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Fatigue in multiple sclerosis: A UK MS-register based study

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ABSTRACT

Background: Fatigue is a widely experienced, incapacitating symptom of MS. It hinders daily functioning and has deleterious effects on quality of life. The UK MS Register is an online registry of over 20,000 participants with MS. The aim of this study was to estimate the prevalence, predictors, and impact of fatigue on people with MS using data from the UKMS register.

Methods: All participants who completed the Fatigue Severity Scale (FSS), WebEDSS, Hospital Anxiety and Depression Scale (HADS) within 28 days of each other were selected from the UK MS Register. Data on age, gender, duration and type of MS, use of disease modifying drugs and comorbidities were obtained from the UKMS register. We categorised people with FSS score of 5 or more as with fatigue and those with scores of 4 or less as without fatigue. Descriptive statistics and logistical and multiple regressions were used to explore predictors of fatigue and the effect of fatigue on mobility (MS Walking Scale), physical and psychological aspects of life (MS Impact Scale) and quality of life (European Quality of Life 5D-3 L).

Results: Amongst the 20,946 participants of the UK MS registry, 4620 completed FSS. Out of these, 775 (mean age= 54.71 years, SD= 10.90; mean duration of MS diagnosis =13.21 years, SD=9.75) had completed the FSS, Web EDSS and Hospital Anxiety and Depression Scale within 28 days of each other. 427 (55.1%) of pwMS had a FSS score >5 consistent with clinical fatigue. Logistic regression analysis showed that depression (p=<0.001), duration of MS ($p = 0.017$), secondary progressive MS ($p = 0.001$) and EDSS (p=<0.001) predicted fatigue. FSS scores had a significant negative impact on both psychological ($p > 0.001$) and physical ($p > 0.001$) domains of the MS Impact scale, MS walking scale ($p = 0.003$) and EQoL ($p = 0.005$).

Conclusions: Fatigue was a common symptom amongst people with MS. Depression, longer duration of MS, secondary progressive MS, and high EDSS predicted fatigue. Fatigue had an adverse effect on physical activities, mobility, psychological wellbeing, and quality of life of people with MS.

1. Introduction

Fatigue is a reversible decline in motor and cognitive capacities associated with decreased motivation and increased need to rest. Such decline may occur spontaneously or be triggered by different factors: physical activity, mental tasks, infection, and weather (Mills and Young, 2008). The fatigue could be either a subjective perception of exhaustion and lack of energy or an objective decline in performance of activities. The prevalence of MS in UK is 199 per 100,000 and incidence is 10 per 100,000, per year. Currently there are more than 131,000 people living with MS in UK (Public Health England, 2020). Multiple sclerosis: prevalence, incidence and smoking status). The fatigue in MS is a complex issue and can be split into primary and secondary types. Primary fatigue is a direct consequence of the disease (Tur, 2016) and the secondary due

Abbreviations: EDSS, expanded disability severity scale; Eq-5d-3 L, European quality of life (5 dimensions, 3 levels) measure; EQOL, European quality of life measure; FSS, fatigue severity scale; HADS, hospital anxiety and depression scale; MSISv2, multiple sclerosis impact scale-29v2; msWS, Multiple Sclerosis Walking Scale; pwMS, people with multiple sclerosis; UKMSR, UK MS register; DMD, disease modifying drug; RRMS, relapsing remitting multiple sclerosis; PPMS, primary progressive multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

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to effects consequential to MS and its treatment (Finlayson et al., 2012). Fatigue impacts between 69% and 83% of people with MS (pwMS) and has been graded as a 'severe' symptom by 74% of pwMS (Rooney et al., 2019; Minden et al., 2006; Hadjimichael et al., 2008). Fatigue in MS often restricts daily functioning, it can be provoked by heat and may improve with cooler temperatures. Fatigue is one of the key precipitants of early retirement from employment in pwMS (Schiavolin et al., 2013). In pwMS, fatigue has been associated with low Health-Related Quality of Life (Tabrizi and Radfar, 2015).

