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Original article

Associations between fatigue impact and lifestyle factors in people with multiple sclerosis – The Danish MS hospitals rehabilitation study

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ABSTRACT

Background: The lack of medical treatment options to reduce fatigue in patients with multiple sclerosis (MS) emphasize the importance of identifying potential non-pharmacological modifiable factors, as this may help advance current treatment strategies. The aim of this study was to identify potential modifiable lifestyle factors as well as patient- and disease-related characteristics, that are associated with fatigue in a large sample of clinically well-characterized patients with MS.

Methods: This study was a secondary analysis of a pragmatic randomized controlled trial of inpatient multidisciplinary rehabilitation in Denmark. MS patients aged 18 to 65 years and with a disease severity score ≤ 7.5 according to the Expanded Disability Status Scale participated. Data on patient- and disease-related characteristics, fatigue impact (Modified Fatigue Impact Scale (MFIS)), and on lifestyle factors (tobacco smoking, alcohol intake, and physical activity), were collected at baseline.

A linear mixed model was used to compare MFIS *total, physical, cognitive*, and *psychosocial* scores across subgroups of selected characteristics. Regression analyses were used to examine associations between lifestyle factors and MFIS *total, physical, cognitive*, and *psychosocial* scores.

Results: In the sample of 417 MS patients, median age was 51 years, 69% were female, median time since diagnosis was 8 years, with 41% having relapsing remitting MS.

Higher MFIS *total* scores were observed in MS patients with shorter time since diagnosis, being a tobacco smoker, and not undertaking regular physical activity. Somewhat similar findings were observed for MFIS subscores (*physical, cognitive, psychosocial*), especially MFIS *physical* scores.

In the multivariate analyses, physical activity was significantly associated with fatigue impact on total, physical and psychosocial functioning. Tobacco smoking was significantly associated with fatigue impact on psychosocial functioning. Alcohol intake was not associated with fatigue impact. None of the lifestyle factors were associated with fatigue impact on cognitive functioning. In the adjusted models time since diagnosis was significantly associated with fatigue impact on total, physical and cognitive functioning, as was disease severity with fatigue impact on physical and cognitive functioning.

Conclusion: Physical activity showed the most pronounced associations with fatigue impact on physical and psychosocial functioning, while the impact on cognitive functioning showed a trend. Tobacco smoking contributed significantly to impact on psychosocial functioning, while alcohol intake did not contribute to fatigue impact. Introducing or supporting maintenance of physical activity/exercise and cessation of tobacco smoking seems to be a useful approach for rehabilitation services to help patients with MS manage fatigue.

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory and degenerative disease in the central nervous system (CNS), causing long-term disability (Compston and Coles, 2008). Depending on the site of lesions in the CNS people with MS experience varying combinations of smoldering and significant disabilities (Kesselring and Beer, 2005; Khan et al., 2007) of neuropsychological nature (cognitively, energetically and mood wise) as well as a wide range of physical impairments affecting mobility and ambulation. As a consequence, people with MS are often afflicted by a substantial negative impact on health status, limitations in daily activities, restrictions in participation in work life and leisure activities (Kesselring and Beer, 2005; Holper et al., 2010; Johansson et al., 2020).

Fatigue, defined in MS as a lack of physical and/or mental energy perceived by the individual to interfere with usual and desired activities (Multiple Sclerosis Council for Clinical Practice Guidelines 1998), is reported by up to 80% of people with MS (Giovannoni, 2006) (Johansson et al., 2007). Fatigue is measured with subjective self-rating scales, but its associations with objective measures of physical or mental performance are often weak [(Dalgas et al., 2018) (Bailey et al., 2007)], reflecting the discrepance between perceptions of fatigue and performance fatigability (Kluger et al., 2013). In qualitative research, fatigue has been found to cause dependency and restrictions in life interfering with one's vital goals and influencing all decisions regarding how to manage being active, responsible and participating in valued societal activities (Flensner et al., 2003). Furthermore, fatigue is a key impairment associated with limited work ability (Flensner et al., 2013; Sweetland et al., 2012) and with worse quality of life (Amato et al., 2001; Pittion-Vouyovitch et al., 2006). Interestingly, there is no consensus regarding fatigues associations neither with age nor sex (Kos et al., 2008).

