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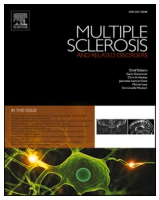

"No association between disease modifying treatment and fatigue in multiple sclerosis"

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ABSTRACT

Background: Fatigue affects 60–90% of people with multiple sclerosis (MS). It reduces quality of life and the ability to work. The cause of fatigue in MS remains unknown. Several disease-modifying treatments (DMTs) slow the disease process in relapsing MS by suppressing neuroinflammation. We aimed to investigate if treatment with a DMT is associated with lower rates of fatigue.

Methods: In this cross-sectional study of the MS population in three counties in Norway, we used the Fatigue Scale for Motor and Cognitive Functions (FSMC) and the Hospital Anxiety and Depression Scale (HADS) to assess patient-reported fatigue, anxiety and depression. Clinical data were retrieved from the electronic patient record system. We categorized DMTs as high-efficacy therapy or moderate-efficacy therapy. High-efficacy drugs included fingolimod, natalizumab, ocrelizumab, rituximab, alemtuzumab, daclizumab, and autologous hematopoietic stem cell transplantation. Moderate-efficacy drugs included interferons, glatiramer acetate, dimethyl fumarate, and teriflunomide. We included persons with relapsing MS only.

Results: Of 1142 patients, 80% had fatigue. Fifty-six percent of the patients were on DMTs (25% on moderate-efficacy treatment and 30% on high-efficacy treatment), 18% had discontinued treatment and 26% had never received any DMT. Sex, level of disability as measured by the Multiple Sclerosis Severity Score, anxiety and depression were independently associated with fatigue. Moderate-efficacy treatment was associated with less fatigue, but not after adjustment for other variables. There was no association between high-efficacy treatment and fatigue.

Conclusion: We found no independent relationship between the use of disease-modifying treatment and fatigue in MS.

1. Introduction

Worldwide, approximately 2.8 million people suffer from multiple sclerosis (MS) (Walton et al., 2020). Fatigue is one of the most common symptoms and is reported by people with MS (pwMS) to have the most negative impact on quality of life. It affects several aspects of daily life, including family life and social life, as well as the ability to work and to stay active (Hadjimichael et al., 2008; Smith and Arnett, 2005; Marrie et al., 2005). Studies have shown that the prevalence of MS-related fatigue is 60–90% (Kister et al., 2013; Lerdal et al., 2003; Rooney et al., 2019). We found a prevalence of 81% in contemporary Norwegian pwMS (Broch et al., 2021). Currently, there is no "gold-standard" definition of fatigue, which might contribute to the difficulty of understanding this important symptom. One of the commonly used definitions is "an overwhelming sense of tiredness, a lack of energy, or feelings of exhaustion, distinct from sadness or weakness, which is perceived by the individual or the caregiver to interfere with usual or desired activity" (Krupp et al., 2010). Primary MS fatigue is related to disease-specific mechanisms.

Newer technologies, like positron emission (PET) studies and

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functional magnetic resonance imaging (MRI), have elucidated pathological changes that may be associated with fatigue (Induruwa et al., 2012). A PET study from 1997 showed reduced glucose metabolism in the frontal cortex and basal ganglia in pwMS with fatigue, possibly caused by dysfunction due to demyelination (Roelcke et al., 1997). In a review from 2019, Palotai et al. suggest that a possible pathophysiological mechanism of MS-related fatigue is a disturbance in the serotoninergic and noradrenergic system, as in depressive illness (Palotai and Guttmann, 2020). Several quantitative neuroimaging studies have found associations between MS-related fatigue and damage to the cortico-striato-thalamo-cortical pathway (CSTC). Yet another possible contributor to MS-related fatigue is a disconnection between the cortex and deep gray matter. MS-related fatigue has also been associated with damage to the Corpus callosum in several studies, which suggests that a disconnection between the right and left CSTC may also play a role (Palotai and Guttmann, 2020).

Secondary fatigue in MS comprises other causes of fatigue, including sleep disturbances, pain, adverse effects of medication and anxiety/depression. We recently found MS-fatigue to be associated with socioeconomic factors like educational level, income level, as well as maternal educational level (Broch et al., 2022). This knowledge may aid in the follow-up of patients at particular risk.

