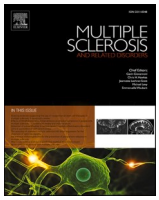
Multiple Sclerosis and Related Disorders 73 (2023) 104630

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard



# Cognitive impairment, fatigue and depression in multiple sclerosis: Is there a difference between benign and non-benign MS?

Hans Bogaardt [a,*], Daniel Golan [b,c], Marissa A Barrera [d], Stacie Attrill [a], Olivia Kaczmarek [e], Myassar Zarif [e], Barbara Bumstead [e], Marijean Buhse [e,f], Jeffrey Wilken [g,h], Glen M Doniger [i], Laura M Hancock [j], Iris-Katharina Penner [k], June Halper [l], Sarah A Morrow [m], Thomas J Covey [n,o], Mark Gudesblatt [d]

[a] School of Allied Health Science and Practice, University of Adelaide, Adelaide, Australia
[b] Multiple Sclerosis and Neuroimmunology Center, Clalit Health Services, Nazareth, Israel
[c] Department of Neurology, Lady Davis Carmel Medical Center, Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel
[d] Katz School of Science and Health, Yeshiva University, New York, United States
[e] South Shore Neurologic Associates, New York, United States
[f] Department of Nursing, State University of Stony Brook, Stony Brook, NY, United States
[g] Georgetown University Dept of Neurology, Washington D.C. United States
[h] Washington Neuropsychology Research Group, LLC., Fairfax, VA, United States
[i] Department of Clinical Research, NeuroTrax Corporation, Modiin, Israel
[j] Department of Neurology, University of Wisconsin School of Medicine and Public Health, Madison, WI, United States
[k] Department of Neurology, Inselspital, Bern University Hospital, University of Bern, Switzerland
[l] Consortium of Multiple Sclerosis Centers, Hackensack, NJ, United States
[m] London Health Sciences Centre, University Hospital, University of Western Ontario (Western), Canada
[n] Division of Cognitive and Behavioral Neurosciences, Department of Neurology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY, United States
[o] Neuroscience Program, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY, United States

## ABSTRACT

*Introduction:* Multiple Sclerosis (MS) is a chronic inflammatory and degenerative disease of the central nervous system (CNS). The severity of disability in people with MS (PwMS) is generally measured with the Expanded Disability Status Scale (EDSS). A variant of MS known as 'benign MS' (BMS) has been defined as an EDSS score of 3 or lower, combined with a disease duration of 10 years or longer; however, there is disagreement in the field about whether BMS really exists. Given that the EDSS does not capture cognitive issues, communication dysfunction, fatigue, depression, or anxiety properly, its ability to accurately represent disability in all PwMS, including BMS, remains questionable.

*Methods:* In this study, 141 persons with BMS (PwBMS) were included, consisting of 115 females (82%) and 26 males (18%) with a mean age of 50.8 (±8.68). A computerized test battery (NeuroTrax®) was used to assess cognition, covering seven cognitive domains (memory, executive function, visual-spatial processing, verbal function, attention, information processing, and motor skills). Fatigue was measured using the Fatigue Severity Scale (FSS). The Beck Depression Inventory (BDI) was used to assess symptoms of depression. Cognitive impairment was defined for this study as when someone has a score lower than 85 in at least two subdomains of the cognitive test battery. Rates of impairment were compared to 158 persons with non-benign MS (PwNBMS; with a disease duration of 10 years and longer and an EDSS score higher than 3) and 487 PwMS with a disease duration of fewer than 10 years.

*Results:* Cognitive impairment was found in 38% of PwBMS and in 66% of PwNBMS ($p<0.001$). In PwBMS, the lowest rate of impairment was found in the verbal function domain (18%) and the highest rate of impairment in the domain of information processing (32%). Fatigue and depression were found in 78% and 55% of all PwBMS, with no difference in these rates between PwBMS and PwNBMS ($p = 0.787$ and $p = 0.316$ resp.)

*Conclusion:* Cognitive impairment, fatigue and depression are common among people with an EDSS-based definition of benign MS. These aspects should be incorporated into a new and better definition of truly benign MS

* Corresponding author at: School of Allied Health Science and Practice, University of Adelaide.
*E-mail address:* hans.bogaardt@adelaide.edu.au (H. Bogaardt).

https://doi.org/10.1016/j.msard.2023.104630
Received 18 October 2022; Received in revised form 13 March 2023; Accepted 18 March 2023
Available online 21 March 2023

## 1. Introduction

Multiple Sclerosis (MS) is a chronic inflammatory and degenerative disease of the central nervous system (CNS), that affects the brain and the spinal cord (Alali et al., 2020). MS affects a range of neurological functions, ranging from mobility disorders to cognitive and communication problems (Barrera, 2017; El-Wahsh et al., 2019).

In order to classify the severity and impact of the disease on persons with MS (PwMS), in 1983, Kurzke introduced the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983). The EDSS is a clinician rating tool, that rates the impact of MS on the functions of the CNS, on an ordinal scale ranging from 0 (no neurological signs) to 10 (death due to MS) using intervals with 0.5 increments in scores above 1.0. The lower end of the EDSS scale is mainly determined by outcomes of a neurological examination, whereas the scores on the EDSS of 6 and higher are strongly influenced by mobility difficulties. The EDSS has been criticized since the scale significantly focuses on the walking capabilities of PwMS (Meyer-Moock et al., 2014) and significant variability of gait velocity within homologous EDSS disability groups has been reported, suggesting more comprehensive metrics are needed to accurately evaluate disability in PwMS (Zanotto et al., 2022). However, since its introduction, the EDSS has become the most popular and widely used assessment tool to classify disease progression in PwMS (Meyer-Moock et al., 2014) with little accounting for other manifestations of the disease such as cognitive impairment or depression.

Despite being the most widely used assessment measure for classifying disability progression in PwMS, the EDSS has noteworthy limitations. For example, due to subjectivity during neurological examinations, EDSS scores can vary across physicians due to complex scoring. Functional areas such as cognitive function, language dysfunction, mood, fatigue and quality of life are not adequately assessed. Additionally, upwards from 4.0, the EDSS heavily focuses on walking ability and undervalues upper body function necessary for self-care and personal independence.

