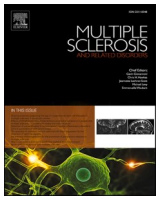
Multiple Sclerosis and Related Disorders 64 (2022) 103955

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

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



Original article

Fatigue in multiple sclerosis is associated with socioeconomic factors

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ARTICLE INFO

Keywords:
Multiple sclerosis
Fatigue
Socioeconomic status

ABSTRACT

Objectives: Fatigue is one of the leading causes of reduced quality of life and inability to work in people with multiple sclerosis (pwMS). Currently, no treatment effectively ameliorates fatigue. We still know little about what causes fatigue and which factors may contribute to fatigue. Knowledge about socioeconomic factors' role in fatigue might help us recognize strategies for the management of fatigue. Our aim was to explore whether socioeconomic factors are associated with the presence or level of perceived fatigue.
Methods: This is a cross-sectional study of the MS population in three Norwegian counties. We used the Fatigue Scale for Motor and Cognitive Functions to assess self-reported fatigue, and obtained socioeconomic data from Statistics Norway and questionnaires. To assess self-reported anxiety and depression, we employed the Hospital Anxiety and Depression Scale. Clinical data were gathered from the hospital record system.
Results: The response rate was 64% (1599/2512). Seventy percent of the respondents were female, and the mean age was 52 years. Higher levels of education were associated with lower levels of fatigue. Receiving a disability pension, being divorced and having children were all factors associated with higher levels of fatigue, as were low parental education, low income, current smoking, and autoimmune comorbidities. We found a higher prevalence of anxiety and depression in pwMS with fatigue compared to those without fatigue
Conclusion: Female sex, high level of disability, anxiety, depression and socioeconomic factors were independently associated with fatigue in contemporary patients with MS. These factors should be considered when devising management strategies.

1. Introduction

The prevalence of multiple sclerosis (MS) is rising. In Norway the prevalence was 203/100 000 in 2012 (Berg-Hansen et al., 2014), in the Norwegian county Buskerud it was 214/100.000 in 2014 (Simonsen et al., 2017) and in Buskerud and Telemark counties it was 232/100 000 in 2018 (Simonsen et al., 2021).

MS-related fatigue is a considerable problem for a large proportion of people with MS (pwMS). It can occur at any stage and at any time of the disease. PwMS report fatigue as one of the leading causes of reduced quality of life and of inability to work (Smith and Arnett, 2005, Hadjimichael et al., 2008, Marrie et al., 2005). In the 1998 Multiple Sclerosis Council for Clinical Practice Guidelines, fatigue is described as "a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual or desired activities" (Multiple Sclerosis Council for Clinical Practice Guidelines, 1998), another commonly used definition 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).

Previous research has shown a prevalence of fatigue in MS at 60–90% (Lerdal et al., 2003, Rooney et al., 2019, Kister et al., 2013). We recently found that 81% of contemporary pwMS experience fatigue. The prevalence of fatigue was significantly higher in females, and increased

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https://doi.org/10.1016/j.msard.2022.103955
Received 20 April 2022; Received in revised form 2 June 2022; Accepted 6 June 2022
Available online 9 June 2022

with the degree of disability (Broch et al., 2021).

Socioeconomic status (SES) influences health, and low SES is a risk factor for many diseases (Kivimäki et al., 2020). Several studies have assessed the associations between SES and the risk of developing MS and on disease progression in MS, with inconsistent results (Goulden et al., 2015, Nielsen et al., 2013, Bjørnevik et al., 2017, Flemmen et al., 2021, Calixto and Anaya, 2014). However, few studies have looked at the association between socioeconomic factors and MS-related fatigue. A study from Oslo in 2003 found a negative relationship between the level of education and fatigue among individuals with relapsing-remitting- and secondary progressive MS, but they found no sex differences (Lerdal et al., 2003).

Currently, we have no effective pharmacological treatment to ameliorate fatigue (Nourbakhsh et al., 2021). Studies have shown that physical activity can reduce the level of fatigue, as for other management strategies, more research is needed (Rottoli et al., 2017).MS-related fatigue imposes a substantial symptomatic burden and has a considerable economic impact on pwMS, as well as on society (Kobelt et al., 2017). It is important to gather more information and insights about causes and drivers of MS-related fatigue to improve management strategies.

2. Objectives

Our objective was to assess associations between the socioeconomic factors education, income, marital status and having children, and the presence and level of perceived fatigue in the current MS population in Norway. We also wanted to explore if low SES in adolescence, measured by the parental educational level at the patients' age 16 years, was associated with fatigue later in life.

3. Material and methods

3.1. Study design

This is a cross-sectional study comprising pwMS in the Norwegian counties Buskerud, Oslo, and Telemark (BOT). The study employed questionnaires on demographics, fatigue, anxiety and depression, clinical data from hospital records and official census data on socioeconomic factors from Statistics Norway (SSB)(Broch et al., 2021). The study was performed in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki)(World Medical Association, 2013) and approved by the Regional Ethics Committee (REK 2015/670). All patients provided written informed consent.

3.2. Setting

The BOT registry comprises 3965 pwMS diagnosed between 1934 and 2017 at the hospitals Vestre Viken Hospital Trust, Telemark Hospital Trust, and Oslo University Hospital (OUS), all of which are located in South-East Norway. These hospitals serve a population of 1.17 million people. The participating centers diagnose and treat all patients with MS within the defined geographical area, and the vast majority of the patients are assessed at regular intervals.

3.3. Participants

The patients in the BOT database were selected as described previously(Broch et al., 2021). In short, we searched the electronic hospital records in the three abovementioned hospitals for the ICD-10 diagnosis G35 MS. All subjects alive and still residing in the counties, with the exception of the ones we knew to be too incapacitated to give written, informed consent, were invited to participate. An overview of patient characteristics of participants compared to non-participants is found in supplementary Table 1.

3.4. Data sources/measurements

The Fatigue Scale for Motor and Cognitive Functions (FSMC) is a self-reported questionnaire measuring perceived cognitive and motor fatigue. The 20 items are scored on a 5-point Likert scale. A subscore of 22 points or higher for either cognitive or motor fatigue, or 43 points or more for the total score, indicate fatigue. A total score less than 43 signifies no fatigue, whereas a score at or above 43 signifies fatigue; 43–52 mild, 53–62 moderate, and $>$ 63 severe fatigue. Subscores for cognitive fatigue 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). Unless specified as either cognitive fatigue or motor fatigue we refer to total fatigue score throughout the text.

The Hospital Anxiety and Depression Scale (HADS) is a scale designed to assess anxiety and depression. There are 14 items of which seven relate to anxiety, and seven relate to depression. HADS has been validated in several studies and in different populations (Bjelland et al., 2002). A subscore of 8 or higher for each subscale indicates anxiety or depression. A subscore of 8–10 is of borderline significance, while a score of 11 or higher denotes clinical depression or anxiety. We used validated Norwegian translations of the two questionnaires (Svenningsson et al., 2013, Leiknes et al., 2016).