There is currently no effective pharmacological treatments against fatigue (Nourbakhsh et al., 2021). Several studies have shown that physical activity improves fatigue, as do self-management programs (Rottoli et al., 2017). Cognitive behavioural therapy has shown promising results, but there are few studies on its long-term efficacy (Phyo et al., 2018). As for other management strategies, more research is necessary (Rottoli et al., 2017).

Over the last two decades, several disease modifying treatments (DMTs) have been discovered and implemented in the treatment of MS. These drugs stall disease progression in relapsing-remitting MS to varying degrees. Despite efforts to determine the cause of fatigue in MS, the etiology of primary MS fatigue remains elusive. It is believed to be multifactorial, with inflammation being one of the proposed mechanisms (Ormstad et al., 2020). Based on this, one could assume that DMTs targeting the neuroinflammation would also improve fatigue in MS. Several studies indicate that natalizumab may improve fatigue (Svenningsson et al., 2013; Masingue et al., 2017; Kallmann et al., 2019; Putzki et al., 2009; Lanzillo et al., 2020), but the results diverge (Chen et al., 2022) and studies are lacking for the majority of the DMTs. Likewise, to our knowledge, no studies have compared different DMTs with regard to their effect on fatigue.

2. Objectives

In this cross-sectional study, we aim to ascertain whether there is an association between the presence and level of fatigue and treatment with high-efficacy DMTs or moderate-efficacy DMTs in persons with MS. The study was conducted on a geographically and clinically well-defined cohort of patients in the counties Buskerud, Oslo and Telemark, the BOT-MS cohort, in the southeast of Norway.

3. Methods

3.1. Study design

This is a cross-sectional study, where prospectively collected data were retrieved from the electronic journal system retrospectively. The cohort is geographically well defined and previously described (Broch et al., 2021). We employed patient reported outcome measures (PROMS). The study was performed in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) (Association, 2013). The Regional Ethics Committee (REK 2015/670) approved the study. All participants provided written informed consent.

3.2. Setting

The study is part of the BOT-MS project; BOT is an acronym for Buskerud, Oslo and Telemark, which are three counties in the southeast of Norway. The BOT-MS registry is a database containing data on the vast majority of the MS-population in the three aforementioned counties. The hospitals serve a population of 1.17 million people. All diagnostics and follow-up of the pwMS within the catchment area of these hospitals are done by the participating centers. The vast majority of the included pwMS are assessed at regular intervals.

3.3. Participants

The BOT-MS registry comprises 3965 pwMS diagnosed with MS at the hospitals Vestre Viken Hospital Trust, Oslo University Hospital, and Telemark Hospital Trust between 1934 and 2017. The participants were identified as previously described (Broch et al., 2021). In short, we conducted a search in the electronic patient record system of the three hospitals for the ICD-10 diagnosis G35 multiple sclerosis in March 2017 and again in January 2018. The pwMS in the registry who were alive and residing within the three counties as of 2017 were invited to participate in the study, with the exception of patients we knew were too incapacitated from advanced disease to participate.

In total, 2512 patients were invited to participate and received questionnaires, including the Fatigue Scale for Motor and Cognitive Functions (FSMC). Of these 2512 patients, 1599 pwMS (64%) consented to participation. Three members of our research team, all experienced neurologists with a special interest in MS, reviewed the hospital records and collated information on disease onset, diagnosis, disease progression, disease severity, and treatment. Due to the lack of treatment options for progressive MS, only pwMS with relapsing MS were included in this study. We excluded patients with primary and secondary progressive MS.

3.4. Data sources/measurements

Clinical data were gathered from the electronic patient record system. The data included MS phenotype, time of disease onset and diagnosis, the number and name of DMTs used, time of DMT initiation, DMT switching, and DMT cessation, the duration of treatment, and reason for switching or ending treatment. As a measure of disease activity, we included data on clinical relapses, EDSS and magnetic resonance imaging (MRI) findings close to the time of the survey.

The participants completed a questionnaire on self-reported fatigue, the Fatigue Scale for Motor and Cognitive functions (FSMC), which measures perceived cognitive and motor fatigue. The questionnaire contains 20 items, scored on a 5-point Likert scale. A total score of less than 43 signifies no fatigue, whereas a score of 43 or above signifies fatigue; 43–52 mild, 53–62 moderate, and 63–100 severe fatigue. Subscores of less than 22 for cognitive or motor fatigue signifies no cognitive fatigue or motor fatigue respectively. For cognitive fatigue, a score of 22–27 indicates mild, 28–33 moderate and $\geq$ 34 severe fatigue. A subscore of 22–26 for motor fatigue indicates mild, 27–31 moderate and $\geq$32 severe fatigue (Penner et al., 2009). We refer to the total fatigue score throughout the text unless otherwise specified.

