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Published in:
Multiple Sclerosis and Related Disorders

DOI:
10.1016/j.msard.2019.01.011

Publication date:
2019

Document Version
Author accepted manuscript

Prevalence of fatigue and its association with clinical features in progressive and non-progressive forms of Multiple Sclerosis

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Abstract

Background: Fatigue is a complex and disabling symptom of Multiple Sclerosis (MS); however, there is conflicting evidence of the relationship between fatigue and clinical features of MS. Furthermore, few studies have considered these relationships specifically in a progressive MS population.

Aims: (1) estimate the prevalence of self-reported fatigue in people with MS; (2) evaluate the relationship between fatigue severity/impact and clinical features of MS; (3) compare the prevalence of fatigue, and the strength of relationship between fatigue severity/impact and clinical features of MS in progressive and non-progressive forms of MS.

Methods: An online survey was conducted to measure the severity (Fatigue Severity Scale (FSS)) and impact of self-reported fatigue (Modified Fatigue Impact Scale) in people with MS. The survey also contained questionnaires related to disability, quality of life, MS impact, anxiety and depression, cognition, and sleep quality.

Results: 412 people responded to the survey, of which 68.7% reported having fatigue (FSS≥5). The prevalence of fatigue was significantly higher in participants with progressive MS (81%) in comparison to those with non-progressive forms of MS (64%, $p=0.01$). Fatigue severity and impact were associated with quality of life, MS impact, anxiety, depression, cognition, and sleep quality in both progressive and non-progressive MS populations ($p<0.05$). However, fatigue severity ($r = 0.335$) and impact ($r = 0.391$) were correlated with disability only in participants with non-progressive MS.

Conclusion: Fatigue was more prevalent amongst participants with progressive MS. In addition, higher fatigue severity and impact were associated with greater physical, cognitive, and psychological impairment, although the strength of association between these outcomes was generally similar regardless of the type of MS.

Key words: Multiple Sclerosis; fatigue; depression; anxiety; cognition; sleep quality

1. Introduction

Fatigue is a complex and multifactorial symptom of Multiple Sclerosis (MS) which can be defined as "a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities" [1]. It is often regarded as the most debilitating symptom of MS which impacts upon cognitive, psychological, and physical functioning [2], while also leading to reduced quality of life and unemployment [3,4]. Estimates of fatigue prevalence range between 52%-88%, making it one of the most common symptoms of MS [5-13]. However, differences in study populations and outcome measures, and differences in the methods used to identify people with or without fatigue explain the large variation in the reported prevalence of fatigue between studies.

While the exact pathophysiological mechanisms of MS-fatigue remain unknown, there is evidence to suggest that fatigue is a direct consequence of the primary pathological mechanisms of MS including inflammation and neurological damage [14]. In addition, secondary mechanisms independent of MS pathophysiology such as depression or disability may contribute to the development of fatigue [15]. However, studies investigating the association of fatigue with concomitant clinical and demographic features have presented conflicting results. For example, several cross-sectional [8, 13, 16, 17] and longitudinal studies [18-21] have demonstrated an association between fatigue and depression, while other studies have demonstrated that fatigue occurs independently of depression [6, 22, 23]. Similarly, there is limited consensus regarding the relationship between fatigue and disability [8, 11, 13, 23, 24], and fatigue and demographic variables such as age, sex, and disease duration [6, 9, 23, 25]. Furthermore, few studies have considered the relationship between fatigue and sleep quality [26-28], or cognition [17, 29] – symptoms which are common in MS [30, 31], and have been suggested to contribute to the development of fatigue [14].

Although fatigue is more prevalent in progressive forms of MS [10, 19, 23], few studies have considered the association between fatigue and relevant clinical features specifically in progressive MS populations (secondary progressive MS (SPMS) and primary progressive MS (PPMS)). Therefore, further work is required to understand which clinical and demographic

features are associated with fatigue to inform the design and evaluation of fatigue management interventions for people with progressive MS. Hence, this study aims to: (1) estimate the prevalence of self-reported fatigue in people with MS; (2) evaluate the relationship between fatigue severity and impact and clinical features of MS and; (3) compare the prevalence of fatigue and the relationships in (2) in progressive and non-progressive MS.

2. Methods

2.1. Design and participant recruitment

This cross-sectional study collected data using an online survey made available for one month between May 30th-June 30th 2018. The open-access survey was designed using RedCap software v6.15 [32] and was accessed via a link distributed online to potential participants through information shared by national and international MS charities and organisations based in the UK, USA, and Australia. Prior to accessing the survey, participants were required to confirm they had a medical diagnosis of MS and were aged 18 years or older. Participants self-reported demographic information (including MS type and disability using the Patient Determined Disease Steps (PDDS)) [33, 34], and completed a series of patient-reported outcome measures related to fatigue, MS impact, quality of life, depression and anxiety, cognition, and sleep. The survey took approximately 30-40 minutes to complete, and participants were allowed to save responses and return to the survey at a later time. Ethical approval for this study was obtained from Glasgow Caledonian University School of Health and Life Sciences Ethics Committee.