1.2. UK MS register

Launched in 2011, the UKMSR was created by the Population Data Science team in Swansea University Medical School and was funded by the MS Society. The UKMSR has ethical approval from the National Research Ethics Service Southwest Central Bristol (21/SW/0085). After obtaining informed consent, the participants of this register are requested to complete a series of online patient reported outcome measurements every six months. The UKMSR collects data from directly from the NHS clinical record following informed consent and from pwMS via an online 'portal'. Eligibility criteria for enroling in UKMSR are (1) over 18 years of age (2) a confirmed MS diagnosis. The diagnosis of MS in the online participants of the UKMSR has been validated (Middleton et al., 2018). As of December 2021, there are 21,457 people registered for the online portal, with 15,985 of them having contributed the minimum dataset consisting of date of diagnosis, MS type, number of relapses, date of conversion to secondary progressive MS, past and current disease modifying medications and current EDSS score (Middleton et al., 2018).

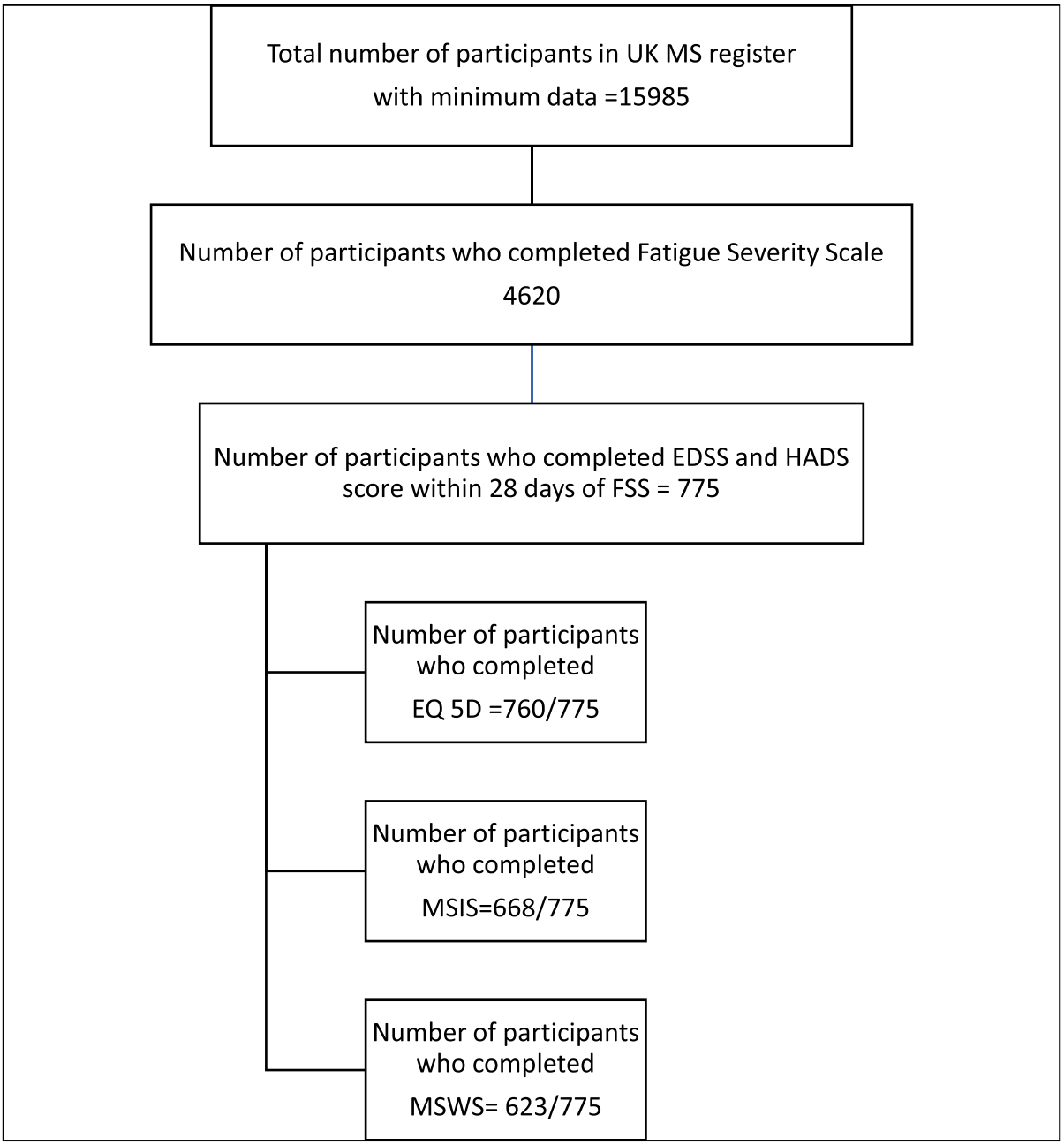

Fig. 1. Sample selection.