The BOT-MS questionnaire was developed by our research team, and has been validated (ECTRIMS Online Library. Flemmen H. 09/12/19; 279,125; P765). It is designed to obtain information on educational-, occupational- and marital status, as well as health- and lifestyle. The MacArthur scale of subjective social status is included in the BOT-MS questionnaire. The pwMS was asked to rate his or her self-perceived social status compared with other people in his or her community (Giatti et al., 2012). The scale contains 10 steps. At the top step are the people who are best off with regards to money, education and jobs, and at the bottom are the ones who are worst off. The person places him or herself on the step they feel is appropriate.

To quantify the level of disability, we used the Kurtzke Expanded Disability Status Scale (EDSS)(Kurtzke, 1983). When performing the statistical analyses, the EDSS scores were viewed as a scale variable.

Comorbidity was defined as the presence or absence of autoimmune comorbidity, as well as if the person had one or more than one concomitant autoimmune disease. Other medical conditions were not assessed.

Educational level was obtained from Statistics Norway and divided into primary level (1–10 years), secondary level (11–13 years) and graduate level ($>$ 13 years) of education.

Income level was obtained from Statistics Norway and assessed individually as well as for the household. We used income level both as a continuous variable and as a dichotomous variable (above or below median). Income was converted to Euro at a currency rate of 1 € = 9.33 NOK, which was the average 2017 rate given by the central bank of Norway. The adjusted household income is presented as the after-tax income per consumption unit, adjusted for differences in household size. Statistics Norway performed the adjustment using the European Union equivalence scale, which assigns a value of 1 to the household head, of 0.5 to each additional adult member and of 0.3 to each child under the age of 17.

For every study subject, Statistics Norway provided socioeconomic data on 15 controls matched for sex, age and area of residence at the age of 16 (reference population).

3.5. Statistical methods

We performed the statistical analyses in IBM SPSS statistics version 25.0.

Depending on distribution, numerical data are presented as means with standard deviation (SD), median (interquartile range [IQR]), or numbers and percentages. Differences between groups were assessed

using *t*-tests, Mann-Whitney U-tests or Chi-square tests depending on the distribution of the data. When testing differences across several categories, we used ANOVA or Chi-square tests depending on the distribution. *Post hoc* tests were performed if there were over-all differences between categories.

Depending on the distribution of the outcome variables, we explored associations using univariable and multivariable linear regression or by binary logistic regression.

To determine possible factors associated with the fatigue score, we used univariable and multivariable linear regression analyses. We used our expertise in the field to select factors for the multivariable analyses. Multicollinearity was defined as a Pearson correlation coefficient or Spearman's rho of above 0.7. The results from linear regression analyses are presented by regression coefficient (B) with 95% confidence interval (CI) and explained variance (R^2).

Logistic regression analysis was performed to investigate the association between whether patients had children and the prevalence of fatigue, and to adjust for the potential confounding effect of age.

For the FSMC questionnaires, missing items were imputed using the mean of the relevant scale (cognitive/motor) if three items, at most, were missing; if more than three items were missing, the whole questionnaire was classified as a missing value (von Bismarck et al., 2018). We categorized fatigue as no, mild, moderate, or severe, and as fatigue vs no fatigue.

4. Results

4.1. Participants

Of the 2512 pwMS in the BOT-MS registry who were alive as of March 2017, 1599 responded (64%). This study comprises the 1454 pwMS who had ≤ 3 missing items on the FSMC questionnaire. Of these, 70% were female. The mean age of the participants was 52 years (range 18–87, SD 13). The participants had a median disease duration of 10 years (range 0–54, IQR 5–18) since the MS diagnosis and 83% had relapsing remitting MS at the time of diagnosis. The median EDSS score was 2.5 (range 0–9.5, IQR 1.5–5.0). Of the 1454 pwMS, 1183 (81%) were deemed to have fatigue, whereas 271 (19%) did not have fatigue. Clinical and socioeconomic characteristics are detailed in Table 1.

Table 1
Patient characteristics.

	All (n = 1454)	Fatigue (n = 1183)	No fatigue (n = 271)	P-value
Female gender, n (%)	1012 (70)	840 (71)	172 (64)	0.02
Age, mean, SD,	52 ± 13	53 ± 13	49 ± 13	<0.001
Marital status, n (%,)				
Married/Cohabitant	865 (60)	684 (58)	181 (67)	0.04
Divorced	190 (13)	166 (14)	24 (9)	
Single	335 (2)	279 (24)	56 (21)	
Widow/widower	50 (4)	42 (4)	8 (3)	
Has children, n (%)	764 (53)	640 (54)	124 (46)	0.01
Years from diagnosis, median, (IQR)	10 (5-18)	10 (5-18)	9 (4-16)	0.01
Years from onset, median, (IQR)	16 (8-26)	17 (8-26)	13 (7-21)	0.001
Relapsing MS, n (%)	1143 (84.9)	915(83.6)	228 (90.1)	0.01
Disease severity, EDSS, median (IQR)	2.5 (1.5–5.0)	3.0 (2.0–5.5)	2.0 (1.0–3.0)	<0.001
Disease severity, EDSS, n (%)				
0–3.0	799 (60)	614 (56)	185 (77)	<0.001
3.5–6.0	325 (24)	299 (27)	26 (11)	<0.001
6.5–8.0	186 (14)	163 (15)	23 (10)	0.02
8.5–9.5	33 (3)	28 (3)	5 (2)	0.60
Income, n (%)				
Above study population median	725 (50)	531 (45)	194 (72)	<0.001
Below study population median	729 (50)	652 (55)	77 (28)	
Educational level, n (%)				
Primary	249 (17)	235 (20)	14 (5)	<0.001
Secondary	500 (35)	432 (37)	68 (25)	<0.001
Graduate	690 (48)	503 (43)	187 (70)	<0.001
Receiving disability pension, n (%)	566 (39)	526 (45)	40 (15)	<0.001
Income 2017, median (IQR)*	45 525 (35 244-60 739)	43 542 (33 599-56 543)	58 436 (44 473–77 172)	<0.001
Adjusted household income, median (IQR)*	42 640 (33 939-55 230)	41 174 (32 913-52 594)	49 909 (39 287-65 446)	<0.001

*Currency rate 2017 €
Median income control-group 2017* (n 23,700) – 48 113 (33 205-65 063)
Adjusted median household income after tax control-group* 2017 (n 24,005) – 34 308 (25 894-45 092)

4.2. Education

The mean FSMC score was 72 (SD 18) for the participants with primary level education, 66 (SD 20) for those with a secondary level education and 57 (SD 21) for the group with a graduate level education (> 13 years, $p < 0.001$) (Fig. 1).

We found a significantly higher rate of severe fatigue at 71% in participants with primary educational level, 62% in those with secondary and 43% of pwMS with graduate level education ($p < 0.001$) (Fig. 2).