Due to the heterogeneous nature of the disease, MS seems to include a subgroup of PwMS that, even after many years, experience minimal physical disability (Amato and Portaccio, 2012). In 1996, based on an international consensus, the term 'benign MS' (BMS) was introduced for this subgroup. BMS was further defined as the stage of the disease "in which the patient remains fully functional in all neurological systems 15 years after disease onset" (Lublin and Reingold, 1996). Although the same consensus suggested also the use of 'malignant MS' to contrast BMS (Lublin and Reingold, 1996), this latter term has become obsolete in clinical settings and research, as non-benign MS (NBMS) is a more recognized term to describe the more advanced stages of MS.

More recently, in their systematic review, Reynders et al. found 26 publications describing BMS and concluded that there appears to be consensus in the literature that BMS is defined as an EDSS score of 3 or lower, combined with a disease duration 10 years or longer. In their review, the authors comment that, although people with BMS (PwBMS) are not in need of aggressive treatments, "the usefulness of this entity in clinical practice remains unclear" (Reynders et al., 2017). This comment gives context to the controversy surround the term BMS since its introduction, sparking an ongoing discussion about whether BMS 'really exists' (Reynders et al., 2017).

The controversy around the term BMS derives from several studies that have found a range of symptoms in PwMS that are not captured or recognized by the EDSS but do suggest physical impairment with a strong impact on activities of daily living and quality of life (Morrow et al., 2021). In addition, monitoring of cognitive function across multiple cognitive domains might not be part of routine care and clinician recognition of cognitive impairment without such monitoring is not optimal (Jackson et al., 2022; Leach et al., 2022). In 2006, Amato et al. reported the cognitive and psychological functioning of 163 PwBMS. In this study, 45% of the included cohort showed cognitive impairment using the Brief Repeatable Neuropsychological Battery and the Stroop Test, 49% showed significant fatigue on the Fatigue Severity Scale (FSS) and 54% were diagnosed with depression based on the Montgomery and Asberg Depression Rating Scale (MADRS) (Amato et al., 2006). These outcomes suggest that PwBMS have significant difficulties that may impact their participation in daily living.

Following this study, in 2019, Tallantyre et al. clinically assessed 60 PwMS with a disease duration of >15 years and an EDSS score of <4.0, who did not receive disease-modifying therapy (Tallantyre et al., 2019). Within this cohort 39 PwMS (65%) classified themselves to be BMS and 21 classified themselves as being 'not benign' MS. Neuropsychological tests revealed no significant difference (with $p<0.01$) in the incidence of cognitive impairment between the two groups (46% in self-reported BMS vs 43% in self-reported non-BMS) or in employment affected by MS (41% in self-reported BMS vs 71 in self-reported non-BMS). Significant differences were found for scores on Beck's Depression Inventory (Beck et al., 1961) and scores on the Fatigue Assessment Instrument (Schwartz et al., 1993) with mean scores of 7 vs 16 and 3 vs 5 respectively between the two groups. These findings indicate that in a select group of PwBMS (according to the consensus definition of BMS), a large proportion of the PwMS can be diagnosed with depression, fatigue and problems with employment. The study revealed that in a group of 39 PwMS who classify themselves as BMS, 18 (46%) had cognitive deficits based on various neurological assessments (Tallantyre et al., 2019).

Although the studies discussed above describe the incidence of BMS within the larger population of PwMS and report on the rates of symptoms in PwBMS, they don't compare rates of clinical symptoms between PwBMS and PwNBMS. As there lacks between-group comparison data, these studies do not provide a clear answer to the question of whether benign MS really is benign. In order to answer that question, a comparison is needed between clinical symptoms in PwBMS and PwNBMS, however, this poses a methodological problem as misclassification might occur, undermining the validity of established outcomes. Any large cross-sectional cohort of PwMS, might include PwMS with a disease duration of fewer than 10 years that might prove to be BMS after several years. In order to make valid comparisons, PwBMS should thus only be compared to PwMS that have an equivalent disease duration (i.e., 10 years or more). Therefore, to contribute to the existing debate on whether benign MS is "really benign" (Amato and Portaccio, 2012; Tallantyre et al., 2019), in this present study, rates of cognitive impairment, depression and fatigue were examined in a large sample of PwBMS ($n = 141$), and compared with a group of disease duration-matched PwMS ($n = 158$), and a larger cohort of PwMS with a disease duration of fewer than 10 years ($n = 458$).

## 2. Methods

### 2.1. Participants

As part of routine clinical care at a single site in the United States, a total of 786 PwMS completed a validated, computerized cognitive assessment battery (NeuroTrax®) designed to evaluate cognitive function (Golan et al., 2019). Additionally, a number of patient-reported outcome measures (PROMs) were completed, including: the Fatigue Severity Scale (Krupp et al., 1989) and the Beck Depression Inventory (Beck et al., 1961). The analysed dataset was completed with demographic data, such as gender, age, disease duration and disease severity as scored on the EDSS. Ethics approval for this study was granted by the local Institutional Review Board (IRB).

### 2.2. Group allocation

Prior to analysis, the data of all included PwMS were divided into three groups: (1) PwMS with a disease duration of 10 years or longer, and with an EDSS-score of 3 or lower. In accordance with previously discussed criteria (Reynders et al., 2017), this group was called 'Persons with Benign MS' (PwBMS); (2) PwMS with a concomitant

disease-duration of 10 years or longer, who by definition do not classify as benign MS. This group was called 'Persons with Non-Benign MS' (PwNBMS) and (3) PwMS with a disease duration of less than 10 years (PwMS<10yrs).

### 2.3. Measures

#### 2.3.1. NeuroTrax

The NeuroTrax comprehensive assessment battery (NeuroTrax Corp., Modiin, Israel), is a neuropsychological assessment with computer-based administration and off-site scoring. NeuroTrax has been validated for use in PwMS and as the test battery does not require movement of a mouse, sensorimotor impairment in PwMS with advanced disease progression is not a potential confounder for the test results (Achiron et al., 2007; Golan et al., 2019). The test-retest reliability and construct validity has been evaluated and found the NeuroTrax battery a reliable tool (Schweiger et al., 2003). In a recent review this computerized cognitive assessment battery was found to have adequate psychometric properties for the assessment of PwMS (Wojcik et al., 2019). NeuroTrax has been previously used in MS research (Covey et al., 2021; Golan et al., 2020, 2018; Gudesblatt et al., 2018; Lapshin et al., 2012) and is sensitive to detect even mild cognitive impairment in patients (de Oliveira and Brucki, 2014; Dwolatzky et al., 2003).