1.3. Aims

The objective of this study was to identify the prevalence, predictors and impacts of fatigue on physical activity and quality of life for pwMS in UK, using data from the UKMSR.

2. Materials and method

2.1. Participants

We selected all participants who completed FSS, Web EDSS and HADS within 28 days. Comorbidities were also analysed. From the sample of 775, those who completed EQ-5D-3 L, MSIS and MSWS within a period of 28 days between 2016 and 2018 were then selected for analysis of impact of fatigue. We included all subjects who completed the FSS and HADS within a period of 28 days to ensure a good temporal relationship between the responses. We excluded the participants who could not complete the FSS and HADS within 28 days of each other. See the flow chart in Fig. 1 detailing how the final sample was selected. To ensure secure access, all data was anonymised, and remote access technology was used to enable analysis. Two-factor authentication was used to assure data security. The data was prepared according to the pre-defined specifications given by the user and reviewed before it was made remotely available to the user.

2.2. Materials

FSS (Middleton et al., 2018) is, a self-reported a nine-item questionnaire, addressing the effects of fatigue on daily functioning. Each item is scored on a seven-point Likert scale (1; completely disagree – 7; completely agree), the mean score of the seven items is used as the FSS score. Those with scores of 5 or more were considered to have fatigue (Krupp et al., 1989; Ottonello et al., 2016). Disease severity was measured using the Web version of the EDSS (WebEDSS) (Leddy et al., 2013) and anxiety/depression were assessed using HADS (Zigmond and Snaith, 1983). The MSISv2 is a 29-item patient-rated scale to measure the physical (20 items) and psychological (nine items) impacts of MS. Two summary scores are generated after summing the terms and transforming them to a scale 0–100 scale. High scores indicate worse health (Hobart, 2011). The MSWS is a twelve-item self-report scale, measuring the impact of MS on gait (walking) ranging from 1 to 5. Items are summed to generate a total score (maximum = 60), then transformed to a scale ranging from 0 to 100. Higher scores signify a greater impact on walking. (Hobart et al., 2003) The EQ-5D-3 L visual analogue scale for general health status (0–worst imaginable health state, 100–best imaginable) was used for assessing impact of fatigue on quality of life in this study (EuroQoL Research Foundation, 2018). EQ-5D-3L User Guide.

2.3. Methods

We collected demographic variables (age, gender), clinical variables (MS duration, MS type, EDSS, FSS, HADS scores, co-morbidities (Box 1) and disease modifying drugs) and patient reported outcomes (MSISv2, MSWS and EQ-5D-3 L).

2.4. Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics 26 (IBM Corp, 2019). Socio-demographics were analysed using descriptive statistics. All ordinal patient reported outcome measures were converted into categorical values based on interquartile ranges. We included people with FSS scores ≥ 5 in the category of people with fatigue and those with <5 as people without not fatigue (Ottonello et al., 2016). Between group comparisons were made using parametric and non-parametric tests (for variables which did not meet assumptions). Independent t-tests were used for continuous variables and, Mann-Whitney, Wilcoxon, Fisher's Exact and Chi Square were used for categorical variables.

A binary multiple logistic regression was conducted to determine the contribution of each predictor variable on fatigue. Presence of fatigue (FSS score >5) was the outcome variable. The age, gender, duration of MS, type of MS, EDSS score, HADS Depression score, HADS Anxiety score and comorbidities were the predictors. Non-significant predictors were removed using backwards elimination. We also performed four linear multiple regression analyses to examine the relationships of EQ-5D-3 L general health status, MSIS–Psychological domain, MSIS–Physical domain and MSWS, with predictor variables (FSS score, age, gender, duration of MS, type of MS, WebEDSS, HADS Depression score, HADS Anxiety score and comorbidities). Statistical significance was set to $P < 0.05$ for all analyses.

3. Results

775 participants who had completed HADS and WebEDSS within 28 days of FSS met the criteria for the data selection. Amongst them EQ-5D-3 L was completed by 760, MSIS by 668 and MSWS by 623 participants, with 28 days of completing FSS. The demographic and clinical data are shown in Table 1.

Box 1
Data on Co-morbidities

Co-morbidities

Cancer

High Cholesterol

High Blood Pressure

Heart Problems

Lung Problems

Diabetes

Thyroid Issues

Anaemia

Smoking

Table 1
Clinical and demographic features of the participants.