The participants also completed the Hospital Anxiety and Depression Scale (HADS), a 14-item scale assessing anxiety and depression. The subjects answered seven claims reflecting anxiety and seven claims measuring depression on a 4-point Likert scale. A score of 0–7 signifies no anxiety/depression, whereas a score of 8–10 and 11–21 signifies borderline or clinical definite anxiety/depression, respectively. We used validated, Norwegian translations of the FSMC and HADS questionnaires (Svenningsson et al., 2013; Leiknes et al., 2016; Bjelland et al., 2002).

The level of disability was determined using the Kurtzke Expanded Disability Status Scale (EDSS) (Kurtzke, 1983).

The Multiple Sclerosis Severity Score (MSSS) is an algorithm that provides a score of disease severity by combining disease duration and disability status measured by EDSS (Roxburgh et al., 2005).

Because the number of pwMS using some of the DMTs were low, we did not analyze fatigue in relation to each drug. Instead, we classified DMTs as moderate-efficacy therapy or high-efficacy therapy. Moderate-efficacy drugs at the time of the study (2017–2018) includes interferons, glatiramer acetate, teriflunomide, and dimethyl fumarate, whereas high-efficacy drugs includes natalizumab, fingolimod, rituximab, daclizumab, alemtuzumab, ocrelizumab and autologous hematopoietic stem cell transplantation.

We did analyses on the population with age stratified as younger than 50 years old and 50 years or older. This was done to illuminate any potential differences in the selection of treatment and, if so, to discover potential differences in the presence or level of fatigue.

3.5. Statistical methods

The statistical analyses were done in IBM SPSS statistics version 28.0.

Data are presented as means with standard deviation (SD), median with interquartile range (IQR) or numbers and percentages, depending on distribution. For the presentation of data in tables and illustrations, we categorized fatigue as mild, moderate, or severe as defined above. We assessed differences between groups using t-tests, Mann-Whitney U-tests, or Chi-square tests or Fishers exact tests, depending on the distribution of data. We used ANOVA or Kruskal- Wallis or Chi-square tests when we tested differences across DMT categories. We did post hoc tests if there were over-all differences between categories.

We performed univariable and multivariable linear regression analyses to investigate the association between DMT treatment and fatigue, and to adjust for possible confounding factors. In the multivariable models we used the FSMC score as a continuous variable, and adjusted for age, gender, disease duration, MSSS, new or enlarging MRI lesion, and clinical relapse (model 1), and additionally anxiety and depression to test their influence (model 2).In addition, the analyses were performed within strata of age (younger than 50 years old versus 50 years or older).

The results from linear regression analyses are presented by regression coefficient (B) with 95% confidence interval (CI). Possible multicollinearity between factors/covariates was assessed using Spearman correlation coefficient with ≥ 0.7 as cut-off.

If up to three items were missing on the FSMC questionnaires, missing items were imputed using the mean of the relevant scale (cognitive/motor). If more than three items were missing, the whole questionnaire was classified as a missing value (von Bismarck et al., 2018). Fatigue was categorized as no fatigue, mild fatigue, moderate fatigue, or severe fatigue, and as fatigue vs no fatigue.

All p-values were two-sided with a significance level of 5%.

4. Results

4.1. Participants

This study comprises the 1142 consenting people with relapsing MS who answered ≥17 of the questions on the FSMC-questionnaire. Of the respondents, 72% were female. The mean age was 50 years (SD 13). The median disease duration from diagnosis was 9 years (IQR: 4.0–17) and the median EDSS score was 2.5 (IQR: 1.5–3.8). Eighty percent had fatigue, including 54% with severe fatigue. Fifty-six percent received a DMT, 18% had discontinued and 26% had never been treated with DMTs. Fifty-nine percent had concomitant anxiety or depression, as measured by HADS. Patient characteristics are presented in Table 1.

4.2. Treatment

In total, 56% of the patients were treated with DMTs; 25% with moderate-efficacy DMT and 30% with high-efficacy DMT. Among participants <50 years, 9.4% had never been treated, 11% had discontinued treatment, 36% received moderate-efficacy DMT, and 43% received high-efficacy DMT. Among those ≥50 years of age, 41% were never treated, 23% had discontinued treatment, 16% received moderate-efficacy DMT, and 20% received high-efficacy DMT. The number of patients on each DMT is depicted in Fig. 1.