The test battery provides age- and education-adjusted "index" scores summarizing performance in seven cognitive domains: memory, executive function, visual-spatial processing, verbal function, attention, information processing, and motor skills. NeuroTrax provides individual scores for all seven cognitive domains with age and education norms as a comparison (Golan et al., 2019). All scores are fit to a standardized scale, with a mean of 100 and standard deviation of 15; scores that are lower than 85 are interpreted as an indication of impairment, as this threshold predicts impairment on a traditional cognitive assessment battery (MACFIMS) with the best sensitivity and specificity (Golan et al., 2019). Lower scores are indicative of greater cognitive dysfunction in the respective domain. By convention, cognitive impairment (CI) has been defined as an impairment (i.e., a score lower than 85) in at least two subdomains of the cognitive test battery (Sumowski et al., 2018).

#### 2.3.2. Expanded disability status scale

Originally developed by Kurtzke in 1983, the Expanded Disability Status Scale (EDSS) is the most commonly used tool to describe the level of disability in PwMS (Meyer-Moock et al., 2014). The scale ranges from 0 to 10, where '0′ indicates a normal neurological examination and '10′ indicates 'death due to MS'. A greater score on the EDSS indicates increased disability status (Kurtzke, 1983).

#### 2.3.3. Fatigue severity scale

The Fatigue Severity Scale (FSS) is a patient-reported outcome measure specially designed for PwMS (Krupp et al., 1989).The FSS contains 9 items, which are scored on a 7-point scale, ranging from 'Strongly Disagree' (a score of 1) to 'Strongly Agree' (a score of 7). A patient's score is determined by the average score for the nine items (Jerković et al., 2022). The higher the FSS reflects greater fatigue in a person with MS. Scores of 4 and higher on the FSS are seen as a cut-off score, indicating clinically relevant fatigue (Gavrilov et al., 2018; Jerković et al., 2022; Valko et al., 2008).

#### 2.3.4. Beck's depression inventory

The BDI (Beck's Depression Inventory) is a 21-item self-reported tool to assess symptoms of depression in a person. Each item is scored from 0 to 3, resulting in a maximum score of 64. Higher scores indicate the presence of more severe depression. The score can be subdivided into six levels of depression (normal score, mild mood disturbance, borderline clinical depression, moderate depression, severe depression and extreme depression) (Beck et al., 1961).

### 2.4. Statistical analysis

Statistics were computed using SPSS 28.0 (IBM Corp., Armonk, NY, USA). All continuous variables were tested for normal distribution by the Kolmogorov-Smirnov test. Based on these results, further parametric tests or non-parametric tests were chosen to examine differences between groups and relationships between variables. Spearman's correlations were used to evaluate relationships between cognitive domain scores, disability (EDSS), fatigue and depression scores. All statistical tests were conducted with an alpha set at 0.05, except for the correlation analyses where an alpha of 0.01 was used to adjust for multiple testing. Additionally, Cohen's $d$ was used to calculate (https://lbecker.uccs.edu/) the effect size of the difference in cognitive performance between pairs of groups. Based on Cohen (1988), effect sizes were interpreted as small ($d > 0.2$), medium ($d > 0.5$), and large ($d > 0.8$) (Cohen, 1988).

## 3. Results

### 3.1. Demographics

In this study, data from 786 consecutive PwMS were included for analysis. Using criteria by Reynders et al. (2017), 141 (17.9%) of the sample were classified as PwBMS, 158 (20.1%) were classified as PwNBMS, leaving 487 (62.0%) as PwMS in an earlier stage of the disease (PwMS<10yrs). The mean age for the total sample ($n = 786$) was 47.5 years old (SD±10.48, range: 19.6–78.2). In the total cohort, there were 591 females (75.2%) and 195 males (24.8%).

The overall ratio of females to males was equally distributed in the three groups (Chi-Square, $p = 0.096$). However, in the PwBMS-group, 82% ($n = 115$) were female and 26 (18%) were male, whereas in the PwNBMS there was a significant lower proportion of females (112 females (71%) and 46 males (29%)) compared to the PwBMS-group (Chi-Square test, $p = 0.031$). The average age in PwBMS was slightly higher compared to PwNBMS (50.8 ± 8.68 vs. 54.0 ± 9.84 years old; independent samples $t$-test, $p = 0.002$), with no significant differences in disease duration (Mann-Whitney U test, $p = 0.140$). The demographics of all PwMS included in this study are described in Table 1.

### 3.2. Comparison of rates of cognitive impairment

The rate of cognitive impairment (CI; ≥2 cognitive domains with score<85) among PwBMS was 37.6%, compared to 65.3% in the PwNBMS (Chi Square, $p<0.001$). Additionally, in the group of PwMS<10yrs the rate of CI was 37.5%, showing no statistical difference with the rate of CI in PwBMS (Chi-Square; $p = 0.998$).

Table 2 shows for each of the three groups the number of subtests that PwMS scored below 85. In the group PwBMS, the median number of tests scored <85 (i.e. indicating an impairment in that specific area) was 1 (range: 0–7), where in the PwNBMS group the median of number of tests scored <85 was 2.5 (range:0–7). PwNBMS had a higher number of scores indicating an impairment than PwBMS (Mann -Whitney U test, $p<0.001$). When comparing these numbers between PwBMS and PwMS<10yrs, no statistical difference was found (Mann-Whitney U test; $p = 0.940$).

The rates of impairment on the seven subtests ranged in the PwBMS from 16.7% (Visual Spatial domain) to 31.8% (Information Processing) and from 24.2% (Verbal Function) to 55.2% (Information Processing) in the PwNBMS group. In five of the seven subtests (Memory, Executive Function, Attention, Information Processing and Motor Skills), the PwNBMS scored significantly lower than the PwBMS with effect-sizes ranging from 0.28 to 0.70. For the subtests Visual Spatial and Verbal Function, no significant difference in scores between PwBMS and PwNBMS was found (Man-Whitney U test, $p = 0.159$ and $p = 0.436$ resp.).