4.3. Income level

The median income for the participants was 45 525 € (IQR 35 250–60 739 €). For comparison, the median income for the reference population was 48 113 € (IQR 33 205–11 473 €). For the fatigue group, the median income was 43 542 € (IQR 33 599–56 543 €) and for the non-fatigue group 58 436 € (IQR 44 473–77 172 €), $p < 0.001$. Fifty-five percent of the patients with fatigue had an income below median, as opposed to 28% of the patients without fatigue.

The median adjusted household income was 42 640 € (IQR 33 939–55 230 €). For the groups with and without fatigue it was 41 174 € (IQR 32 913–52 594 €) and 49 909 € (IQR 39 287–65 446 €), respectively, $p < 0.001$. The adjusted household income level was lower than median in 54% of the patients who had fatigue and in 32% of the patients who did not experience fatigue. The median household income in the control group was 34 308 € (IQR 25 894–45 092 €). Regardless of whether the subjects were working or receiving disability pension, those with fatigue had lower income than the ones without fatigue ($p < 0.001$).

4.4. Marital status

The prevalence of fatigue differed significantly between patients who were married/cohabitant, divorced, widowed, and single (Fig. 3).

It was 79% amongst married/cohabiting pwMS, versus 85% in the other groups combined ($p < 0.004$). In contrast, the prevalence was significantly higher among the divorced at 87%, versus 80% in the other groups combined ($p = 0.02$). In the married/cohabitant group, 52% had severe fatigue compared to the other groups combined at 58% ($p = 0.03$). The divorced participants had a higher rate of severe fatigue than the other groups combined at 63% versus 53% ($p = 0.05$), respectively. There was no significant difference in the prevalence or severity of fatigue between pwMS who were single and the other groups, or between widowed participants and the other groups.

5. Number of children

Among pwMS with children, the prevalence of fatigue was

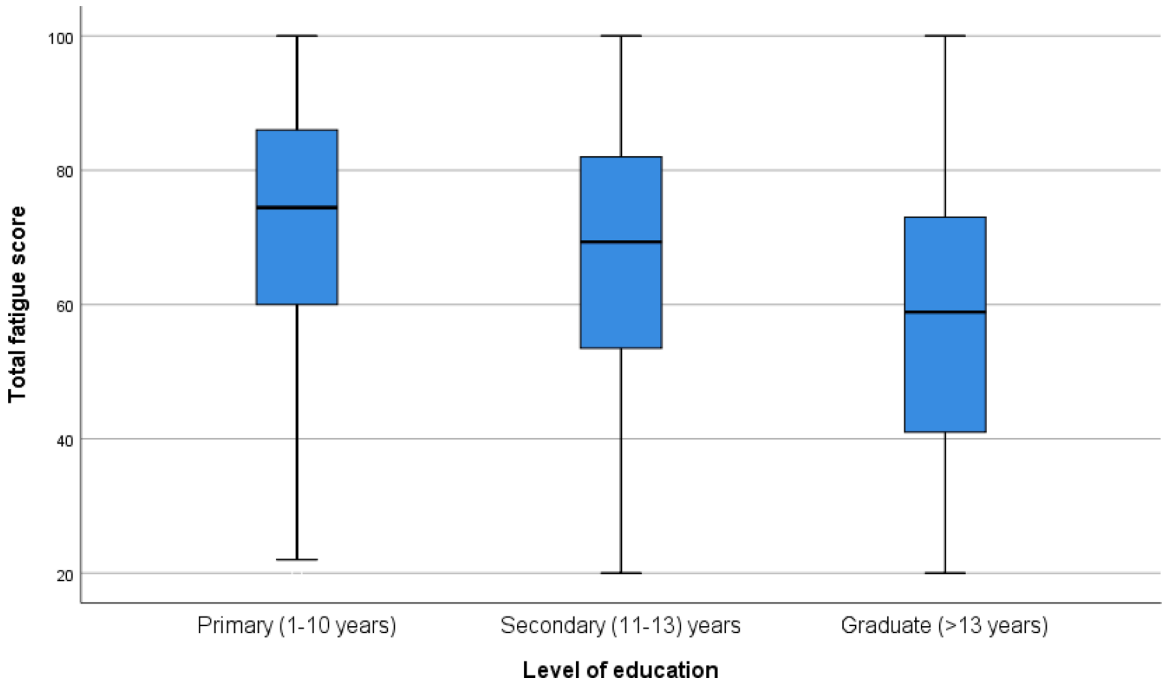

Fig. 1. The fatigue score is inversely related to the level of education.

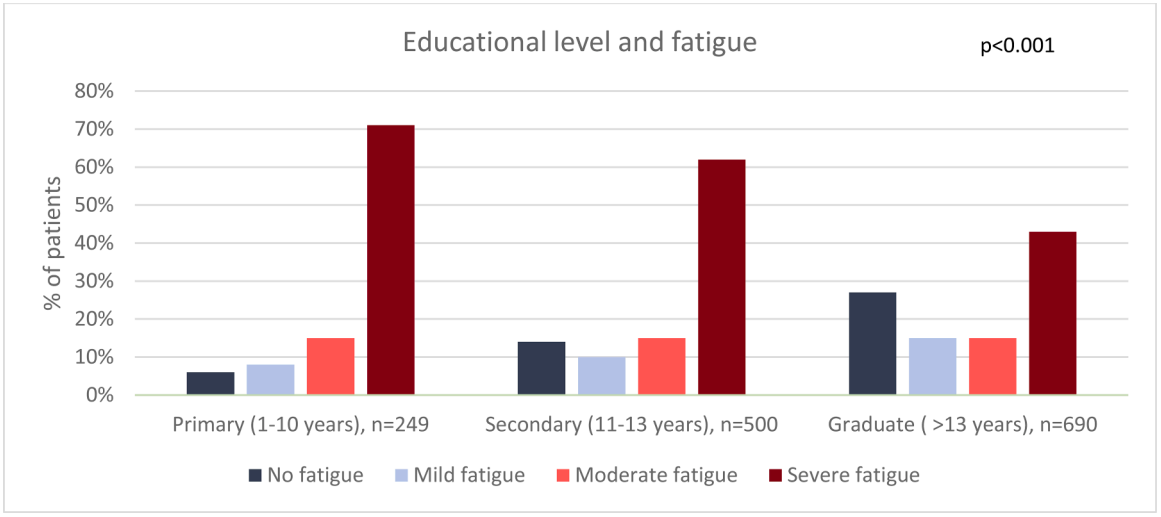

Fig. 2. The prevalence of severe fatigue decreases with increasing level of education.

significantly higher than in pwMS without children (OR = 1.40 (95% CI 1.07–1.82, $p = 0.01$). However, the number of children did not affect the rate or severity of fatigue (Fig. 4).