Total number of participants	775
Age	54.7 ± 10.9 years
Duration since diagnosis of MS	13.21± 9.75 years
Men: Women	205 (26.5%):570 (73.5%)
Type of MS	
RRMS	462 (59.6%)
SPMS	159 (20.5%)
PPMS	131(16.9%)
Unknown	23 (3%)
On DMD	268
Not on DMD	507

MS- Multiple Sclerosis, RRMS- Remitting and relapsing Multiple Scleroses, SPMS- Secondary Progressive Multiple Sclerosis, PPMS- Primary Progressive Multiple Sclerosis, DMD- Disease Modifying Drugs

Table 2
Comparison of pwMS with and without fatigue.

	Without fatigueFSS<5348	With fatigueFSS>5427	p
Age	55.29 ± 11.41	55.06 ± 10.57	0.966 [1]
Men: Women	99: 249 (28.4%: 71.6%)	106: 321 (24.8%: 75.2%)	0.287 [2]
Duration of MS	12.4 ± 9	14.41 ± 9.57	0.001* [3]
EDSS	4.42 ± 1.87	5.6 ± 1.63	<0.001*[3]
HADS (D)	5.55 ± 10.85	8.64 ± 3.74	<0.001*[3]
HADS(A)	5.14 ± 3.41	8.17 ± 4.31	<0.001*[3]
PPMS: RRMS: SPMS: Unknown	55: 214: 67: 12 (15.8%: 61.5%: 19.3%: 3.4%)	76: 248: 92: 11 (17.8%: 58.1%: 21.5%: 2.6%)	0.613[2]
DMDs			0.510[2]
Yes	116 (15%)	152 (19.6%)	
No	232 (29.9%)	275 (35.5%)	
Smoked			0.001*[2]
Yes	147 (42.2%)	232 (54.3%)	
No	201 (57.8%)	195 (45.7%)	
Cancer			0.357[2]
Yes	17 (4.9%)	28 (6.6%)	
No	331 (95.1%)	399 (93.4)	
Cholesterol			0.689[2]
Yes	55 (15.8%)	63 (14.8%)	
No	293 (84.2%)	364 (85.2%)	
Hypertension			0.416[2]
Yes	47 (13.5%)	67 (15.7%)	
No	301 (86.5%)	360 (84.3%)	
Heart disease			1.000[2]
Yes	10 (2.9%)	12 (2.8%)	
No	No: 338 (97.1%)	415 (97.2%)	
Lung disease			0.722[2]
Yes	34 (9.8%)	46 (10.8%)	
No	314 (90.2%)	381 (89.2%)	
Diabetes			1.99[2]
Yes	2 (0.6%)	8 (1.9%)	
No	346 (99.4%)	419 (98.1%)	
Thyroid dysfunction			0.102[2]
Yes	20 (5.7%)	38 (8.9%)	
No	328 (94.3%)	389 (91.1%)	
Anaemia			0.509[2]
Yes	15 (4.3%)	24 (5.6%)	
No	333 (95.7%)	403 (94.4%)	

Note: * - $p < 0.05$.
[1] -independent T test.
[2] -Chi square test.
[3] – Mann Whitney test MS- Multiple Sclerosis, RRMS- Remitting and relapsing Multiple Scleroses, SPMS- Secondary Progressive Multiple Sclerosis, PPMS- Primary Progressive Multiple Sclerosis, DMD- Disease Modifying Drugs, EDSS- Extended Disability Status Scale, HADS (D)- Hospital Anxiety and Depression Scale (Depression), HADS (A)- Hospital Anxiety and Depression Scale (Anxiety).

.Amongst the participants 427 (55.1%) had fatigue and 348 did not meet our criteria for fatigue (FSS ≥5). Table 2 shows the comparison between pwMS with and without fatigue. The pwMS with fatigue had MS for significant longer duration. They had significantly higher EDSS, HADS (D) and HADS (A) scores. There were no significant differences in comorbidities between those with and without fatigue.

Logistic regression analyses (after removal of non-significant predictors using backwards elimination) showed that MS duration (OR 1.025, CI 1.005–1.046, $P = 0.017$), WebEDSS score (OR 1.442, CI 1.276–1.629, $P < 0.001$), HADS–Depression score (OR 1.174, CI 1.083 – 1.272, $P < 0.001$), and SPMS (OR 0.395, CI 0.234–0.668, $P = 0.001$) significantly predicted fatigue (FSS scores ≥5). None of the comorbidities were significant predictors of fatigue.