When comparing the three groups (PwBMS, PwNBMS and

**Table 1**
Demographics of included PwMS ($n = 786$).

| | PwBMS $n = 141$ | PwNBMS $n = 158$ | $p^1$ | PwMS<10yrs $n = 487$ | $p^2$ |
|---|---|---|---|---|---|
| **Age** | | | | | |
| *Mean, SD* | 50.8, ±8.68 | 54.0, ±9.84 | .002[3] | 44.5, ±9.91 | <0.001[4] |
| *Min-Max* | 31.5–78.2 | 29.3–75.7 | | 19.6–70.1 | |
| **Education (yrs)** | | | | | |
| *Mean, SD* | 14.4, ±2.77 | 14.3, ±2.91 | .654[5] | 14.6, ±2.66 | .279[6] |
| *Min-Max* | 6–25 | 7–25 | | 4–25 | |
| **Sex** | | | | | |
| *Female* | 115 (81.6%) | 112 (70.9%) | .031[7] | 364 (74.7%) | .096[7] |
| *Male* | 26 (18.4%) | 46 (29.1%) | | 123 (25.3%) | |
| **EDSS score** | | | | | |
| *Median, Var* | 2.0, 0.44 | 6.5, 2.20 | <0.001[2] | 2.0, 2.92 | <0.001[6] |
| *Range* | 3 | 5 | | 8 | |
| **Disease duration** | | | | | |
| *<5 yrs* | | | | 231 (47.4%) | <0.001[6] |
| *5–10 yrs* | | | | 256 (52.6%) | |
| *10–15 yrs* | 115 (81.6%) | 119 (75.3%) | .140[2] | | |
| *15–20 yrs* | 13 (9.2%) | 12 (7.6%) | | | |
| *>20 years* | 13 (9.2%) | 27 (17.1%) | | | |

[1] comparison between PwBMS and PwNBMS.
[2] comparison between all three groups (PwBMS, PwNBMS, PwMS<10yrs).
[3] Independent samples *t*-test.
[4] One-way ANOVA.
[5] Mann-Whitney U test.
[6] Kruskal Wallis test.
[7] Chi-Square test.

**Table 2**
PwMS with number of subtests <85 and rates of cognitive impairment (CI).

| # of subtests | PwBMS $n = 141$ | % CI | PwNBMS $n = 158$ | % CI | PwMS<10yrs $n = 487$ | % CI |
|---|---|---|---|---|---|---|
| 0 | 59 (41.8%) | 62.4% | 37 (23.4%) | 34.7% | 198 (40.7%) | 62.5% |
| 1 | 29 (20.6%) | | 18 (11.4%) | | 106 (21.8%) | |
| 2 | 11 (7.8%) | 37.6% | 24 (15.2%) | 65.3% | 57 (11.7%) | 37.5% |
| 3 | 13 (9.2%) | | 20 (12.7%) | | 41 (8.4%) | |
| 4 | 14 (9.9%) | | 19 (12.0%) | | 32 (6.6%) | |
| 5 | 7 (5.0%) | | 21 (13.3%) | | 23 (4.7%) | |
| 6 | 6 (4.3%) | | 15 (9.5%) | | 19 (3.9%) | |
| 7 | 2 (1.4%) | | 4 (2.5%) | | 11 (2.3%) | |
| *median* | 1.0 | | 2.5 | | 1.0 | |
| *var* | 3.75 | | 4.56 | | 3.65 | |
| *range* | 7 | | 7 | | 7 | |

PwMS<10yrs) no statistical difference was found between these groups for the scores on Visual Spatial and Verbal Function (Kruskal Wallis; $p = 0.065$ and $p = 0.738$ resp.). For all other subtests a significant difference between the three groups was found. The rates of impairment in the group PwBMS ranged from 16.7% (Visual Spatial) to 31.8% (Information Processing), whereas in the group PwNBMS the rates of impairment ranged from 24.2% (Verbal Function) to 55.2% (Information Processing). For the group PwMS<10yrs, impairment rates ranged from 18.1% (Motor Skills) to 33.8% (Information Processing). Table 3 shows the detailed results of the computerized cognitive test battery for each of the three groups.

### 3.3. Comparison between fatigue and depression in PwBMS and PwNBMS

No statistical differences on the Fatigue Severity Scale between PwBMS and PwNBMS (5.1 ± 1.59 vs. 5.1 ± 1.58; Mann Whitney U test; $p = 0.774$) were found. When comparing the two groups to the PwMS<10yrs, a significant lower score was found for PwMS<10yrs (Kruskal Willis; $p<0.001$). Based on a cut-off score of 4, in the PwBMS group 94 persons (77.7%) were diagnosed with fatigue, whereas in 93 persons (76.2%) in the PwNBMS were fatigued (Chi-Square; $p = 0.787$). The rate of fatigue in the group PwMS<10yrs (65.7%) was significantly lower than in the other groups (Chi-Square; $p = 0.010$).

Using the Beck's Depression Inventory, no significant differences between any of the groups were found in depression severity based on the raw scores (Kruskal Wallis; $p = 0.702$). When converting the raw scores into a scale, in the PwBMS group, 44.7% scored as not having a depression, compared to 48.7% in the PwNBMS group and 43.4% in the PwMS<10yrs group. No statistical differences were found in the ratings on the Beck's Depression Inventory e between the three groups (Kruskal Willis; $p = 0.559$) (Table 4).

## 4. Discussion

This study explored the differences in cognition, depression, and fatigue between persons with benign MS and non-benign MS in a large cohort of PwMS in order to contribute to this discussion. In our cohort of 786 PwMS, 18% ($n = 141$) could be classified as PwBMS which is consistent with a recent study (Tallantyre et al., 2019), which suggests that 15% of PwMS can be classified as PwBMS, although other studies suggest that the rate of BMS could be even higher (Amato et al., 2006; Ellenberger et al., 2020).

This is the first study comparing the rate of CI in PwBMS and PwNBMS in a large cohort using a computerized cognitive test battery (CCTB). As included PwMS completed the CCTB for the first time, no practice or learning effects could have influenced the results. A possible limitation could be the relationship between depression and cognitive functioning. However, a study by Golan et al. (2018) has shown that depression severity has a negligible impact on the test results of the CCTB, except when PwMS have very severe depression (Golan et al., 2018). As the rate of PwMS with extreme depression in the group PwBMS and PwNBMS in this study is low (3.3% vs 2.5%), the effects of severe depression on reported outcomes would be minimal.