2.2. Outcome measures

2.2.1. Fatigue

Fatigue severity was assessed using the Fatigue Severity Scale (FSS). The FSS is a seven-point ordinal scale where participants rate the severity of fatigue in response to nine items, with total scores ranging between 0-7 [35]. The FSS has demonstrated moderate test-retest reliability and high precision in MS populations [24, 36, 37], and has strong internal

consistency [38]. In line with previous studies, participants that scored ≥5 on the FSS were classified as fatigued [8, 10, 17-19, 21, 25].

Fatigue impact was measured using the Modified Fatigue Impact Scale (MFIS). The MFIS is a multidimensional scale that evaluates the impact of fatigue on physical, cognitive, and psychosocial domains [25]. The MFIS contains 21 items (nine physical, ten cognitive, and two psychosocial) with a five-point ordinal scale (maximum score of 84), and requires participants to recall the impact of fatigue, with higher scores indicating a greater impact of fatigue [25]. The MFIS is widely used in MS populations, and has strong validity and test-retest reliability [24, 36, 37, 39].

2.2.2. MS impact

MS impact was assessed using the MS Impact Scale-29 (MSIS-29) version one, a valid and reliable disease specific questionnaire which assesses the physical and psychological impact of MS over 29 items using an ordinal scale [40-42]. Physical and psychological subscale scores range between 20-100 and 9-45 respectively, with higher scores indicating greater impact of MS.

2.2.3. Quality of life

Quality of life was assessed using the EQ-5D-3L, which consists of five domains – mobility, self-care, usual activities, pain/discomfort, and anxiety/depression – and generates a health index ($EQ\text{-}5D_{index}$) with a maximum score of 1 indicating 'full health' [43]. The weighted health index was calculated using the UK value set [44]. The EQ-5D-3L also captures self-reported health status ($EQ\text{-}5D_{status}$) using a visual analogue scale ranging between 0 (worst imagined health state) and 100 (highest health state).

2.2.4. Anxiety and depression

Anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS). The HADS consists of separate anxiety and depression scales that are comprised of seven items – scores range between 0-21 with higher scores indicating greater severity of anxiety or depression [45]. The validity of the HADS has been demonstrated in MS populations [46].

2.2.5. *Cognition*

Cognition was assessed using the MS Neuropsychological Screening Questionnaire (MSNSQ) – a valid screening tool for cognitive dysfunction in people with MS which has been shown to correlate with Symbol Digit Modalities Test scores [47-49]. Participants rate the impact and severity of problems with attention, memory, processing speed, emotional control, and social skills across 15 items using an ordinal scale [47]. Scores range from 0-60, with higher scores indicating greater cognitive dysfunction.

2.2.6. Sleep quality

Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI), a 19-item questionnaire comprised of seven components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction during the previous month [50]. Scores range from 0-21, with higher scores indicating poorer sleep quality. Validity of the PSQI has been demonstrated in clinical populations [51], and the PSQI has been used in other MS studies [17, 24].

2.3. Data analysis

Data analysis was performed using IBM SPSS v23 (IBM Corporation, Armonk, NY, USA). Survey responses of participants who provided complete demographic information and FSS scores were included in the data analysis, and missing data were excluded from subsequent analysis using pairwise deletion. The prevalence of fatigue (percentage of people who reported FSS≥5), mean questionnaire scores, and participant demographics were compared

between those with progressive and non-progressive forms of MS (relapsing-remitting MS (RRMS), Benign MS, or an unknown form of MS) using Chi-square tests for categorical variables and unpaired t-tests for continuous variables as data were normally distributed according to the Shapiro-Wilk statistic. Pearson correlation coefficients were used to assess the relationship of the FSS and MFIS with questionnaire responses (MSIS-29, EQ-5D, HADS, MSNSQ, PSQI) and demographic variables (disability, disease duration, age) – correlation coefficients <0.3 were interpreted as weak, ≥0.3 to <0.7 as moderate, and ≥0.7 as strong [52]. Subsequently, correlation coefficients were compared between people with progressive non-progressive MS using z values derived from Fisher's transformation [53]. Finally, two separate multiple linear regression analyses were performed using FSS (fatigue severity) and MFIS (fatigue impact) as the dependent variables for both progressive MS and non-progressive MS populations. Independent variables (FSS/MFIS (total score), age, time since diagnosis, PDDS, EQ-5D$_{index}$, MSIS-29, HADS, MSNSQ, and PSQI) were entered using stepwise backwards elimination methods with probability values of ≤0.05 for variable entry and ≥0.10 for variable removal. For all tests, a significance level of $p<0.05$ was used.

