shows that onset ages between 30 and 35 years define a change in the association between this variable and MSSS. Thus, before this range, increasing age is not associated with a change in MSSS while during and after this age range, MSSS is significantly higher. Clearly, we do not believe that onset age defines a sharp cut-off. Indeed, in an attempt to smooth out the association we applied a quadratic regression (onset age²) to the data which showed a weak but significant positive correlation (r=0.31) suggesting a period of gradual change in the relationship between onset age and disability. However, while it is difficult to precisely define the relationship, the data suggest that MS patients comprise younger and older onset subgroups with different mechanisms determining changes in disability assessed by MSSS. The difference in the relationship between onset age and disability was evident in the total case group and in the female patients, the relatively small number of male patients prevents determining the situation in males.

It seems noteworthy that a relatively small difference in age at onset is associated with a significant difference in the accumulation of disability. The importance of age in the pathogenesis of MS is well recognized from migration studies (Dean and Kurtzke, 1971) though the mechanisms that underlie greater disability with older onset age are largely unknown. The interplay between neuro-inflammation and neurodegenerative processes hypothesized to be central in the pathogenesis of multiple sclerosis may be accentuated by age-related factors. Thus, a relatively lower repair/regenerative response to the immune insult within a central nervous system that is under oxidative stress may facilitate axonal degeneration. Clearly, such processes are likely to be mediated by an interplay between genetic e.g. HLA-DRB1*15 (Weatherby et al., 2001) and multiple, poorly understood environmental factors including lower exposure to sunlight, greater Epstein-Barr viral load and other socioeconomic factors (Lünenmann et al., 2007; Woolmore et al., 2007; Westberg et al., 2009). Thus, it is possible that onset age is a surrogate marker for a particular combination of genetic and environmental risk factors that is associated with a level of progressive neuronal damage that causes a critical threshold to be reached beyond which any further injury to the central nervous system results in overt clinical disability. Future studies are required to further understand the prognostic value of onset age, which might influence the choice of disease modifying therapies in multiple sclerosis.

Conflict of interest
Authors confirm that there are no conflicts of interest relevant to this work and preparation of this manuscript.

Role of the funding source
This work was not supported by any external source of funding.
References