As BMS is based on an EDSS-score of 3.0 or lower, it is evident that PwBMS do not have large impairment in gait and other areas of motor function. However, the EDSS is less sensitive to the impact of MS on cognitive function (Alonso et al., 2020; Sharrack and Hughes, 1996). As such, this study explored the 'invisible' symptoms of MS: cognitive impairment, fatigue and depression in MS. In the group PwBMS ($n = 141$) in this study, 38% of all PwBMS had a cognitive impairment, compared to 65% in the group PwNBMS ($n = 158$). Almost 80% of PwBMS experienced clinically relevant fatigue and 55% of PwBMS scored atypically on the Beck Depression Scale. No significant differences were found in the rates of fatigue and depression between PwBMS and PwNBMS meaning these symptoms were equally prevalent in this sample.

Overall, the rate of CI in the total included cohort of 786 PwMS was 43%. Literature suggest that the rate of CI in PwMS varies from 50% to 80%, based on phenotype, age and disease duration (DeLuca et al., 2020). Differences in rates of CI in PwMS could also be explained by the use of different diagnostic criteria for CI and the use of different assessment tools (DeLuca et al., 2020). In this study, an objective and validated assessment tool was used to assess cognitive functioning and clear criteria were applied to classify CI. Although the rate of cognitive impairment in PwNBMS is higher than in PwBMS, 38% of PwBMS

**Table 3**
Scores on cognitive tests and rates of cognitive impairment.

| | PwBMS $n = 141$ | PwNBMS $n = 158$ | p[1] | $d$[2] | PwMS<10yrs $n = 487$ | p[3] |
|---|---|---|---|---|---|---|
| **Memory** | *N* = 141 | *N* = 158 | | | *N* = 487 | |
| *Mean, SD* | 92.7, ±16.18 | 87.6, ±19.84 | .040[4] | 0.28 | 92.7, ±16.77 | .025[5] |
| *Min-Max* | 33.8–114.1 | 33.4–116.5 | | | 25.0–116.1 | |
| *N < 85 cut-off (%)* | 38 (27.0%) | 55 (34.8%) | .143[6] | | 113 (23.2%) | .015[6] |
| **Executive Function** | *N* = 141 | *N* = 158 | | | *N* = 487 | |
| *Mean, SD* | 94.2, ±15.91 | 85.3, ±16.17 | <0.001[1] | 0.54 | 94.0, ±15.50 | <0.001[5] |
| min-max | 47.6–126.2 | 41.3–125.4 | | | 30.7–130.3 | |
| *N < 85 cut-off (%)* | 39 (27.7%) | 77 (48.7%) | <0.001[6] | | 111 (22.8%) | <0.001[6] |
| **Visual Spatial** | *N* = 138 | *N* = 156 | | | *N* = 480 | |
| *Mean, SD* | 99.6, ±16.18 | 96.5, ±17.00 | .159[4] | | 99.8, ±18.00 | .065[5] |
| min-max | 29.5–133.4 | 56.2–128.7 | | | 33.7–142.0 | |
| *N < 85 cut-off (%)* | 23 (16.7%) | 45 (28.8%) | .013[6] | | 99 (20.6%) | .029[6] |
| **Verbal Function** | *N* = 138 | *N* = 149 | | | *N* = 473 | |
| *Mean, SD* | 97.1, ±15.38 | 91.6, ±24.14 | .436[4] | | 92.9, ±2336 | .738[5] |
| min-max | 25.0–115.9 | 25.0–116.9 | | | 25.0–117.4 | |
| *N < 85 cut-off (%)* | 25 (18.1%) | 36 (24.2%) | .211[6] | | 101 (21.4%) | .458[6] |
| **Attention** | *N* = 141 | *N* = 158 | | | *N* = 487 | |
| *Mean, SD* | 91.8, ±19.70 | 82.4, ±19.81 | <0.001[4] | 0.48 | 93.2, ±16.88 | <0.001[5] |
| min-max | 25.0–116.7 | 25.0–112.2 | | | 25.0–121.0 | |
| *N < 85 cut-off (%)* | 40 (28.4%) | 80 (50.6%) | <0.001[6] | | 112 (23.0%) | <0.001[6] |
| **Information Processing** | *N* = 132 | *N* = 134 | | | *N* = 458 | |
| *Mean, SD* | 92.3, ±18.00 | 82.7, ±17.48 | <0.001[7] | 0.54 | 92.1, ±16.53 | <0.001[8] |
| min-max | 46.3–137.9 | 49.3–132.7 | | | 42.1–150.3 | |
| *N < 85 cut-off (%)* | 42 (31.8%) | 74 (55.2%) | <0.001[6] | | 155 (33.8%) | <0.001[6] |
| **Motor Skills** | *N* = 138 | *N* = 143 | | | *N* = 474 | |
| *Mean, SD* | 98.3, ±15.66 | 86.0, ±19.38 | <0.001[4] | 0.70 | 97.9, ±17.09 | <0.001[5] |
| min-max | 41.6–120.4 | 25.0–114.2 | | | 29.2–123.6 | |
| *N < 85 cut-off (%)* | 24 (17.4%) | 58 (40.6%) | <0.001[6] | | 86 (18.1%) | <0.001[6] |

[1] comparison between PwBMS and PwNBMS.
[2] Cohen's *d*.
[3] comparison between all three groups (PwBMS, PwNBMS, PwMS<10yrs).
[4] Mann-Whitney U test.
[5] Kruskal Wallis test.
[6] Chi-Square test.
[7] Independent samples *t*-test.
[8] One-way ANOVA.

showed CI on CCTB. This percentage is equal to the rate of CI in a larger group of PwMS ($n = 487$) with a disease duration of less than 10 years. When looking at the subtests on the CCTB, for the majority of subtests, PwBMS achieved higher scores (i.e., better cognitive functioning) than PwNBMS. This suggests that the benign group scores were better than the disease duration matched group of PwNBMS. Whilst this finding could be interpreted as an indicator that 'benign' has better cognitive function than 'non-benign', this overlooks that more than one out of three PwBMS in this sample experiences cognitive impairment. The subscores on the CCTB suggest that over 25% of PwBMS will have problems in the domains Memory, Executive Function, Attention and Information Processing. The unrecognized impact is even more concerning considering the lack of routine multi-domain cognitive monitoring in the management of PwMS and the sub-optimal clinical validity of current screening tools for cognitive function, like the SDMT (Leach et al., 2022).