3. Results

3.1. Demographic data and fatigue prevalence

Of the 498 people who participated in the survey, 412 (83%) provided full demographic data and FSS scores and were included in the analysis (Table 1). In total 308 participants (75%) provided complete survey responses. 111 (27%) participants reported having a progressive form of MS (SPMS = 74, PPMS = 37), whereas 301 (73%) reported having a non-progressive form (RRMS = 291, benign MS = 2, unknown type = 8). Participants were mostly female (81.3%) and had a mean (SD) age of 46 years (11.5) and time since diagnosis of 9.6 years (8.6). People with progressive MS were significantly older ($p<0.001$), had a longer time since diagnosis ($p<0.001$), reported higher levels of disability ($p<0.001$), and had a higher proportion not in employment ($p<0.001$) in comparison to participants with non-progressive MS (Table 1).

Table 1 (near here)

The prevalence of fatigue was significantly higher amongst participants with progressive MS (81.1%, 95% CI = 72.8-87.3) compared to the non-progressive MS population (64.1%, 95% CI = 58.6-69.3) (Table 2). In addition, participants with progressive MS reported greater fatigue severity (FSS = 5.6±1.3, p=0.012), and greater physical (MFIS (physical) = 27.8±6.1, p<0.001) and psychosocial impact of fatigue (MFIS (psychosocial) = 5.7±1.8, p = 0.009). However, mean MFIS (total) (p = 0.149) did not differ between participants with progressive or non-progressive MS. Across the other outcome measures, participants with progressive MS reported lower quality of life (p<0.001), and higher depression (p<0.001) and physical impact of MS (p<0.001) (Table 2). There were no differences between the progressive MS and non-progressive MS populations in cognition (MSNSQ, p = 0.2), impact of fatigue on cognition (MFIS (cognition), p = 0.371), psychological impact of MS (p = 0.924), anxiety (p = 0.667) and sleep quality (p = 0.416).

Table 2 (near here)

3.2. Correlation of fatigue severity with clinical variables

In the total study population, fatigue severity (FSS) was moderately correlated with fatigue impact (MFIS total) (r = 0.646, p<0.001) in addition to the physical (r = 0.690, p<0.001), cognitive (r = 0.451, p<0.001), and psychosocial (r = 0.616, p<0.001) subscales of the MFIS (Table 3). Furthermore, FSS scores demonstrated moderate correlation with quality of life ($EQ\text{-}5D_{index}$: r = -0.330, p<0.001; $EQ\text{-}5D_{status}$: r = -0.415, p<0.001), MS impact (MSIS-29 (physical): r = 0.547, p<0.001; MSIS-29 (psychological): r = 0.466, p<0.001), depression (HADS (depression): r = 0.364, p<0.001), and cognition (MSNSQ: r = 0.321, p<0.001), and weak correlation with anxiety (HADS (anxiety): r = 0.234, p<0.001) and sleep quality (PSQI: r = 0.288, p<0.001). There was no relationship between fatigue severity and time since diagnosis (r = 0.055, p = 0.269) or fatigue severity and age (r = 0.096, p = 0.051).

There were few significant differences when comparing the strength of correlation between fatigue severity and clinical variables in the progressive MS and non-progressive MS populations. However, PDDS was moderately correlated with FSS scores in the non-progressive MS population ($r = 0.335$, $p<0.001$) and demonstrated no association with fatigue severity in those with progressive MS ($r = 0.092$, $p = 0.335$). For all other correlation coefficients, there was no difference between participants with progressive and non-progressive forms of MS ($p>0.05$).

Table 3 (near here)

3.3. Correlation of fatigue impact with clinical variables

Fatigue impact (MFIS (total)) demonstrated moderate to strong correlation with quality of life ($EQ\text{-}5D_{index}$: $r = -0.542$, $p<0.001$; $EQ\text{-}5D_{status}$: $r = -0.516$, $p<0.001$), MS impact (MSIS-29 (physical): $r = 0.660$, $p<0.001$; MSIS-29 (psychological): $r = 0.721$, $p<0.001$), anxiety (HADS (anxiety): $r = 0.442$, $p<0.001$), depression (HADS (depression): $r = 0.559$, $p<0.001$), cognition (MSNSQ: $r = 0.665$, $p<0.001$), and sleep quality (PSQI: $r = 0.438$, $p<0.001$) in the total study population (Table 4).