Table 1
Patient characteristics, exclusively relapsing-remitting disease course.

	All (n 1142)	Fatigue (n 915)	No fatigue (n 227)	p-value
Sex - female - n (%)	823 (72)	674 (82)	149 (18)	**0.011**
Age – mean (SD), years	50±13	51±13	47±12	**<0.001**
Years from diagnosis – median (IQR)	9.0 (4.0–17)	10 (4.0–18)	9.0 (4.0–14)	**0.021**
EDSS - median (IQR)[1]	2.5 (1.5–3.8)	2.5 (1.5–4.0)	1.5 (1.0–2.5)	**<0.001**
MSSS – median (IQR)[2]	2.3 (1.1–4.1)	2.6 (1.3–4.4)	1.4 (0.6–2.8)	**<0.001**
Treatment – no (%)				
Never treated	300 (26)	246 (27)	54 (24)	0.343
Moderate-efficacy DMT	289 (25)	211 (23)	78 (34)	**<0.001**
High-efficacy DMT	346 (30)	281 (31)	65 (29)	0.542
Discontinued DMT	202 (18)	172 (19)	30 (13)	0.049
Treatment duration – median (IQR)				
Moderate efficacy DMT	41 (22–77)	40 (22–74)	49 (22–85)	0.362
High efficacy DMT	36 (14–67)	36 (15–67)	38 (10–70)	0.411
New or enlarging MRI lesion(s), n (%)[3]	170 (24)	132 (23)	38 (26)	0.309
Clinical relapse[3]	125 (11)	107 (12)	18 (7.9)	0.062
HADS				
Anxiety	423 (37)	398 (44)	25 (11)	**<0.001**
Depression	244 (21)	244 (27)	0 (0.0)	**<0.001**†

IQR=inter quartile range, EDSS=Expanded Disability Status Scale, MSSS=Multiple Sclerosis Severity Score, DMT=Disease modifying treatment, MRI=Magnetic resonance imaging, HADS=Hospital Anxiety and Depression Scale.

[1] EDSS at prevalence.

[2] MSSS=Multiple Sclerosis Severity Score.

[3] in 2017/2018, † Fischer's exact test.

Treatment with moderate-efficacy DMT as compared to no treatment was associated with fatigue in the univariable analysis (Table 2), but there was no association between treatment with DMTs and fatigue after adjustment for confounding factors (Table 3). Sex, disease severity as measured by MSSS, and anxiety and depression were associated with fatigue, both in univariable and multivariate analyses. Age 50 or older was associated with higher fatigue score in the univariable analysis but not when adjusting for other clinical variables (Tables 2 and 3). The association between DMT categories with fatigue did not differ within strata of age in multivariable analysis (data not shown).

4.3. Fatigue

Eighty percent of the patients had fatigue; 54% had severe fatigue, 14% had moderate fatigue and 12% had mild fatigue. Seventy-six percent had cognitive fatigue and 80% had motor fatigue. Age>=50, sex, median MSSS, receiving moderate-efficacy DMT, and having anxiety/depression were associated with fatigue in univariable analysis (Table 2).

In the multivariable analysis, only sex, MSSS and anxiety/depression remained independently associated with fatigue (model 1). When excluding anxiety/depression from the analysis (model 2), age stratified as <50 or ≥50 years reached significance. Age as a continuous variable was not significantly associated with fatigue.