The correlation between fatigue and depression in MS is described in detail by others (Tarasiuk et al., 2021). In this study, no differences in fatigue and depression were found between PwBMS and PwNBMS. Compared to the group of PwMS with a disease duration of 10 years or less, the group of PwBMS scores significantly higher on the FSSS. In almost 78% of PwBMS their level of fatigue can be labelled as clinically significant fatigue. For depression there is no difference in severity between either benign MS, non-benign MS, and the group of PwMS with a shorter disease duration. Around 55% of PwBMS in the current cohort had an abnormal (i.e., a mild mood disturbance or a more severe classification) rating on the Beck's Depression Inventory. The rate of cognitive impairment, fatigue and depression demonstrated in this sample confirms findings from other studies that fatigue and depression are a common finding in PwBMS (Amato et al., 2006; Reynders et al., 2017; Tallantyre et al., 2019), and contributes further evidence to the discussion surrounding the classification of this condition as 'benign'. Differences in fatigue and depression rates found between different studies, again, could be explained by the use of different criteria and assessment tools. However, it is clear that depression and fatigue are common findings in PwBMS.

In a recent study, the relation between cognitive impairment and functional communication was described (El-Wahsh et al., 2021), confirming that language impairment has a large effect on health-related quality of life (El-Wahsh et al., 2019). The high rate of CI, depression and fatigue in PwBMS found in this study raises the question how PwBMS are coping in everyday life, and how the rate of 38% of cognitive impairment in this group would reflect on their employability, their social life and their partners. Further research is also needed into how people with 'benign' MS have currently access to health services and how their needs are supported.

## 5. Conclusion

Cognitive impairment, fatigue and depression are common among people with an EDSS-based definition of BMS. In a group of 141 PwBMS, 38% persons were found to have cognitive impairment.

Fatigue (78%) and depression (55%) were also a common finding. Multi-domain cognitive testing in routine MS care would improve the awareness of such impact. Our data suggests that unfortunately only a very small fraction of PwMS will likely have disease progression without any visible or invisible symptoms, which questions the further use of the term 'benign MS'.

**Table 4**
Comparison of fatigue and depression scores in PwMS.

| | PwBMS | PwNBMS | p[1] | PwMS<10yrs | p[2] |
|---|---|---|---|---|---|
| **Fatigue Severity Scale** | *N* = 121 | *N* = 122 | | *N* = 405 | |
| *Mean, SD* | 5.1, ±1.59 | 5.1, ±1.58 | .774[3] | 4.5, ±1.63 | <0.001[4] |
| *Min-Max* | 1–7 | 1–7 | | 1–7 | |
| *Fatigue (N,%)* | 94 (77.7%) | 93 (76.2%) | .787[5] | 266 (65.7%) | .010[5] |
| **Beck Depression Score** | *N* = 123 | *N* = 119 | | *N* = 401 | |
| *Mean, SD* | 14.3, ±11.15 | 13.2, ±10.73 | .456[3] | 13.6, ±9.82 | |
| *Min-Max* | 0–51 | 0–51 | | 0–44 | .702[4] |
| **Beck Depression Scale** | *N* = 123 | *N* = 119 | | *N* = 401 | |
| *Normal* | 55 (44.7%) | 58 (48.7%) | .316[3] | 174 (43.4%) | .559[4] |
| *Mild mood disturbance* | 23 (18.7%) | 27 (22.7%) | | 100 (24.9%) | |
| *Borderline depression* | 13 (10.6%) | 13 (10.9%) | | 37 (9.2%) | |
| *Moderate depression* | 21 (17.1%) | 9 (7.6%) | | 61 (15.2%) | |
| *Severe depression* | 7 (5.7%) | 9 (7.6%) | | 24 (6.0%) | |
| *Extreme depression* | 4 (3.3%) | 3 (2.5%) | | 5 (1.2%) | |

[1] Comparison between PwBMS and PwNBMS.
[2] Comparison between all three groups (PwBMS, PwNBMS, PwMS<10yrs).
[3] Mann-Whitney U test.
[4] Kruskal Wallis test.
[5] Chi-Square test.

## CRediT authorship contribution statement

**Hans Bogaardt:** Conceptualization, Formal analysis, Data curation, Writing – original draft, Writing – review & editing. **Daniel Golan:** Conceptualization, Writing – review & editing. **Marissa A Barrera:** Conceptualization, Writing – review & editing. **Stacie Attrill:** Conceptualization, Writing – review & editing. **Olivia Kaczmarek:** Data curation, Resources, Writing – review & editing. **Myassar Zarif:** Data curation, Resources, Writing – review & editing. **Barbara Bumstead:** Data curation, Resources, Writing – review & editing. **Marijean Buhse:** Data curation, Resources, Writing – review & editing. **Jeffrey Wilken:** Conceptualization, Writing – review & editing. **Glen M Doniger:** Writing – review & editing. **Laura M Hancock:** Writing – review & editing. **Iris-Katharina Penner:** Writing – review & editing. **June Halper:** Writing – review & editing. **Sarah A Morrow:** Writing – review & editing. **Thomas J Covey:** Writing – review & editing. **Mark Gudesblatt:** Conceptualization, Formal analysis, Supervision, Data curation, Resources, Writing – review & editing.

## Declaration of Competing Interest

Glen M. Doniger is an employee of NeuroTrax Corporation. The authors declare no other potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## References


Achiron, A., Doniger, G.M., Harel, Y., Appleboim-Gavish, N., Lavie, M., Simon, E.S., 2007. Prolonged response times characterize cognitive performance in multiple sclerosis. Eur. J. Neurol. 14 (10), 1102–1108. https://doi.org/10.1111/j.1468-1331.2007.01909.x.

Alali, D., El-Wahsh, S., Bogaardt, H, 2020. Multiple sclerosis. In: Weissbrod, P.A., Francis, D.O. (Eds.), Neurologic and Neurodegenerative Diseases of the Larynx. Springer International Publishing, pp. 171–176. https://doi.org/10.1007/978-3-030-28852-5_14.