In the progressive MS population, age was negatively correlated with fatigue impact ($r = -0.236$, $p = 0.014$), and HADS (anxiety) had a significantly stronger association with fatigue impact in comparison to those with non-progressive MS ($r = 0.578$ vs. 0.388, $p = 0.037$). Conversely, in the non-progressive MS population PDDS was moderately correlated with fatigue impact ($r = 0.391$, $p<0.001$) and MSIS-29 (physical) was more strongly associated with fatigue impact in comparison to the progressive MS population ($r = 0.747$ vs. 0.599, $p = 0.02$). All other correlation coefficients were comparable between the progressive and non-progressive MS populations ($p>0.05$).

Table 4 (near here)

3.4. Variables predicting fatigue severity and impact

In participants with progressive MS, MFIS (total) scores were the strongest predictor of fatigue severity ($\beta = 0.816$, $p<0.001$) (Table 5). In addition, MSIS-29 (psychological) ($\beta = 0.309$, $p = 0.053$), HADS (anxiety) ($\beta = -0.249$, $p = 0.05$), and MSNSQ ($\beta = -0.290$, $p<0.001$) predicted an increase in fatigue severity; although MSIS-29 (psychological) and HADS (anxiety) did not reach the threshold for statistical significance ($p<0.05$). Overall, these variables accounted for 55.7% ($R^2 = 0.557$) variance in FSS scores ($F(4, 78) = 24.5$, $p<0.001$).

Similarly, fatigue impact was a strong predictor of FSS score in participants with non-progressive MS ($\beta = 0.566$, $p<0.001$), while EQ-$5D_{index}$ ($\beta = 0.117$, $p = 0.086$), MSIS-29 (physical) ($\beta = 0.279$, $p = 0.001$), and MSNSQ ($\beta = -0.124$, $p = 0.071$) also contributed to the prediction of fatigue severity, with this model accounting for 43.3% ($R^2 = 0.433$) variance in FSS scores ($F(4, 220) = 42$, $p<0.001$). However, only the MFIS and MSIS-29 (physical) were significant predictors of FSS scores in this model ($p<0.05$).

Table 5 (near here)

FSS scores predicted fatigue impact in both the progressive MS ($\beta=0.428$, $p<0.001$) and non-progressive MS populations ($\beta = 0.248$, $p<0.001$) (Table 6). In the progressive MS population, EQ-$5D_{index}$ ($\beta = -0.109$, $p = 0.09$), MSIS-29 (psychological) ($\beta = 0.230$, $p = 0.01$), and MSNSQ ($\beta = 0.349$, $p<0.001$) also predicted fatigue impact, accounting for 77% ($R^2 = 0.77$) variance in MFIS (total) scores ($F(4,78) = 65.4$, $p<0.001$); whereas in participants with non-progressive MS, MSIS-29 (physical) ($\beta = 0.305$, $p<0.001$), MSIS-29 (psychological) ($\beta = 0.269$, $p<0.001$), HADS (anxiety) ($\beta = -0.106$, $p = 0.032$), and MSNSQ ($\beta = 0.320$, $p<0.001$) accounted for 74.4% ($R^2 = 0.744$) variance in MFIS (total) scores ($F(5,219) = 127$, $p<0.001$).

Table 6 (near here)

4. Discussion

This large cross-sectional study found that fatigue was a prevalent symptom of MS, reported in 68.7% of the population. In addition, a higher proportion of participants with progressive MS (81.1%) reported fatigue compared to those with non-progressive forms of MS (64.1%), which confirms evidence from previous studies that fatigue is more prevalent amongst people with progressive forms of the disease [13, 19, 23]. Furthermore, in terms of the correlation between fatigue and clinical features of MS, both fatigue severity and impact were associated with higher levels of disability, poorer quality of life, greater depression and anxiety, and poor cognition and sleep quality. However, despite fatigue being more prevalent and severe in participants with progressive MS, the strength of association between fatigue severity/impact and the clinical features examined was generally comparable between the progressive MS and non-progressive MS populations.

Due to the different outcome measures and criteria used to define those with/without fatigue, it is difficult to directly compare the prevalence of fatigue in this progressive MS population with previously reported estimates of fatigue prevalence. However, the overall proportion of participants who reported fatigue in this study (68.7%) is higher than other studies that defined fatigue using the same methods (FSS≥5), with estimates of prevalence reported as 54% [21], 55% [18], 58% [17], and 65% [8]. Heterogeneity in MS type between studies may account for some difference in the reported estimates of fatigue prevalence – for example, the study by Bakshi et al. [8] did not include people with PPMS, whereas the study by Andreasen et al. [17] only included people with RRMS. Nevertheless, despite differences in estimates of prevalence, this study confirms that fatigue is a common symptom of MS and highlights the need for effective fatigue management interventions – especially in those with progressive MS [54].