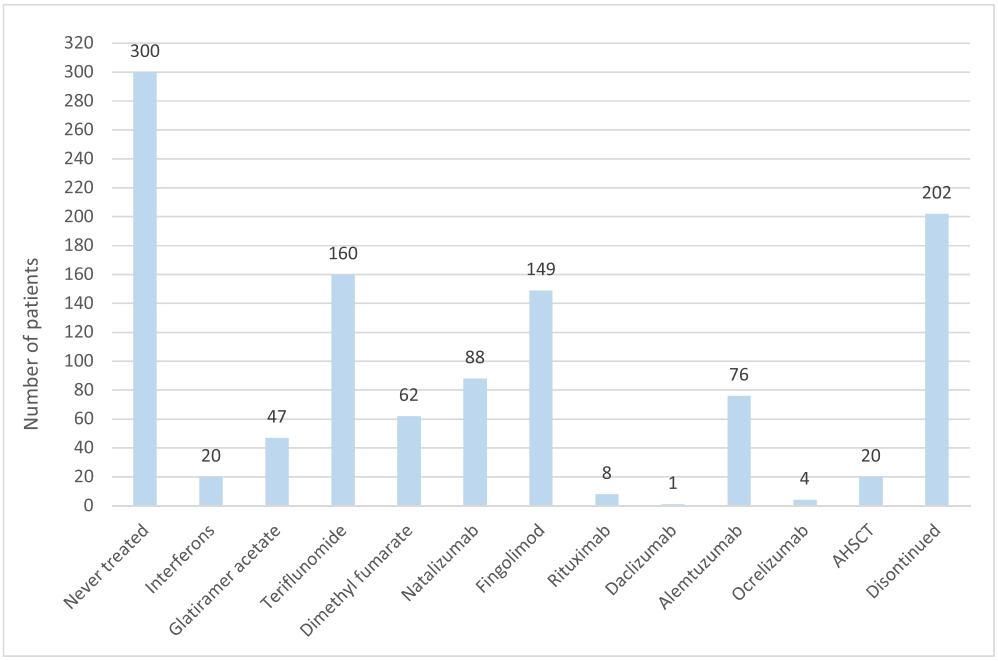

Fig. 1. Distribution of current treatment.