The mean age was 54 years (SD 12, range 26–87) among the participants who had children, and 50 years (SD 14, range 18–87) among those who did not have children. After adjustment for age, the association between parenthood and the presence of fatigue was no longer significant (adjusted OR = 1.25 (95% CI 0.96–1.64, $p = 0.10$).

6. Work/disability status

As previously described, 1183 out of 1454 of the pwMS had fatigue. Forty-five percent of the patients with fatigue received disability pension versus 15% of the patients without fatigue ($p < 0.001$). The median fatigue score among those who received disability pension was 75 vs 58 among those who did not receive disability pensions ($p < 0.001$). Among the pwMS with severe fatigue, 53% received disability pension.

7. Comorbidities

In this cohort, 20% had one or more additional autoimmune diseases. The prevalence of fatigue in the patients who had concomitant autoimmune disease was 87% versus 80% in the patients without concomitant autoimmune conditions ($p < 0.005$). The mean FSMC score was 67 (SD20) for the pwMS with autoimmune comorbidity and 62 (SD21) for the patients without autoimmune comorbidity ($p < 0.001$). It was 67 (SD±20) for those with one and 70 (SD19) for those with more than one additional autoimmune disease ($p = 0.311$). The pwMS with one or more additional autoimmune disease also had a higher rate of severe fatigue (Fig. 5).

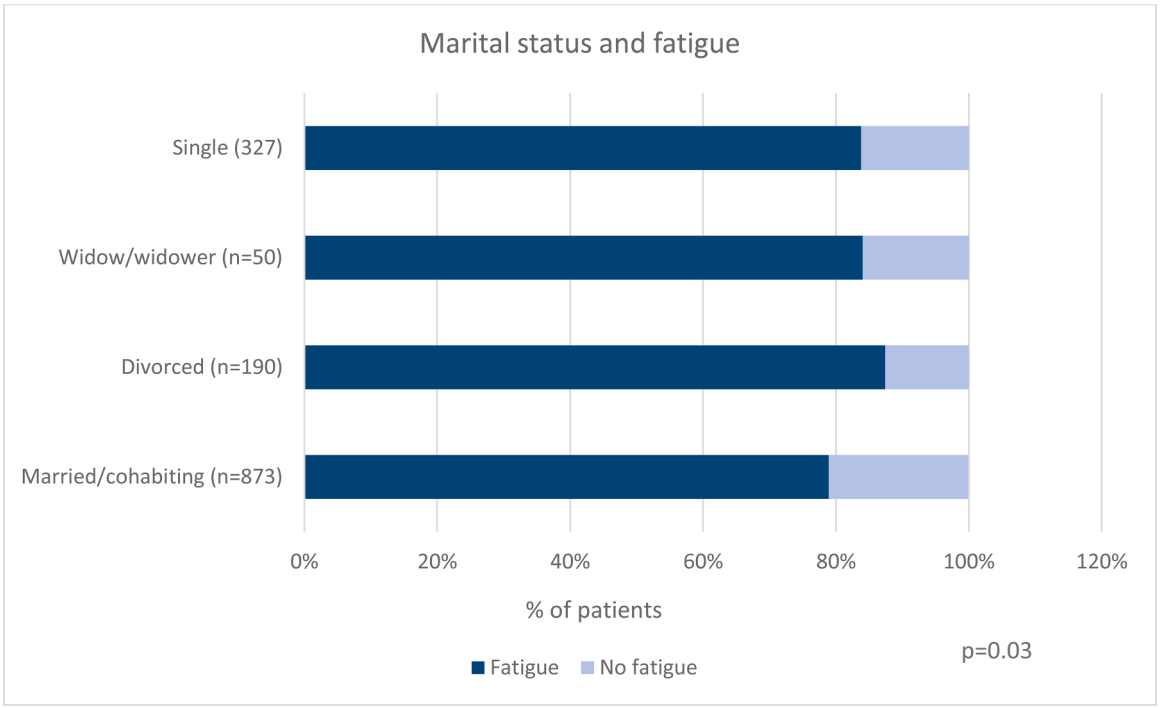

Fig. 3. The prevalence of fatigue was lower among married/cohabitant pwMS.

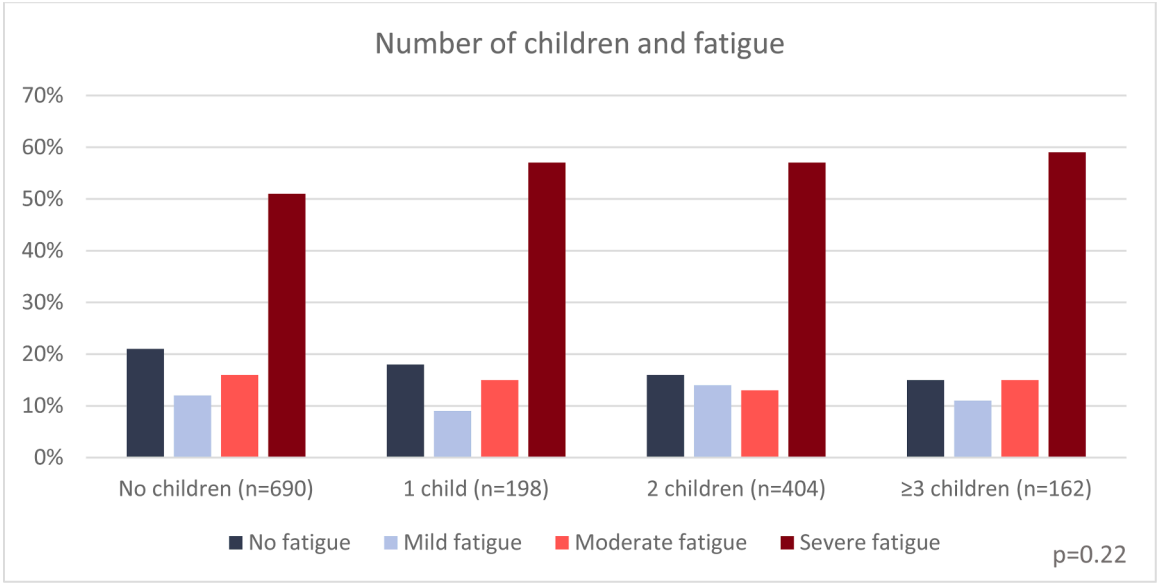

Fig. 4. There was no significant difference in the rate of fatigue in relation to the number of children.

8. Anxiety and depression

Twenty two percent of the participants had depression and 34% had anxiety. In the fatigue group 41% had anxiety and 26% had depression, in the non-fatigue group 11% had anxiety and 1% had depression ($p < 0.001$).

9. Smoking

The rate of fatigue among smokers and ex-smokers was 86% and 83%, respectively, while 76% of the never-smokers had fatigue ($p = 0.001$). Smokers had a mean FSMC score of 66 (SD20), ex-smokers had a mean score of 64 (SD20), and never-smokers had a mean FSMC score of 59 (SD21) ($p < 0.001$). The rate of severe fatigue was 61% among the smokers, 57% among the ex- smokers and 46% among the never-smokers ($p < 0.001$).