The exact mechanisms of fatigue in MS have still to be fully elucidated, but are likely to include issues with inflammation and function of demyelinated nerve pathways in addition to secondary factors (e.g. clinical features such as depression and disability) independent of the primary MS pathophysiology [14, 15]. While several studies have investigated the association between fatigue and relevant outcomes, results remain equivocal with the presence and strength of association varying between studies. However, the findings from the overall study population confirm the results from previous studies that demonstrate fatigue is associated with physical [11, 13, 24], psychological [20, 21], and cognitive outcomes [17, 29] and, therefore, highlight the multifactorial and debilitating impact of fatigue in MS.

While causality cannot be inferred from these results, it is likely that fatigue is associated with these outcomes in a bi-directional relationship, as higher levels of fatigue could be the cause or consequence of impaired physical, cognitive, and psychological functioning [15]. For example, fatigue is often considered symptomatic of depression, although depression may develop as a result of fatigue and the resultant impact on daily living [20]. Similarly, mobility impairments may induce fatigue due to increased energy expenditure, whereas fatigue may limit mobility due to restrictions in physical activity [15]. Accordingly, longitudinal studies are required to establish the potential causal association between these outcomes and fatigue to improve fatigue management strategies for both progressive and non-progressive MS populations.

A novel finding of this study was that the strength of association between fatigue severity/impact and clinical features of MS were generally comparable between the progressive MS and non-progressive MS populations. However, there were a few exceptions as fatigue severity and impact were only correlated with disability in the non-progressive MS population, whereas fatigue impact was more strongly correlated with age and anxiety in the progressive MS population. Therefore, cognitive and psychological outcomes should be given greater prominence when designing and evaluating fatigue management interventions for people with progressive MS, as they were more strongly associated with fatigue in comparison to physical outcomes. Conversely, disability and physical outcomes may have greater importance when evaluating fatigue in a non-progressive MS population.

Interestingly, in both the progressive and non-progressive MS populations, the clinical features examined in this study were more strongly associated with fatigue impact (MFIS) in comparison to fatigue severity (FSS). This result may suggest that the MFIS is a more sensitive measure of MS-related fatigue due to the multidimensional nature of fatigue and ceiling effect of the FSS [38, 55]; however, it may also reflect the content validity of the MFIS and the limited ability to distinguish between global levels of function (e.g. physical, cognitive and psychosocial function) and the impact of fatigue on these domains [56]. Alternatively, outcomes other than those included in this study may be associated with the development and severity of fatigue – such as the primary disease mechanisms of MS. For example, it has been suggested that inflammation is associated with the development of fatigue, with levels of inflammatory biomarkers (interferon γ and tumour necrosis factor α) correlating with fatigue in MS [57, 58] – although this association may have limited relevance to progressive MS due to the absence of a marked inflammatory response [59, 60]. Additionally, structural neurological damage – including cortical atrophy and grey matter lesions – and patterns of neural re-organisation have also been found to be associated with fatigue in MS [15, 57]. However, further longitudinal studies are required to determine the primary and secondary pathophysiological pathways involved in the development of MS related fatigue.

4.1. Limitations

Due to the cross-sectional nature of this study, it was not possible to determine causality in the relationship between fatigue and the selected clinical and demographic variables. In addition, although the FSS and MFIS were selected to independently measure the severity and impact of fatigue, the strong association between these outcome measures may suggest they measure related aspects of fatigue. Furthermore, as data were collected through an open online survey, our study population may have been biased towards people experiencing fatigue, and was limited to those who were able to access the internet which potentially excluded those with more severe disabilities (for example, advanced cognitive, visual or physical impairments). In addition, the study design dictated that self-reported outcome measures were used to assess all clinical features; therefore, although the MSNSQ has limited reliability in measuring cognitive function (particularly in people with depression and cognitive impairment) [48], it was included in this study as it could be feasibly used as a self-reported outcome measure and provides a quick and valid estimation of cognitive function

[47]. However, the online nature of this study enabled a large international population to be recruited, and although MS diagnosis and type were self-reported, the participant demographics of this study sample were representative of a typical MS population [61, 62]. Lastly, as the number of potentially eligible participants was unknown, it was not possible to determine the survey response rate.

5. Conclusions

To our knowledge, this was the first study to compare the association between fatigue severity/impact and selected clinical and demographic variables in people with progressive and non-progressive forms of MS. This study confirmed that fatigue is a common symptom of MS, and that fatigue is more prevalent and severe amongst those with progressive MS. In addition, fatigue severity and impact were found to correlate with quality of life, MS impact, depression, anxiety, cognition, and sleep quality, and the strength of these relationships were similar in participants with progressive and non-progressive forms of MS. Therefore, this study highlights the multifactorial nature of fatigue and the importance of considering these outcomes as potential mediator or moderator variables when comprehensively designing and evaluating interventions aimed at improving fatigue. Furthermore, these associations may underline potential causal pathways of fatigue in both progressive and non-progressive forms of MS, and justifies the need for longitudinal assessment to explore the mechanisms of MS-related fatigue.