Alonso, R.N., Eizaguirre, M.B., Silva, B., Pita, M.C., Yastremiz, C., Vanotti, S., Cáceres, F., Garcea, O., 2020. Brain function assessment of patients with multiple sclerosis in the expanded disability status scale: a proposal for modification. Int. J. MS Care 22 (1), 31–35. https://doi.org/10.7224/1537-2073.2018-084.

Amato, M.P., Portaccio, E., 2012. Truly benign multiple sclerosis is rare: let's stop fooling ourselves-Yes. Mult. Scler. J. 18 (1), 13–14. https://doi.org/10.1177/1352458511431732.

Amato, M.P., Zipoli, V., Goretti, B., Portaccio, E., De Caro, M.F., Ricchiuti, L., Siracusa, G., Masini, M., Sorbi, S., Trojano, M., 2006. Benign multiple sclerosis. J. Neurol. 253 (8), 1054–1059. https://doi.org/10.1007/s00415-006-0161-8.

Barrera, M., 2017. The Effect of a Single Bout of Physical Exertion On Expressive Language and Word Finding in Individuals with Multiple Sclerosis. City University of New York]. New York. https://academicworks.cuny.edu/gc_etds/1829/.

Beck, A.T., Ward, C.H., Mendelsohn, M., Mock, J., Erbaugh, J., 1961. An inventory for measuring depression. Arch. Gen. Psychiatry 4 (6), 561–571. https://doi.org/10.1001/archpsyc.1961.01710120031004.

Cohen, J., 1988. Set correlation and contingency tables. Appl. Psychol. Meas. 12 (4), 425–434. https://doi.org/10.1177/014662168801200410.

Covey, T.J., Golan, D., Doniger, G.M., Sergott, R., Zarif, M., Srinivasan, J., Bumstead, B., Wilken, J., Buhse, M., Mebrahtu, S., Gudesblatt, M., 2021. Visual evoked potential latency predicts cognitive function in people with multiple sclerosis. J. Neurol. 268 (11), 4311–4320. https://doi.org/10.1007/s00415-021-10561-2.

de Oliveira, M.O., Brucki, S.M.D., 2014. Computerized Neurocognitive Test (CNT) in mild cognitive impairment and Alzheimer's disease. Dement. Neuropsychol. 8 (2), 112–116. https://doi.org/10.1590/s1980-57642014dn82000005.

DeLuca, J., Chiaravalloti, N.D., Sandroff, B.M., 2020. Treatment and management of cognitive dysfunction in patients with multiple sclerosis. Nat. Rev. Neurol. 16 (6), 319–332. https://doi.org/10.1038/s41582-020-0355-1.

Dwolatzky, T., Whitehead, V., Doniger, G.M., Simon, E.S., Schweiger, A., Jaffe, D., Chertkow, H., 2003. Validity of a novel computerized cognitive battery for mild cognitive impairment. BMC Geriatr. 3, 4. https://doi.org/10.1186/1471-2318-3-4.

El-Wahsh, S., Ballard, K., Kumfor, F., Bogaardt, H., 2019. Prevalence of self-reported language impairment in multiple sclerosis and the association with health-related quality of life: an international survey study. Mult. Scler. Relat. Disord. 39, 101896 https://doi.org/10.1016/j.msard.2019.101896.

El-Wahsh, S., Heard, R., Bogaardt, H., Kumfor, F., Ballard, K.J., 2021. Variables Associated with Self-reported Language Impairment in Multiple Sclerosis: a Regression Analysis. Int. J. MS Care 23 (2), 85–92. https://doi.org/10.7224/1537-2073.2020-096.

Ellenberger, D., Flachenecker, P., Haas, J., Hellwig, K., Paul, F., Stahmann, A., Warnke, C., Zettl, U.K., Rommer, P.S., Scientific Advisory Group by the German MS-Register of the German MS Society, 2020. Is benign MS really benign? What a meaningful classification beyond the EDSS must take into consideration. Mult. Scler. Relat. Disord. 46, 102485 https://doi.org/10.1016/j.msard.2020.102485. Epub 2020 Sep 3. PMID: 32980646.

Gavrilov, Y.V., Shkilnyuk, G.G., Valko, P.O., Stolyarov, I.D., Ivashkova, E.V., Ilves, A.G., Nikiforova, I.G., Shchelkova, O.Y., Vasserman, L.I., Vais, E.E., Valko, Y., 2018. Validation of the Russian version of the Fatigue Impact Scale and Fatigue Severity Scale in multiple sclerosis patients. Acta Neurol. Scand. 138 (5), 408–416. https://doi.org/10.1111/ane.12993.

Golan, D., Doniger, G.M., Srinivasan, J., Sima, D.M., Zarif, M., Bumstead, B., Buhse, M., Van Hecke, W., Wilken, J., Gudesblatt, M., 2020. The association between MRI brain volumes and computerized cognitive scores of people with multiple sclerosis. Brain Cogn. 145, 105614 https://doi.org/10.1016/j.bandc.2020.105614.

Golan, D., Doniger, G.M., Wissemann, K., Zarif, M., Bumstead, B., Buhse, M., Fafard, L., Lavi, I., Wilken, J., Gudesblatt, M., 2018. The impact of subjective cognitive fatigue and depression on cognitive function in patients with multiple sclerosis. Mult. Scler. 24 (2), 196–204. https://doi.org/10.1177/1352458517695470.

Golan, D., Wilken, J., Doniger, G.M., Fratto, T., Kane, R., Srinivasan, J., Zarif, M., Bumstead, B., Buhse, M., Fafard, L., Topalli, I., Gudesblatt, M., 2019. Validity of a multi-domain computerized cognitive assessment battery for patients with multiple sclerosis. Mult. Scler. Relat. Disord. 30, 154–162. https://doi.org/10.1016/j.msard.2019.01.051.

Gudesblatt, M., Wissemann, K., Zarif, M., Bumstead, B., Fafard, L., Wilken, J., Blitz, K., Buhse, M., Santra, S., Hotermans, C., Lee, L., 2018. Improvement in cognitive function as measured by neurotrax in patients with relapsing multiple sclerosis treated with natalizumab: a 2-year retrospective analysis. CNS Drugs 32 (12), 1173–1181. https://doi.org/10.1007/s40263-018-0553-1.