10. Self-perceived social status

As shown in Fig. 6, the patients' self-perceived social status declined with increasing level of fatigue, as measured by the McArthur scale.

11. Multivariable analysis

Sex, income, the patients' educational level and disability level (EDSS) were significantly associated with fatigue score in the

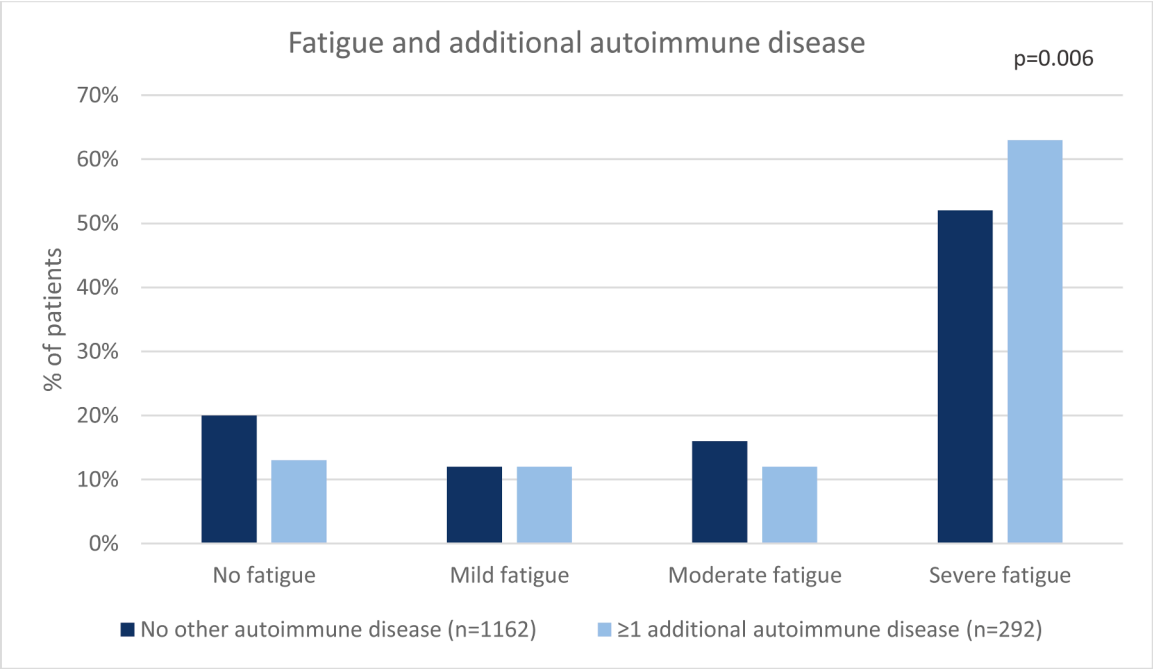

Fig. 5. Having one or more additional autoimmune disease was associated with higher rates of severe fatigue.

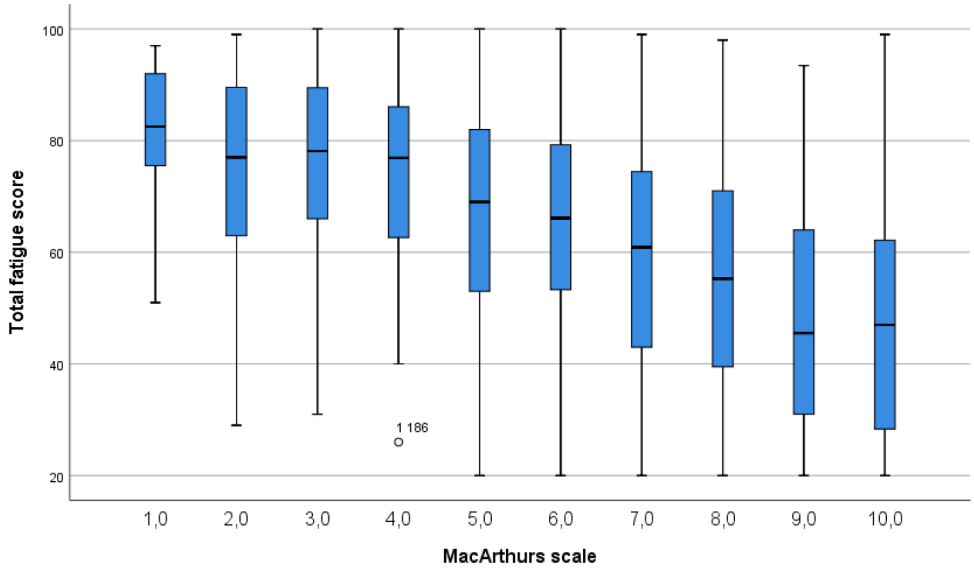

Fig. 6. Self-reported social status and fatigue score

multivariable analysis, as well as receiving disability pension and having anxiety or depression (Table 2).

Having parents with graduate education or a mother with at least secondary education was protective against fatigue score in the univariable analysis. Because receiving disability benefits might be a result of fatigue rather than the other way around, and because fatigue might not only be the cause of but also can cause anxiety and depression, we chose to create an alternative model for the multivariable analysis without these variables. When excluding disability pension, anxiety and depression from the multivariable analysis, sex, EDSS, comorbidity, current smoking, educational level and income remained independently associated with fatigue (Table 2). A low income and a high EDSS was independently associated with a higher fatigue score, whereas a graduate educational level was independently associated with a lower fatigue score. The association between parental education and fatigue did not remain significant in the multivariable analysis. When performing multivariable analyses for cognitive and motor fatigue separately, we found that sex, education and income, as well as anxiety, depression and disability pension were independently associated with both cognitive and motor fatigue, but EDSS was only associated with motor fatigue (Table 3).

12. Discussion

The main finding in this study was that socioeconomic variables are associated with fatigue in pwMS, in particular educational level and income. Married/cohabitant pwMS had less fatigue than divorced pwMS, and those who did not have children had less fatigue then those who had children. In line with a previous study (Lerdal et al., 2003), we found an inverse relationship between educational level and fatigue, as

Table 2
Associations with fatigue score; univariable and multivariable linear regression analysis.