Declaration of conflicting interests: The Authors declare that there is no conflict of interest

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Table 1 Participant demographics

	Total population (n=412)	**Progressive MS** (SPMS, n=74; PPMS, n=37; total, n=111)	**Non-progressive MS** (RRMS, n=291; Benign MS, n=2; unknown, n=8; total, n= 301)	**p**
Age (years), mean ± SD (range)	46 ± 11.5 (22-79)	56 ± 8.9 (30-79)	42 ± 10.1 (22-69)	< 0.001
Time since diagnosis (years), mean ± SD (range)	9.6 ± 8.6 (0-44)	15.4 ± 10.6 (0-44)	7.4 ± 6.5 (0-36)	< 0.001
PDDS, mean ± SD (range)	3.1 ± 2.3 (0-8)	5.6 ± 1.4 (2-8)	2.2 ± 1.9 (0-7)	< 0.001
Sex, % (n)				
Female	81.3% (335)	77.5% (86)	82.7% (249)	0.225
Male	18.7% (77)	22.5% (25)	17.3% (52)	
Work status, % (n)				
Working	47.1% (194)	18% (20)	57.8% (174)	< 0.001
Not working	52.9% (218)	82% (91)	42.2% (127)	
Highest level of education, % (n)				
University or college	69.7% (287)	66.7% (74)	70.8% (213)	0.576
Trade/vocational training	10.4% (43)	9% (10)	11% (33)	
High school	19.2% (79)	23.4% (26)	17.6% (53)	
Did not complete high school	0.7% (3)	0.9% (1)	0.7% (2)	

Abbreviations: MS, Multiple Sclerosis; PDDS, Patient Determined Disease Steps; PPMS, Primary Progressive Multiple Sclerosis; RRMS, Relapsing Remitting Multiple Sclerosis; SPMS, Secondary Progressive Multiple Sclerosis

Table 2 Prevalence of fatigue and response to questionnaires

	Total population (n=412)	**Progressive MS** (n=111)	**Non-progressive MS** (n= 301)	**p**
Fatigue prevalence* (95% CI)	68.7% (64.1-73) (n=283)	81.1% (72.8-87.3) (n=90)	64.1% (58.6-69.3) (n=193)	0.010
FSS	5.4 ± 1.4 (n=412)	5.6 ± 1.3 (n=111)	5.2 ± 1.4 (n=301)	0.012
MFIS (total)	54.6 ± 16 (n=385)	56.5 ± 15.8 (n=107)	53.9 ± 16.1 (n=278)	0.149
MFIS (physical)	25.5 ± 7.3 (n=385)	27.8 ± 6.1 (n=107)	24.7 ± 7.5 (n=278)	< 0.001
MFIS (cognitive)	23.7 ± 9.1 (n=385)	23 ± 10.3 (n=107)	24 ± 8.6 (n=278)	0.371
MFIS (psychosocial)	5.4 ± 2 (n=385)	5.7 ± 1.8 (n=107)	5.2 ± 2 (n=278)	0.009
EQ-5D$_{index}$	0.51 ± 0.34 (n=375)	0.33 ± 0.36 (n=105)	0.58 ± 0.3 (n=270)	< 0.001
EQ-5D$_{status}$	56.5 ± 22.7 (n=372)	49.3 ± 24 (n=104)	59.3 ± 21.5 (n=268)	< 0.001
MSIS-29 (physical)	61.5 ± 20.1 (n=365)	76.1 ± 16.6 (n=102)	55.9 ± 18.5 (n=263)	< 0.001
MSIS-29 (psychological)	27.8 ± 8.9 (n=365)	27.8 ± 9.2 (n=102)	27.7 ± 8.8 (n=263)	0.924
HADS (anxiety)	8.9 ± 4.7 (n=357)	8.7 ± 5 (n=99)	8.9 ± 4.6 (n=258)	0.667
HADS (depression)	7.9 ± 4.3 (n=357)	9.34 ± 4.5 (n=99)	7.3 ± 4.1 (n=258)	< 0.001
MSNSQ	30.4 ± 14.6 (n=347)	28.8 ± 15.3 (n=97)	31 ± 14.3 (n=250)	0.200
PSQI	9.5 ± 4.1 (n=308)	9.2 ± 3.9 (n=83)	9.6 ± 4.2 (n=225)	0.416

Abbreviations: FSS, Fatigue Severity Scale; HADS, Hospital Anxiety and Depression Scale; MFIS, Modified Fatigue Impact Scale; MS, Multiple Sclerosis; MSIS-29, Multiple Sclerosis Impact Scale-29; MSNSQ, Multiple Sclerosis Neuropsychological Screening Questionnaire; PSQI, Pittsburgh Sleep Quality Index