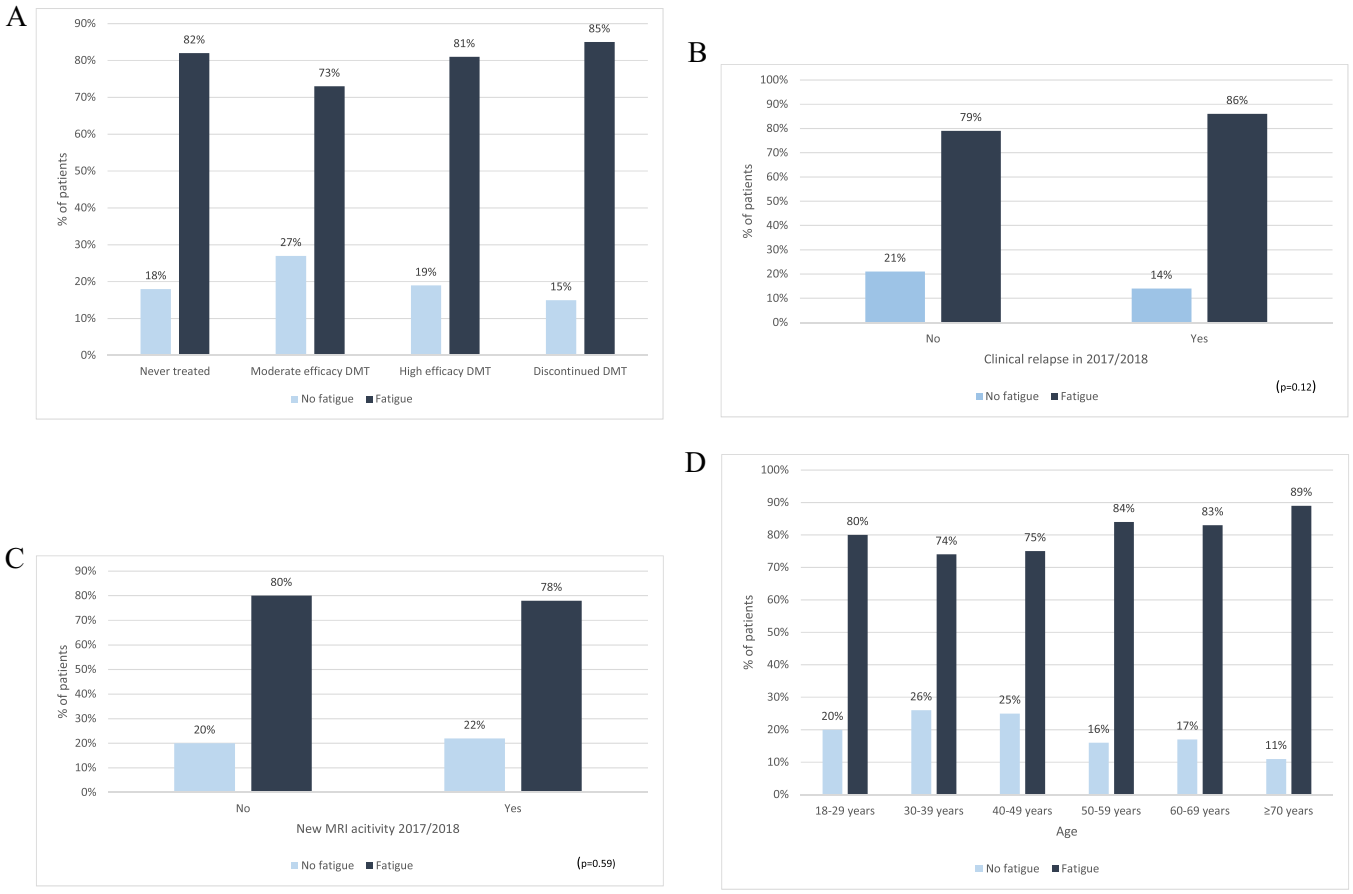

Fig. 2. (panel of Figs. 2A-D)
2a: Treatment with a moderate-efficacy disease-modifying drug was associated with less fatigue in univariable analysis, but there was no significant difference between treatment and fatigue after adjusting for confounding factors.
2b: There was no significant association between disease activity measured by clinical relapse and fatigue.
2c: There were no association between disease activity measured by magnetic resonance imaging (MRI) and fatigue.
2d: The prevalence of fatigue was higher in people with multiple sclerosis $\geq$ 50 years of age.

Table 2
Univariable analysis, total fatigue score.

	Unstandardized B (95% CI)	Standardized B-coefficient	p-value
Sex	3.97 (1.25, 6.69)	0.09	**0.004**
Age ≥ 50 years	5.11 (2.68, 7.55)	0.12	**<0.001**
Disease duration[1]	0.09 (−0.04, 0.22)	0.04	0.184
MSSS	2.70 (2.14, 3.26)	0.29	**<0.001**
Treatment level			
Never treated	Ref	Ref	Ref
Moderate-efficacy DMT	−4.77 (−7.57, −1.96)	−0.10	**<0.001**
High-efficacy DMT	1.90 (−0.76, 4.56)	0.04	0.162
New or enlarging MRI lesion(s)[2]	−1.39 (−5.04, 2.26)	−0.03	0.456
Clinical relapse[2]	2,80 (−1.12, 6.72)	0.04	0.161
HADS Anxiety	2.24 (1.99, 2.49)	0.46	**<0.001**
HADS Depression	3.45 (3.19, 3.71)	0.61	**<0.001**

MSSS=Multiple Sclerosis Severity Score, HADS=Hospital Anxiety and Depression Scale.
[1] Disease duration since diagnosis.
[2] In 2017/2018.

Table 3
Multivariable analysis, total fatigue score.

Variables	Model 1		Model 2	
	Unstandardized B (95% CI)	p-value	Unstandardized B (95% CI)	p-value
Sex	5.40 (1.92, 8.88)	**0.002**	4.96 (2.13, 7.80)	**<0.001**
Age ≥50	3.44 (0.003, 6.88)	**0.050**	2.74 (−0.04, 5.51)	0.054
Disease duration[1]	0.16 (−0.12, 0.44)	0.246	0.18 (−0.04, 0.40)	0.105
MSSS[2]	3.03 (2.25, 3.81)	**<0.001**	1.82 (1.18, 2.47)	**<0.001**
Treatment level				
Never treated	Ref	Ref	Ref	Ref
Moderate-efficacy DMT	−1.92 (−6.52, 2.68)	0.413	−1.44 (−5.13, 2.25)	0.443
High-efficacy DMT	−0.89 (−5.10, 3.32)	0.678	−0.38(−2.99, 3.75)	0.825
New or enlarging MRI lesion (s)[3]	−1.85 (−5.69, 2.00)	0.346	−0.86 (−3.94, 2.22)	0.585
Clinical relapse[3]	2.66 (−1.71, 7.02)	0.233	3.20 (−0.30, 6.70)	0.073
HADS Anxiety			0.84 (0.46, 1.22)	**<0.001**
HADS Depression			2.54 (2.10, 2.99)	**<0.001**

Model 1 is adjusted for age, gender, disease duration, MSSS, new or enlarging MRI lesion, and clinical relapse. Model 2 is adjusted for anxiety and depression in addition to the variables in model 1.
MSSS=Multiple Sclerosis Severity Score, HADS=Hospital Anxiety and Depression Scale.
[1] Disease duration since diagnosis.
[2] MSSS=Multiple Sclerosis Severity Score.
[3] In 2017/2018.