	Univariable analysis		Model 1 (R^2=0.45)		Model 2 (R^2=0.15)	
Variables	B (95% CI)	*P*-value	B (95% CI)	*P*-value	B (95% CI)	*P*-value
Sex, female	3.76 (1.45,6.09)	0.002	4.00 (2.07, 5.94)	<0.001	3.35 (1.11, -5.77)	0.004
Age, years	0.18 (0.10, 0.26)	<0.001	0.02 (-0.06, 0.10)	0.63	-0.10 (-0.20, -0.004)	0.04
Marital status						
Single/widowed	Ref.		Ref.		Ref.	
Married/cohabitant	-3.13(-5.33, -0.93)	0.01	-0.24 (-2.27, 1.79)	0.82	-1.91 (-4.42, 0.60)	0.14
Divorced	3.96 (0.77, 7.14)	0.02	0.82 (-2.10, 3.75)	0.58	0.18 (-3.43, 3.79)	0.92
EDSS closest to 2017	2.37 (1.89, 2.85)	<0.001	1.20 (0.72, 1.68)	<0.001	2.21 (1.65, 2.77)	<0.001
Autoimmune comorbidity	5.34 (2.67, 8.00)	<0.001	0.56 (-1.56, 2.69)	0.60	4.63 (2.04, 7.23)	<0.001
Smoking						
Never	Ref.		Ref.		Ref.	
Current smoker	3.81 (1.40, 6.22)	0.002	-1.55 (-3.83, 0.74)	0.18	3.15 (0.35, 5.95)	0.03
Ex-smoker	1.75 (-0.44, 3.91)	0.12	0.79 (-1.25, 2.82)	0.45	2.35 (-0.15, 4.85)	0.07
Educational level*						
Primary	Ref.		Ref.		Ref.	
Secondary	5.33 (3.09, 7.57)	<0.001	-1.48 (-3.96, 1.01)	0.24	0.78 (-2.81, 4.36)	0.67
Graduate	-11.1 (-13.2, -9.05)	<0.001	-4.07 (-6.69, -1.46)	0.002	6.36 (2.68, 10.0)	0.001
Mothers educational level**						
Primary	Ref.		Ref.		Ref.	
Secondary	-1.80 (-3.97, 0.37)	0.11	-1.00 (-3.04, 1.04)	0.33	-2.36 (-4.87, 0.15)	0.07
Graduate	-7.60 (-10.5, -4.63)	<0.001	0.24 (-2.92, 3.40)	0.88	-2.37 (-6.27, 1.52)	0.23
Fathers educational level*						
Primary	Ref.		Ref.		Ref.	
Secondary	2.45 (0.25, 4.65)	0.03	1.30 (-0.74, 3.35)	0.21	1.78 (-0.76, 4.32)	0.17
Graduate	-8.50 (-11.1, -5.95)	<0.001	-2.06 (-4.86, 0.75)	0.15	-2.35 (-5.83, 1.12)	0.18
Patients total income 2017	-11.4 (-14.7, -8.04)	<0.001	-3.67 (-6.56, 0.78)	0.01	-5.95 (-9.52, -2.38)	0.001
Disability pension/AAP***	15.1 (13.0, 17.1)	<0.001	7.01 (5.12, 8.90)	<0.001		
HADS score						
Anxiety	2.09 (1.86–2.32)	<0.001	0.80 (0.54–1.05)	<0.001		
Depression	3.32 (3.09–3.56)	<0.001	2.31 (2.01–2.61)	<0.001		

Model 1: full model, Model 2: without disability pension/APP, and HADS score
*Educational level: Secondary 11–13 years, graduate >13 years; **Mother/fathers educational level at the patients age 16; ***AAP=Work assessment allowance

well as fatigue severity. We also found that, on average, pwMS with fatigue had lower median personal income and lower household income than the ones without fatigue. PwMS receiving disability pension had more severe fatigue than those who did not.

Parental educational level was also found to be associated with fatigue. Having a father with graduate education or a mother with at least secondary education was associated with less fatigue. Adolescents with well-educated parents may have higher health literacy (Fretian et al., 2020), making them more able to deal with stressors that trigger or exacerbate fatigue. We have previously shown that pwMS who had mothers with higher educational levels had less pronounced disease progression (Flemmen et al., 2021). On the other hand, parental education may be a surrogate marker of an over-all more resourceful background. Parental education did not remain associated with fatigue severity after multivariable adjustment, suggesting that parental education may in itself have little effect on the development of fatigue later in life.

We found that patients with fatigue were more likely to have concomitant autoimmune diseases. The mean FSMC score was higher in patients with autoimmune comorbidity. Fatigue is also a prevalent symptom in several other autoimmune diseases (Zielinski et al., 2019), and having more autoimmune comorbidities seem to increase the fatigue severity. In a Danish study, the researchers evaluated fatigue in relation to disease-specific and socioeconomic factors in patients with rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis (Esbensen et al., 2020). They found that fatigue was more prevalent in women, in "experienced patients", in patients who had changed medication in the past 12 months, were unemployed, had less education, and had lower household income. Thus our findings in pwMS are comparable with other autoimmune diseases.

The prevalence of fatigue was lower in never-smokers compared to current- and ex-smokers. Current smoking was independently associated with fatigue in the regression model in which disability pension, anxiety and depression was not included, but not when these variables were included. In a Danish study, the researchers examined the impact of different lifestyle factors on MS fatigue, including smoking, alcohol habits and physical activity (Johansson et al., 2021). They found that physical activity reduced the impact of fatigue, and that smoking had a negative effect, while alcohol intake was not associated with fatigue.

Higher socioeconomic status is associated with health literacy, healthier risk behavior, and less morbidity (Morkevičius et al., 2020, Muscatell et al., 2020). Highly educated patients may have the ability to cope with fatigue or lead a healthier lifestyle. Conversely, patients with fatigue might have difficulties in obtaining higher education. A low educational level may also be associated with health risk behavior such as smoking and a sedentary lifestyle (Drieskens et al., 2010). Fatigue was less prevalent in married pwMS, but more prevalent among those who had children compared to those with no children. Several studies have shown that being married protects against morbidity, partly because healthy individuals have a greater chance of being selected for marriage (Robards et al., 2012, Rendall et al., 2011) On the other hand, being a parent may leave less time for health promoting behavior such as physical exercise, which is known to reduce fatigue (Asano and Finlayson, 2014).

Education and income were both associated with fatigue in our study. Interestingly, we found that non-fatigued pwMS had a higher educational level and income than the general population. This may suggest that protection against MS-related fatigue requires a socioeconomic standing that is higher than average, and this deserves further studies.

We included the MacArthur scale in the MS questionnaire to assess the patient's own perception of socioeconomic position in society. This tool has hardly been used in MS-research so far, but variants of it have been used in assessment of other chronic and autoimmune diseases (Rafiee et al., 2020, Vassilev et al., 2014). We found that self-perceived SES was just as associated with fatigue as were the objective measures of socioeconomic factors, as shown in Fig. 6. This may be an expression of the impact fatigue has on perceived social status, in the same way that

Table 3
Associations with cognitive and motor fatigue score; multivariable linear regression analysis.