Values reported as mean ± SD unless otherwise specified; values in brackets indicate the number of participants who completed each questionnaire

*Percentage of participants who reported FSS ≥ 5

Table 3 Correlation (r) of the Fatigue Severity Scale with clinical and demographic features in the progressive MS and non-progressive MS population

	FSS				
	Total population (n=412)	Progressive MS (n=111)	Non-progressive MS (n=301)	**z†**	**p**
Age	0.096 (-0.012, 0.200)	-0.158 (-0.308, 0.001)	0.095 (-0.020, 0.212)	-2.27	0.023*
Time since diagnosis	0.055 (-0.037, 0.150)	-0.067 (-0.253, 0.089)	0.043 (-0.081, 0.163)	-0.98	0.327
PDDS	0.297*** (0.199, 0.393)	0.092 (-0.078, 0.264)	0.335*** (0.224, 0.445)	-2.28	0.022*
MFIS (total)	0.646*** (0.553, 0.726)	0.700*** (0.572, 0.801)	0.624*** (0.506, 0.729)	1.18	0.235
MFIS (physical)	0.690*** (0.603, 0.766)	0.75*** (0.603, 0.866)	0.666*** (0.551, 0.769)	1.47	0.142
MFIS (cognitive)	0.451*** (0.347, 0.542)	0.520*** (0.368, 0.648)	0.439*** (0.312, 0.549)	0.09	0.358
MFIS (psychosocial)	0.616*** (0.529, 0.621)	0.674*** (0.513, 0.811)	0.592*** (0.489, 0.688)	1.19	0.234
EQ-5D$_{index}$	-0.330*** (-0.430, -0.242)	-0.275** (-0.446, -0.103)	-0.331*** (-0.444, -0.202)	0.53	0.596
EQ-5D$_{status}$	-0.415*** (-0.511, -0.317)	-0.317** (-0.467, -0.142)	-0.440*** (-0.552, -0.308)	1.23	0.219
MSIS-29 (physical)	0.547*** (0.457, 0.630)	0.517*** (0.329, 0.686)	0.569*** (0.462, 0.665)	-0.62	0.535
MSIS-29 (psychological)	0.466*** (0.365, 0.560)	0.523*** (0.340, 0.679)	0.448*** (0.320, 0.561)	0.83	0.407
HADS (anxiety)	0.234*** (0.125, 0.339)	0.297** (0.093, 0.490)	0.214*** (0.068, 0.333)	0.74	0.459

HADS (depression)	0.364*** (0.257, 0.457)	0.328** (0.115, 0.527)	0.357*** (0.236, 0.470)	-0.27	0.787
MSNSQ	0.321*** (0.217, 0.423)	0.350*** (0.199, 0.484)	0.325*** (0.192, 0.445)	0.23	0.818
PSQI	0.288*** (0.177, 0.399)	0.374*** (0.183, 0.544)	0.268*** (0.139, 0.393)	0.91	0.363

Abbreviations: FSS, Fatigue Severity Scale; HADS, Hospital Anxiety and Depression Scale; MFIS, Modified Fatigue Impact Scale; MS, Multiple Sclerosis; MSIS-29, Multiple Sclerosis Impact Scale-29; MSNSQ, Multiple Sclerosis Neuropsychological Screening Questionnaire; PDDS, Patient Determined Disease Steps; PSQI, Pittsburgh Sleep Quality Index

Values reported as Pearson correlation coefficients (95% CI)

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; otherwise value is not significant ($p > 0.05$)

†z score for the comparison of correlation coefficients between Progressive MS and Non-progressive MS populations

Table 4 Correlation (r) of the Modified Fatigue Impact Scale with clinical and demographic features in the progressive MS and non-progressive MS population