Table 3 shows the results of multiple regression analyses to investigate the association of EQ-5D-3 L Health State, MSIS (Physical), MSIS (psychological) and MSWS-12 with predictor variables. The regression equation was highly significant for EQoL 5D-3 L general health state, ($F(19, 739) = 24.50$, $P < 0.001$) and was able to explain 38.6% of variance. FSS scores ($P = 0.005$), HADS–Anxiety ($P = 0.041$), HADS–Depression ($P < 0.001$), EDSS scores ($P < 0.001$), the presence of cancer ($P = 0.006$) and high blood pressure ($P = 0.041$) were independently associated with lower quality of life.

The regression equation for MSIS Psychological scores was highly significant ($F(19,648) = 74.37$, $P < 0.001$) and was able to explain 68.6% of variance in MSIS psychological scores. FSS ($P < 0.001$), HADS–anxiety ($P < 0.001$), HADS–Depression ($P < 0.001$), smoking ($P = 0.037$) and cholesterol ($P = 0.030$) were significantly associated with MSIS scores showing a high impact of MS on psychological wellbeing. The regression was again, highly significant for the association of MSIS Physical Score ($F(19,648) = 117.84$, $P < 0.001$) and was able to explain 77.6% of variance in MSIS physical scores. FSS ($P < 0.001$), HADS–Depression ($P < 0.001$) and EDSS scores ($P < 0.001$) were significantly associated with MSIS Physical scores indicating high impact of MS on physical functions.

The regression equation for MSWS was also highly significant ($F(19,603) = 112.35$, $P < 0.001$) and was able to explain 78% of variance in scores. Age ($P = 0.004$), SPMS ($P = 0.011$), cholesterol ($P = 0.019$), FSS ($P = 0.004$), depression ($P = 0.001$), and EDSS scores ($P < 0.001$) were significantly associated with reduced walking ability.

Table 3
Multiple regression for predictors of fatigue.

Variable	EQoL	MSISPsychological	MSIS Physical	MSWS
Age	0.477	0.085	0.285	0.05*
MS Duration	0.062	0.561	0.179	0.154
Gender	0.068	0.125	0.957	0.081
MS Type	0.148	0.352	0.414	0.009*
DMDs	0.685	0.959	0.961	0.069
Smoker	0.237	0.037	0.108	0.988
FSS	0.005*	0.000*	0.000*	0.003*
EDSS Score	0.000*	0.051	0.000*	0.000*
Anxiety	0.041*	0.000*	0.906	0.221
Depression	0.000*	0.000*	0.000*	0.001*
Cancer	0.006*	0.181	0.788	0.789
Cholesterol	0.867	0.030*	0.693	0.019
Blood Pressure	0.041*	0.215	0.097	0.829
Heart	0.1	0.716	0.096	0.208
Lungs	0.732	0.893	0.589	0.704
Thyroid	0.301	0.734	0.374	0.921
Anaemia	0.583	0.834	0.971	0.583

Note: *indicates $p < 0.05$ Multiple Sclerosis, RRMS- Remitting and relapsing Multiple Scleroses, SPMS- Secondary Progressive Multiple Sclerosis, PPMS- Primary Progressive Multiple Sclerosis, DMD- Disease Modifying Drugs, EQoL- European Quality of Life scale, MSIS- Multiple Sclerosis Impact Scale, MSWS- Multiple Sclerosis Walking Scale.

4. Discussion

Fatigue is a multi-dimensional symptom and different scales measure specific dimensions of fatigue. Differences in the population studied and fatigue assessment tools used could account for the wide differences in prevalence. Even though there is wide variation, around half of the pwMS experience fatigue. Prevalence of fatigue in pwMS in our study is like other studies using validated fatigue assessment tools like the FSS. (Rooney et al., 2019; Hobart et al., 2003; Oliva Ramirez et al., 2021). Studies using only visual analogue scales tend to report a higher prevalence of fatigue (more than 90%) than the prevalence in studies like ours which used validated patient reported questionnaires (Wood et al., 2013).

Fatigue in MS is often linked to female gender. A couple of studies showed that female gender is an independent determinant of fatigue (Wood et al., 2013; Broch et al., 2021). We did not find any significant differences in prevalence of between the genders. amongst participants of UK MS register, fatigue was a significant issue for both genders.