Variables	Cognitive fatigue B (95% CI)	*P*-value	Motor fatigue B (95% CI)	*P*-value
Sex, female	2.458 (1.421, 3.495)	<0.001	1.546 (0.525, 2.566)	0.003
Age, years	0.005 (-0.040, 0.049)	0.84	0.016 (-0.028, 0.059)	0.48
Marital status				
Single/Widowed	Ref.		Ref.	
Married/cohabitant	-0.039 (-1.127, 1.049)	0.94	-0.196 (-1.267, 0.875)	0.72
Divorced	0.755 (-0.814, 2.324)	0.35	0.068 (-1.476, 1.613)	0.93
EDSS closest to 2017	0.157 (-0.099, 0.413)	0.23	1.041 (0.790, 1.293)	<0.001
Autoimmune comorbidity	-0.014 (-1.152, 1.123)	0.98	0.578 (-0.542, 1.698)	0.31
Smoking				
Never	Ref.		Ref.	
Current smoker	-0.986 (-2.212, 0.240)	0.12	-0.563 (-1.770, 0.644)	0.36
Ex-smoker	0.506 (-0.585, 1.597)	0.36	0.280 (-0.793, 1.354)	0.61
Educational level*				
Primary	Ref.		Ref.	
Secondary	-0.880 (-2.211, 0.450)	0.20	-0.595 (-1.904, 0.715)	0.37
Graduate	-2.107 (-3.502, -0.712)	0.003	-1.959 (-3.332, -0.586)	0.005
Mothers educational level**				
Primary	Ref.		Ref.	
Secondary	-0.536 (-1.631. 0.559)	0.34	-0.463 (-1.541, 0.614)	0.40
Graduate	0.301 (-1.392, 1.995)	0.73	-0.060 (-1.727, 1.607)	0.94
Fathers educational level**				
Primary	Ref.		Ref.	
Secondary	0.811 (-0.286, 1.908)	0.15	0.492 (-0.588, 1.572)	0.37
Graduate	-0.930 (-2.431, 0.572)	0.23	-1.125 (-2.603, 0.353)	0.14
Patients total income 2017	-1.822 (-3.372, -0.272)	0.02	-1.849 (-3.375, -0.323)	0.02
Disability pension/ AAP***	3.773 (2.760, 4.785)	<0.001	3.239 (2.242, 4.235)	<0.001
HADS score				
Anxiety	0.492 (0.355, 0.629)	<0.001	0.304 (0.169, 0.439)	<0.001
Depression	1.175 (1.014, 1.336)	<0.001	1.136 (0.978, 1.295)	<0.001

*Educational level: Secondary 11–13 years, graduate >13 years; **Mother/fathers educational level at the patients age 16; ***AAP=Disability benefits

fatigue has been found to reduce the quality of life in pwMS (Gil-González et al., 2020, Berrigan et al., 2016).

13. Strengths and limitations

The strengths of our study is the size and the geographically well-defined, population-based and thoroughly examined cohort. The patient-reported outcomes were collected through validated questionnaires, whereas disease specific information was gathered from the electronic medical record system by three experienced neurologists in our research group. Governmental agencies were the source of data regarding income, education and marital status, eliminating recall bias.

This is a cross-sectional study that cannot establish causality. We evaluated fatigue by self-report questionnaires. Fatigue is a subjective symptom for which we have no objective measures. With regard to marital status, cohabitant was not registered as a separate category. Therefore, some patients registered as single may in fact be cohabitant. Some of the patients registered as receiving disability pension might actually be old-age pensioners who have used their option to retire early from the age of 62.

14. Conclusion

Our results suggest that demographic and socioeconomic factors should be taken into account when counselling patients and when devising management strategies. A short education, low income and a lack of employment seem to be associated with fatigue independent of disease severity, age and gender. These sociodemographic factors can identify patients who may be at particular risk of suffering from fatigue, and who may require extra attention and close follow-up.

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 and Biogen.

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

PBH has received an unrestricted research grant from Novartis and 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 Novartis and Sanofi, and advisory board and/or speaker honoraria from Biogen, Merck, Roche, Novartis, Sanofi and Teva.

Acknowledgment

We would like to thank all the pwMS that were included in this study.

References

Berg-Hansen, P., Moen, S.M., Harbo, H.F., Celius, E.G., 2014. High prevalence and no latitude gradient of multiple sclerosis in Norway. Mult. Scler. 20 (13), 1780–1782.
Simonsen, C.S., Edland, A., Berg-Hansen, P., Celius, E.G., 2017. High prevalence and increasing incidence of multiple sclerosis in the Norwegian county of Buskerud. Acta Neurol. Scand. 135 (4), 412–418.
Simonsen, C.S., Flemmen, H., Broch, L., Brunborg, C., Berg-Hansen, P., Moen, S.M., et al., 2021. The course of multiple sclerosis rewritten: a Norwegian population-based study on disease demographics and progression. J. Neurol. 268 (4), 1330–1341.
Smith, M.M., Arnett, P.A., 2005. Factors related to employment status changes in individuals with multiple sclerosis. Mult. Scler. 11 (5), 602–609.
Hadjimichael, O., Vollmer, T., Oleen-Burkey, M., 2008. Fatigue characteristics in multiple sclerosis: the North American research committee on multiple sclerosis (NARCOMS) survey. Health Qual. Life Outcomes 6, 100.