	MFIS				
	Total population (n=385)	Progressive MS (n=107)	Non-progressive MS (n=278)	**z†**	**p**
Age	-0.007 (-0.128, 0.101)	-0.236* (-0.422, -0.062)	0.006 (-0.130, 0.139)	-2.14	0.032*
Time since diagnosis	0.056 (-0.053, 0.152)	0.007 (-0.184, 0.189)	0.040 (-0.090, 0.158)	-0.29	0.772
PDDS	0.291*** (0.189, 0.389)	0.090 (-0.073, 0.268)	0.391*** (0.280, 0.495)	-2.80	0.005**
FSS	0.646*** (0.553, 0.726)	0.700*** (0.572, 0.801)	0.624*** (0.506, 0.729)	1.18	0.235
EQ-5D$_{index}$	-0.542*** (-0.609, -0.471)	-0.485*** (-0.613, -0.337)	-0.585*** (-0.654, -0.525)	1.21	0.226
EQ-5D$_{status}$	-0.516*** (-0.587, -0.439)	-0.490*** (-0.619, -0.346)	-0.526*** (-0.605, -0.432)	0.42	0.675
MSIS-29 (physical)	0.660*** (0.592, 0.718)	0.599*** (0.431, 0.729)	0.747*** (0.689, 0.757)	-2.33	0.020*
MSIS-29 (psychological)	0.721*** (0.668, 0.775)	0.752*** (0.626, 0.836)	0.711*** (0.651, 0.769)	0.75	0.453
HADS (anxiety)	0.442*** (0.345, 0.525)	0.578*** (0.408, 0.711)	0.388*** (0.280, 0.490)	2.09	0.037*
HADS (depression)	0.559***(0.478, 0.624)	0.562*** (0.391, 0.693)	0.561*** (0.476, 0.642)	0.01	0.992
MSNSQ	0.665*** (0.600, 0.722)	0.702*** (0.587, 0.786)	0.659*** (0.579, 0.724)	0.66	0.509
PSQI	0.438*** (0.339, 0.530)	0.465*** (0.266, 0.617)	0.434*** (0.314, 0.538)	0.30	0.764

Abbreviations: FSS, Fatigue Severity Scale; HADS, Hospital Anxiety and Depression Scale; MFIS, Modified Fatigue Impact Scale; MS, Multiple Sclerosis; MSIS-29, Multiple Sclerosis Impact Scale-29; MSNSQ, Multiple Sclerosis Neuropsychological Screening Questionnaire; PDDS, Patient Determined Disease Steps; PSQI, Pittsburgh Sleep Quality Index

Values reported as Pearson correlation coefficients (95% CI)

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; otherwise value is not significant ($p > 0.05$)

†z score for the comparison of correlation coefficients between Progressive MS and Non-progressive MS populations

Table 5 Results of regression analysis indicating the variables which predicted Fatigue Severity Scale scores in the progressive MS and non-progressive MS populations

	FSS			
Variables	R^2	b (SE)	β	p
(a)	0.557*			
Constant		1.810 (0.403)	.	<0.001
MFIS (total)		0.690 (0.010)	0.816	<0.001
MSIS-29 (psychological)		0.045 (0.023)	0.309	0.053
HADS (anxiety)		-0.066 (0.033)	-0.249	0.05
MSNSQ		-0.025 (0.010)	-0.290	0.013
(b)	0.433†			
Constant		1.378 (0.478)	.	0.004
MFIS (total)		0.051 (0.008)	0.566	<0.001
$EQ\text{-}5D_{index}$		0.556 (0.323)	0.117	0.086
MSIS-29 (physical)		0.022 (0.006)	0.279	0.001
MSNSQ		-0.012 (0.007)	-0.124	0.071

Abbreviations: FSS, Fatigue Severity Scale; HADS, Hospital Anxiety and Depression Scale; MFIS, Modified Fatigue Impact Scale; MS, Multiple Sclerosis; MSIS-29, Multiple Sclerosis Impact Scale-29; MSNSQ, Multiple Sclerosis Neuropsychological Screening Questionnaire

(a), Progressive MS; (b), Non-progressive MS

* $F(4, 78)=24.5$, $p<0.001$

† $F(4, 220)=42$, $p<0.001$

Table 6 Results of regression analysis indicating the variables which predicted Modified Fatigue Impact Scale scores in the progressive MS and non-progressive MS populations

	MFIS			
Variables	R^2	b (SE)	β	p
(a)	0.770*			
Constant		8.089 (4.562)	.	0.08
EQ-5D$_{index}$		-4.822 (2.808)	-0.109	0.09
MSIS-29 (psychological)		0.395 (0.150)	0.230	0.01
MSNSQ		0.360 (0.078)	0.349	<0.001
FSS		5.071 (0.755)	0.428	<0.001
(b)	0.744†			
Constant		2.984 (2.287)	.	0.193
MSIS-29 (physical)		0.265 (0.046)	0.305	<0.001
MSIS-29 (psychological)		0.492 (0.120)	0.269	<0.001
HADS (anxiety)		-0.371 (0.172)	-0.106	0.032
MSNSQ		0.359 (0.049)	0.320	<0.001
FSS		2.780 (0.469)	0.248	<0.001

Abbreviations: FSS, Fatigue Severity Scale; HADS, Hospital Anxiety and Depression Scale; MFIS, Modified Fatigue Impact Scale; MS, Multiple Sclerosis; MSIS-29, Multiple Sclerosis Impact Scale-29; MSNSQ, Multiple Sclerosis Neuropsychological Screening Questionnaire

(a), Progressive MS; (b), Non-progressive MS

* $F(4,78)=65.4$, $p<0.001$

† $F(5, 219)=127$, $p<0.001$