4.4. Disease activity

The proportion of patients with new or enlarging MRI lesion(s) or clinical relapse in 2017/2018 did not differ significantly between patients with and without fatigue. In line with this, there were no associations between fatigue and new or enlarging MRI lesions or clinical relapse on univariable (Table 2) or multivariate (Table 3) analyses.

4.5. Age, below or above 50 years

Almost half of our patients were <50 years old. Compared with those aged ≥50 years, these patients had a lower burden of MS symptoms and shorter disease duration (Table 4). A higher proportion of the pwMS ≥50 years of age had never been treated or had discontinued treatment, and fewer were receiving ongoing DMT compared to the pwMS <50 years old. Clinical relapses were more frequent in the group <50 years, whereas the proportion of patients with new or enlarging T2 lesion(s) were similar in both groups (Table 4).

In multivariable analysis, age ≥50 years was independently associated with fatigue. When anxiety/depression was included in the model, the effect of age ≥50 years was of borderline significance (Table 3).

4.6. Anxiety and depression

In the fatigue group, 44% had anxiety and 27% had depression, whereas in the non-fatigue group 11% had anxiety and none had depression ($p<0.001$). Anxiety was more common in the pwMS <50 years of age compared to those 50 years or older (44% vs 32%, $p<0.001$), whereas no difference was seen regarding depression. In the multivariable analysis, anxiety and depression were both independently associated with fatigue (Table 3).

5. Discussion

In this large cross-sectional study, we found no associations between fatigue and treatment with DMTs. There was an association between fatigue and treatment with moderate-efficacy DMTs in univariable analysis, but the association was not significant in multivariable analysis. We also found no association between disease activity as measured by new MRI changes or clinical relapse activity and fatigue. These findings contrast with our hypothesis that high-efficacy treatment would ameliorate disease activity and thereby reduce the burden of fatigue. However, our current results suggest that mechanisms beyond the disease process *per se* underlie fatigue in MS.

Our findings are in line with a recently published article by (Glasmacher et al., 2022), who assessed the effect of DMTs on "hidden disability" like anxiety, depression and fatigue in a population of newly diagnosed pwMS over one year. They found no significant effect of treatment on hidden disability, including fatigue. They found a trend for fingolimod and cladribine to improve hidden disability, but the number of patients on these treatments was low, and the results should be interpreted with caution.

Fatigue is also prevalent among patients with other autoimmune

Table 4
Characteristics in pwMS below or above 50 years of age.

	Age < 50 years	Age ≥ 50 years	p-value
Fatigue – no (%)	396 (43)	519 (57)	<0.001
Disease duration since diagnosis – median (IQR)	6.0 (2.0–10)	14 (8.0–22)	<0.001
EDSS – median (IQR)[1]	1.5 (1.0–2.5)	3.0 (2.0–5.5)	<0.001
MSSS – median (IQR)[2]	2.1 (1.0–3.6)	2.6 (1.4–4.8)	<0.001
Treatment level – no (%)			
Never treated	49 (9.3)	251 (41)	<0.001
Moderate-efficacy DMT	189 (36)	100 (16)	<0.001
High-efficacy DMT	226 (43)	120 (20)	<0.001
Discontinued DMT	60 (11)	142 (23)	<0.001
Highly-efficacy as first DMT	79 (15)	24 (3.9)	<0.001
New or enlarging MRI lesion(s) – no (%)[3]	104 (25)	66 (22)	0.267
Clinical relapse – no (%)[3]	93 (18)	32 (5.2)	<0.001
HSDS Anxiety – no (%)	229 (44)	194 (32)	<0.001
HADS Depression – no (%)	111 (21)	133 (22)	0.931

IQR=inter quartile range, EDSS=Expanded Disability Status Scale, MSSS=Multiple Sclerosis Severity Score, HADS=Hospital Anxiety and Depression Scale.
[1] EDSS at prevalence.
[2] MSSS=Multiple Sclerosis Severity Score.
[3] in 2017/2018.

disorders, i.e. rheumatic disorders. A recent Dutch meta-analysis assessed the effect of disease modifying anti-rheumatic drugs (DMARD) on patient reported outcomes, including fatigue. They found a reduction in the burden of fatigue, as well pain and activity limitation when comparing the effect of DMARDs to methotrexate and placebo (van den Dikkenberg et al., 2022).