Marrie, R.A., Cutter, G., Tyry, T., Hadjimichael, O., Campagnolo, D., Vollmer, T., 2005. Validation of the NARCOMS registry: fatigue assessment. Mult. Scler. 11 (5), 583–584.
Multiple Sclerosis Council for Clinical Practice Guidelines, 1998. Fatigue and Multiple Sclerosis: Evidence-Based Management Strategies for Fatigue in Multiple Sclerosis. Paralyzed Veterans of America, Washington, DC.
Krupp, L.B., Serafin, D.J., Christodoulou, C., 2010. Multiple sclerosis-associated fatigue. Expert. Rev. Neurother. 10 (9), 1437–1447.
Lerdal, A., Celius, E.G., Moum, T., 2003. Fatigue and its association with sociodemographic variables among multiple sclerosis patients. Mult. Scler. 9 (5), 509–514.
Rooney, S., Wood, L., Moffat, F., Paul, L., 2019. Prevalence of fatigue and its association with clinical features in progressive and non-progressive forms of multiple sclerosis. Mult. Scler. Relat. Disord. 28, 276–282.
Kister, I., Bacon, T.E., Chamot, E., Salter, A.R., Cutter, G.R., Kalina, J.T., et al., 2013. Natural history of multiple sclerosis symptoms. Int. J. MS Care 15 (3), 146–158.
Broch, L., Simonsen, C.S., Flemmen, H., Berg-Hansen, P., Skardhamar, Å., Ormstad, H., et al., 2021. High prevalence of fatigue in contemporary patients with multiple sclerosis. Mult. Scler. J. Exp. Transl. Clin. 7 (1), 2055217321999826.
Kivimäki, M., Batty, G.D., Pentti, J., Shipley, M.J., Sipilä, P.N., Nyberg, S.T., et al., 2020. Association between socioeconomic status and the development of mental and physical health conditions in adulthood: a multi-cohort study. Lancet Public Health 5 (3), e140–e1e9.
Goulden, R., Ibrahim, T., Wolfson, C., 2015. Is high socioeconomic status a risk factor for multiple sclerosis? A systematic review. Eur. J. Neurol. 22 (6), 899–911.
Nielsen, N.M., Jørgensen, K.T., Bager, P., Stenager, E., Pedersen, B.V., Hjalgrim, H., et al., 2013. Socioeconomic factors in childhood and the risk of multiple sclerosis. Am. J. Epidemiol. 177 (11), 1289–1295.
Bjørnevik, K., Riise, T., Benjaminsen, E., Celius, E.G., Dahl, O.P., Kampman, M.T., et al., 2017. Level of education and multiple sclerosis risk over a 50-year period: registry-based sibling study. Mult. Scler. 23 (2), 213–219.
Flemmen, H., Simonsen, C.S., Broch, L., Brunborg, C., Berg-Hansen, P., Moen, S.M., et al., 2021. Maternal education has significant influence on progression in multiple sclerosis. Mult. Scler. Relat. Disord. 53, 103052.
Calixto, O.J., Anaya, J.M., 2014. Socioeconomic status. The relationship with health and autoimmune diseases. Autoimmun. Rev. 13 (6), 641–654.
Nourbakhsh, B., Revirajan, N., Morris, B., Cordano, C., Creasman, J., Manguinao, M., et al., 2021. Safety and efficacy of amantadine, modafinil, and methylphenidate for fatigue in multiple sclerosis: a randomised, placebo-controlled, crossover, double-blind trial. Lancet Neurol. 20 (1), 38–48.
Rottoli, M., Gioia, S.L., Frigeni, B., Barcella, V., 2017. Pathophysiology, assessment and management of multiple sclerosis fatigue: an update. Expert. Rev. Neurother. 17 (4), 373–379.
Kobelt, G., Thompson, A., Berg, J., Gannedahl, M., Eriksson, J., 2017. New insights into the burden and costs of multiple sclerosis in Europe. Mult. Scler. 23 (8), 1123–1136.
WM Association, 2013. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects, 310. World Medical Association, pp. 2191–2194. JAMA.
Penner, I.K., Raselli, C., Stocklin, M., Opwis, K., Kappos, L., Calabrese, P., 2009. The fatigue scale for motor and cognitive functions (FSMC): validation of a new instrument to assess multiple sclerosis-related fatigue. Mult. Scler. 15 (12), 1509–1517.
Bjelland, I., Dahl, A.A., Haug, T.T., Neckelmann, D., 2002. The validity of the hospital anxiety and depression scale. An updated literature review. J. Psychosom. Res. 52 (2), 69–77.
Svenningsson, A., Falk, E., Celius, E.G., Fuchs, S., Schreiber, K., Berkö, S., et al., 2013. Natalizumab treatment reduces fatigue in multiple sclerosis. Results from the TYNERGY trial; a study in the real life setting. PLoS One 8 (3), e58643.
Leiknes, K., Dalsbø, T.K., Siqveland, J., 2016. Psychometric Assessment of the Norwegian Version of the Hosptial Anxiety and Depression Scale (HADS). Institute of Public Health, Health DoP, Oslo, Norway.
Giatti, L., Camelo Ldo, V., Rodrigues, J.F., Barreto, S.M., 2012. Reliability of the MacArthur scale of subjective social status - Brazilian longitudinal study of adult health (ELSA-Brasil). BMC Public Health 12, 1096.
Kurtzke, J.F., 1983. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 33 (11), 1444–1452.
von Bismarck, O., Dankowski, T., Ambrosius, B., Hessler, N., Antony, G., Ziegler, A., et al., 2018. Treatment choices and neuropsychological symptoms of a large cohort of early MS. Neurol. Neuroimmunol. Neuroinflamm. 5 (3), e446.
Fretian, A., Bollweg, T.M., Okan, O., Pinheiro, P., Bauer, U., 2020. Exploring associated factors of subjective health literacy in school-aged children. Int. J. Environ. Res. Public Health 17 (5), 1720.
Zielinski, M.R., Systrom, D.M., Rose, N.R., 2019. Fatigue, sleep, and autoimmune and related disorders. Front. Immunol. 10, 1827.
Esbensen, B.A., Stallknecht, S.E., Madsen, M.E., Hagelund, L., Pilgaard, T., 2020. Correlations of fatigue in Danish patients with rheumatoid arthritis, psoriatic arthritis and spondyloarthritis. PLoS One 15 (8), e0237117.
Johansson, S., Skjerbæk, A.G., Nørgaard, M., Boesen, F., Hvid, L.G., Dalgas, U., 2021. Associations between fatigue impact and lifestyle factors in people with multiple sclerosis - the Danish MS hospitals rehabilitation study. Mult. Scler. Relat. Disord. 50, 102799.
Morkevičius, V., Norkus, Z., Markevičiūtė, J., 2020. Risky health behaviours and socioeconomic inequalities in European countries: new insights from European social survey. Cent. Eur. J. Public Health 28 (4), 251–259.
Muscatell, K.A., Brosso, S.N., Humphreys, K.L., 2020. Socioeconomic status and inflammation: a meta-analysis. Mol. Psychiatry 25 (9), 2189–2199.
Drieskens, S., Van Oyen, H., Demarest, S., Van der Heyden, J., Gisle, L., Tafforeau, J., 2010. Multiple risk behaviour: increasing socio-economic gap over time? Eur. J. Public Health 20 (6), 634–639.
Robards, J., Evandrou, M., Falkingham, J., Vlachantoni, A., 2012. Marital status, health and mortality. Maturitas 73 (4), 295–299.
Rendall, M.S., Weden, M.M., Favreault, M.M., Waldron, H., 2011. The protective effect of marriage for survival: a review and update. Demography 48 (2), 481–506.
Asano, M., Finlayson, M.L., 2014. Meta-analysis of three different types of fatigue management interventions for people with multiple sclerosis: exercise, education, and medication. Mult. Scler. Int. 2014, 798285.
Rafiee, F., Tarjoman, T., Moghadasi, A.N., Sahraian, M.A., Azimi, A., Rezaeimanesh, N., et al., 2020. Stressful life events, socioeconomic status, and the risk of neuromyelitis optica spectrum disorder: a population-based case-control study. Mult. Scler. Relat. Disord. 46, 102544.
Vassilev, I., Rogers, A., Sanders, C., Cheraghi-Sohi, S., Blickem, C., Brooks, H., et al., 2014. Social status and living with a chronic illness: an exploration of assessment and meaning attributed to work and employment. Chronic Illn. 10 (4), 273–290.
Gil-González, I., Martín-Rodríguez, A., Conrad, R., Pérez-San-Gregorio, M., 2020. Quality of life in adults with multiple sclerosis: a systematic review. BMJ Open 10 (11), e041249.
Berrigan, L.I., Fisk, J.D., Patten, S.B., Tremlett, H., Wolfson, C., Warren, S., et al., 2016. Health-related quality of life in multiple sclerosis: direct and indirect effects of comorbidity. Neurology 86 (15), 1417–1424.