The duration, type and severity of MS have been linked to fatigue. Our study, like the Norwegian one, showed that disease severity is a strong predictor of fatigue (Broch et al., 2021). As previously reported, we also noted that fatigue is more associated amongst people with a longer duration of MS and higher EDSS scores (Veauthier et al., 2013; Fiest et al., 2016; Homorodean et al., 2016). An international online survey showed that fatigue is more common amongst people with progressive forms of MS (Rooney et al., 2019). Our logistical regression analysis also revealed SPMS to be an independent predictor of fatigue. We did not find PPMS to be a significant predictor of fatigue. This could be due to relatively smaller numbers of people with PPMS in our study cohort. Our data indicates that clinicians should proactively look for fatigue in people with longer duration of MS, SPMS and high EDSS.

Several studies have noted the positive impacts of DMDs on reducing fatigue levels, particularly with Natalizumab (Svenningsson et al., 2013) and Fingomilod (Calkwood et al., 2014; Fox et al., 2014). Despite this, other research has found little difference in the impact of DMDs on fatigue levels (Ziemssen et al., 2016; Putzki et al., 2008; Phyo et al., 2019). We did not notice any significant association between fatigue and use of DMD (Table 2). Different DMDs have different actions and could have different effects on fatigue. We did not have enough participants to analyse the effect of individual DMDs on fatigue. The DMDs could reduce the inflammation and fatigue and further studies are required to answer this question.

Studies have found significant associations between depression, and fatigue in pwMS (Fiest et al., 2016; Homorodean et al., 2016). A longitudinal study also showed that fatigue and depression progress in tandem (Greeke et al., 2017). Gobbi et al. reported that MRI changes in white matter tracts of frontal and fronto-temporal pathways were independently associated with both fatigue and depression in pwMS (Gobbi et al., 2014). We also found that depression is significantly associated with fatigue. As fatigue and depression co-exist in pwMS, it is important to screen for the other in presence of one of them.

There are studies linking comorbidities, like diabetes (Homorodean et al., 2016), cholesterol levels (Browne et al., 2019), and anaemia (Knyszyńska et al., 2020) with MS related fatigue. We did not find any significant independent associations with any of these co-morbidities with fatigue.

In pwMS, fatigue restricted participation in previously enjoyable activities. Our multiple regression analysis showed that fatigue is strongly associated with poor scores on psychological domains of MSISv2.

Fatigue is a significant barrier to participation in physical activity for pwMS. A study from Israel showed that perceived fatigue contributes significantly towards low levels of physical activity in people with mild MS (Yusuf et al., 2021). The pwMS with high fatigue levels exhibit more sedentary behaviours and significantly higher mobility impairments (Kalron et al., 2020; Neal et al., 2020; Dalgas et al., 2018). Our multiple regression analysis of MSIS Physical domain and MSWS scores showed that fatigue is strongly associated with poor physical activity and mobility.

Fernández-Muñoz et al. (2015) found that increased self-perceived fatigue was significantly associated with a worse perception of quality of life, especially impacting cognitive, physical and emotional aspects of people' lives. In another study using the EQ-5D-3 L, the presence of fatigue influenced self-assessment of quality of life (Łabuz-Roszak et al., 2013). Our multiple regression analysis also showed that there was highly significant association between for health state in EQ-5D-3 L and fatigue. The influence of fatigue on quality of life highlights the need to understand this problem better and develop cost effective solutions.

4.1. Strengths and limitations

This was the largest study from UK on fatigue related to MS. It was also the first study to investigate MS related fatigue using data from the UKMS register. The UKMS register provided extensive data using patient reported outcome measures from a large number of pwMS. Due to the self-report nature of the data collection, the data provided was subjective. We had to exclude many participants who did not complete the FSS, WebEDSS and HADS within 28 days. Fatigue has been stated by pwMS as the most common factor for prematurely leaving employment (Schiavolin et al., 2013). We did not collect the data on employment. Another limitation is that the cross-sectional design and the bi-variate analyses prevented causal inferences being made.

5. Conclusion

Fatigue is a frequent problem amongst pwMS. MS of long duration, SPMS, high WebEDSS scores and depression are independent predictors of fatigue. MS-related fatigue has an independent adverse impact on walking, physical activities, psychological wellbeing, and overall quality of life. Further research into mechanisms of MS related fatigue and its mitigation is warranted.

Delaration of Competing Interest

Dr KPS Nair has participated as a clinical investigator on drug trials of disease modifying drugs in MS and Sativex (nabiximol) for GWS pharma. Dr Rod Middleton is the project lead for UK MS register.

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