In a mini-review, a Norwegian-Brazilian research team assessed the effect of hydrochloroquine, dehydroepiandrosterone and rituximab on fatigue in patients with Sjögren`s syndrome. They found no improvement in fatigue (Mæland et al., 2021).

In our study, fatigue was independently associated with disease severity as measured by MSSS, sex, age above or below 50 years, as well as anxiety and depression. A higher MSSS implies a higher EDSS and longer disease duration. We have previously shown that a higher EDSS is associated with higher rates of fatigue (Broch et al., 2021). Age as a continuous variable was not associated with fatigue, but fatigue was more prevalent in patients aged $>$ 50 years. Several factors may contribute to fatigue in the elderly patients, e.g. the load of comorbidity and menopause. Many patients in their fifties have an EDSS score of between 3.0 and 5.0. At this level of disability, people are usually still able to work. The combination of a considerable disease burden and employment may lead to more fatigue.

Anxiety and depression were associated with fatigue. We have previously found that motor fatigue has a stronger association with depression, whereas cognitive fatigue is strongly associated with both anxiety and depression (Broch et al., 2021). The relationship between fatigue and anxiety and depression is not straightforward. Fatigue causes anxiety and depression or the other way around. Also, the symptoms of fatigue may overlap considerably with symptoms of depression and anxiety (Ormstad et al., 2020).

Current DMTs mainly suppress relapses and focal inflammation on MRI, but have limited effect on chronic inflammation (Kuhlmann et al., 2023). If chronic inflammation and pathological processes causing progression independent of relapses is the main cause of fatigue, this may explain the negligible effect of current DMTs on fatigue.

5.1. Strengths

The strength of this study is the large, geographically well-defined population. The clinical data have been gathered from the patient records by three experienced neurologists with a special interest and competence in MS. All patients were invited to participate, mitigating selection bias. All data were collected prospectively, minimizing recall bias.

5.2. Limitations

Cross-sectional studies are not suited to determine causality. We investigated fatigue, which is a subjective symptom with no means for objective testing. The participants answered questionnaires sent by postal mail. Our set of responders may not be representative of the patient population at large: Patients with fatigue may be more inclined to answer than patients who do not experience fatigue. On the other hand, patients with severe fatigue may lack the initiative to fill in and submit the questionnaires. Another drawback is that the number of patients on each DMT was limited, making it impossible to investigate each drug separately. Some of the drugs in current use, such as cladribine and rituximab, were not in widespread use before 2018 and consequently were not assessed in this study.

6. Conclusion

In this large, cross-sectional study, we found no associations between treatment with high-efficacy or moderate-efficacy DMTs and MS-related fatigue. There was no association between disease activity measured by clinical relapse and new MRI changes and fatigue. Our results suggest that there are other underlying causes of fatigue than focal inflammation, on which DMTs have their effect.

CRediT authorship contribution statement

Line Broch: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization. **Heidi Øyen Flemmen:** Conceptualization, Methodology, Software, Validation, Investigation, Data curation, Writing – review & editing. **Cecilia Smith Simonsen:** Conceptualization, Methodology, Software, Validation, Investigation, Data curation, Writing – review & editing. **Pål Berg-Hansen:** Conceptualization, Methodology, Software, Validation, Writing – review & editing. **Heidi Ormstad:** Conceptualization, Methodology, Validation, Writing – review & editing. **Cathrine Brunborg:** Methodology, Formal analysis, Writing – review & editing. **Elisabeth Gulowsen Celius:** Conceptualization, Methodology, Software, Validation, Writing – review & editing, Supervision, Project administration.

Declaration of Competing Interest

LB has received unrestricted research grants from Sanofi, and advisory board honoraria from Sanofi, Merck and Biogen

CSS has received unrestricted research grants from Sanofi and Novartis, and advisory board and/or speaker honoraria from Sanofi, Merck, BMS, Novartis and Biogen

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PBH has received funding for travel or speaker's fees from Novartis, UCB, Biogen, Teva and Sanofi.

HO has no conflicts of interest.

CB has no conflicts of interest.

EGC has received unrestricted research grants from Sanofi, and advisory board and/or speaker honoraria from Biogen, BMS, Janssen, Merck, Novartis, Roche, Sanofi and Teva.

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