Jackson, D.A., Nicholson, R., Bergmann, C., Wilken, J., Kaczmarek, O., Bumstead, B., Buhse, M., Zarif, M., Penner, I.K., Hancock, L.M., Golan, D., Doniger, G.M., Bogaardt, H., Barrera, M., Covey, T.J., Gudesblatt, M., 2022. Cognitive impairment in people with multiple sclerosis: perception vs. performance - factors that drive perception of impairment differ for patients and clinicians. Mult. Scler. Relat. Disord. 69, 104410 https://doi.org/10.1016/j.msard.2022.104410.

Jerković, A., Proroković, A., Matijaca, M., Katić, A., Košta, V., Mihalj, M., Dolić, K., Đogaš, Z., Vidaković, M.R., 2022. Validation of the fatigue severity scale in Croatian population of patients with multiple sclerosis disease: factor structure, internal consistency, and correlates. Mult. Scler. Relat. Disord. 58, 103397 https://doi.org/10.1016/j.msard.2021.103397.

Krupp, L.B., LaRocca, N.G., Muir-Nash, J., Steinberg, A.D., 1989. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch. Neurol. 46 (10), 1121–1123. https://doi.org/10.1001/archneur.1989.00520460115022.

Kurtzke, J.F., 1983. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 33 (11), 1444–1452. https://doi.org/10.1212/wnl.33.11.1444.

Lapshin, H., O'Connor, P., Lanctôt, K.L., Feinstein, A., 2012. Computerized cognitive testing for patients with multiple sclerosis. Mult. Scler. Relat. Disord. 1 (4), 196–201. https://doi.org/10.1016/j.msard.2012.05.001.

Leach, J.M., Cutter, G., Golan, D., Doniger, G., Zarif, M., Bumstead, B., Buhse, M., Kaczmarek, O., Sethi, A., Covey, T., Penner, I.K., Wilken, J., Gudesblatt, M., 2022. Measuring cognitive function by the SDMT across functional domains: useful but not sufficient. Mult. Scler. Relat. Disord. 60, 103704 https://doi.org/10.1016/j.msard.2022.103704.

Lublin, F.D., Reingold, S.C., 1996. Defining the clinical course of multiple sclerosis. Res. Int. Sur. 46 (4), 907–911. https://doi.org/10.1212/wnl.46.4.907.

Meyer-Moock, S., Feng, Y.S., Maeurer, M., Dippel, F.W., Kohlmann, T., 2014. Systematic literature review and validity evaluation of the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC) in patients with multiple sclerosis. BMC Neurol. 14, 58. https://doi.org/10.1186/1471-2377-14-58.

Morrow, S.A., Conway, D., Fuchs, T., Wojcik, C., Unverdi, M., Yasin, F., Pol, J., Eckert, S., Hojnacki, D.H., Dwyer, M., Zivadinov, R., Weinstock-Guttman, B., Benedict, R.H., 2021. Quantifying cognition and fatigue to enhance the sensitivity of the EDSS during relapses. Mult. Scler. 27 (7), 1077–1087. https://doi.org/10.1177/1352458520973618.

Reynders, T., D'Haeseleer, M., De Keyser, J., Nagels, G., D'Hooghe, M., .B.., 2017. Definition, prevalence and predictive factors of benign multiple sclerosis. eNeurologicalSci 7, 37–43. https://doi.org/10.1016/j.ensci.2017.05.002.

Schwartz, J.E., Jandorf, L., Krupp, L.B., 1993. The measurement of fatigue: a new instrument. J. Psychosom. Res. 37 (7), 753–762. https://doi.org/10.1016/0022-3999(93)90104-N.

Schweiger, A., Doniger, G.M., Dwolatzky, T., Jaffe, D., Simon, E.S., 2003. Reliability of a novel computerized neuropsychological battery for mild cognitive impairment. Acta Neuropsychol. 1, 407–413.

Sharrack, B., Hughes, R.A., 1996. Clinical scales for multiple sclerosis. J. Neurol. Sci. 135 (1), 1–9. https://doi.org/10.1016/0022-510x(95)00261-y.

Sumowski, J.F., Benedict, R., Enzinger, C., Filippi, M., Geurts, J.J., Hamalainen, P., Hulst, H., Inglese, M., Leavitt, V.M., Rocca, M.A., Rosti-Otajarvi, E.M., Rao, S., 2018. Cognition in multiple sclerosis: state of the field and priorities for the future. Neurology 90 (6), 278–288. https://doi.org/10.1212/wnl.0000000000004977.

Tallantyre, E.C., Major, P.C., Atherton, M.J., Davies, W.A., Joseph, F., Tomassini, V., Pickersgill, T.P., Harding, K.E., Willis, M.D., Winter, M., Robertson, N.P., 2019. How common is truly benign MS in a UK population? J. Neurol. Neurosurg. Psychiatry 90 (5), 522–528. https://doi.org/10.1136/jnnp-2018-318802.

Tarasiuk, J., Kapica-Topczewska, K., Czarnowska, A., Chorąży, M., Kochanowicz, J., Kułakowska, A., 2021. Co-occurrence of fatigue and depression in people with multiple sclerosis: a mini-review. Front. Neurol. 12, 817256 https://doi.org/10.3389/fneur.2021.817256.

Valko, P.O., Bassetti, C.L., Bloch, K.E., Held, U., Baumann, C.R., 2008. Validation of the fatigue severity scale in a Swiss cohort. Sleep 31 (11), 1601–1607. https://doi.org/10.1093/sleep/31.11.1601.

Wojcik, C.M., Beier, M., Costello, K., DeLuca, J., Feinstein, A., Goverover, Y., Gudesblatt, M., Jaworski 3rd, M., Kalb, R., Kostich, L., LaRocca, N.G., Rodgers, J.D., Benedict, R.H., 2019. Computerized neuropsychological assessment devices in multiple sclerosis: a systematic review. Mult. Scler. 25 (14), 1848–1869. https://doi.org/10.1177/1352458519879094.

Zanotto, T., Sosnoff, J.J., Ofori, E., Golan, D., Zarif, M., Bumstead, B., Buhse, M., Kaczmarek, O., Wilken, J., Muratori, L., Covey, T.J., Gudesblatt, M., 2022. Variability of objective gait measures across the expanded disability status scale in people living with multiple sclerosis: a cross-sectional retrospective analysis. Mult. Scler. Relat. Disord. 59, 103645 https://doi.org/10.1016/j.msard.2022.103645.