The underlying mechanisms explaining MS-related fatigue are poorly understood but can be separated into primary and secondary mechanisms, i.e., directly related to the disease mechanisms or caused by non-disease-specific factors. A recent review (Langeskov-Christensen et al., 2017) concluded that the main pathophysiological reason for primary fatigue is dysfunctional neuronal circuits. Among contributing secondary pathways, impaired sleep (Kos et al., 2008; Krupp et al., 2010), depressive symptoms, cognitive impairment and physical deconditioning (Langeskov-Christensen et al., 2017; Krupp et al., 2010; Pilutti et al., 2013) are often reported to be associated with fatigue and reduced activity (Kos et al., 2008; Langeskov-Christensen et al., 2017; Krupp et al., 2010; Pilutti et al., 2013).

It is well-known that lifestyle factors influence health and function in the general population (de Frias and Dixon, 2014). This has directed MS research to begin investigating potential associations between lifestyle factors and fatigue. In people with MS it has been found that modifiable lifestyle factors such as physical activity (Motl and Pilutti, 2012; Reider et al., 2017), diet (Hadgkiss et al., 2015; Strober et al., 2018), body mass index (Leong et al., 2018; Marck et al., 2016), alcohol intake (Weiland et al., 2014), tobacco smoking (Weiland et al., 2014; Di Pauli et al., 2008; Kahraman et al., 2020), social support (Schwartz and Frohner, 2005) and engagement in social activities (Pittion-Vouyovitch et al., 2006; D'hooghe et al., 2013) are associated with quality of life, and studies have suggested that a healthy lifestyle behavior influence disease progression (D'hooghe et al., 2013; Stuifbergen et al., 2006). Increased physical exercise (Pilutti et al., 2013; Bansi et al., 2013; Kierkegaard et al., 2016), better diet (Albrechtsen et al., 2020) and non-smoking (Kahraman et al., 2020) have shown potential to reduce fatigue, whereas no association has been reported for alcohol intake (Bombardier et al., 2004). Recently, a large-numbered study ($n = 6989$) reported that a combination of lifestyle factors (a composite implying adherence to better diet, lower body mass index, non-smoking, and engagement in physical activity) contributed to reduced fatigue (Fitzgerald et al., 2018). However, the study was solely based on patient reported outcomes, limiting the validity of the reported clinical and physical data and, further, only a composite score of the studied lifestyle factors was analyzed.

Taken together, the lack of significant medical treatment options to reduce fatigue in patients with MS emphasize the importance of identifying non-pharmacological modifiable lifestyle factors as this may help advance current treatment strategies. Therefore, the aim of the present study was to identify potential modifiable lifestyle factors, as well as patient- and disease-related characteristics, that are associated with fatigue in a large sample of clinically well-characterized patients with MS.

Methods

This study was a secondary analysis of a pragmatic randomized controlled trial performed in Denmark – The Danish MS Hospitals Rehabilitation Study. A detailed description of the main study is presented in the study protocol (Sorensen et al., 2012) and in previously published papers (Boesen et al., 2020); (Boesen et al., 2018); (Skjerbaek et al., 2019). In the present paper, data on the presence of fatigue and its associations with various lifestyle and other contributing factors are reported. The study was approved by the Danish Research Ethics Committee (No 1–01–83–0002–07) and registered at www.controlled-trials.com (ISRCTN05245917). The Danish Data Authority granted permission to collect and store the required project information (No 2011-41-6751).

Participants

MS patients referred to four weeks of inpatient multidisciplinary rehabilitation at one of the two MS hospitals in Denmark, Ry and Haslev, from March 2012 to June 2014 were recruited to the study. The recruitment process was performed by a study coordinator followed by a consultation with a neurologist who made the final decision about inclusion (Sorensen et al., 2012; Boesen et al., 2018). All participants received information about the study and written informed consent was obtained before enrolment.

Only patients diagnosed with MS and aged between 18 and 65 years were included. A disease severity score ≤ 7.5 according to the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) was allowed and patients had to be familiar with computer use. MS patients were excluded if they were diagnosed within the previous six months, had experienced a relapse within the previous three months, had participated in inpatient rehabilitation during the previous six months, had an EDSS cognitive subscale score >2 (implying moderate cognitive impairment) or any other illness present that could hinder participation.

Measurements

Data were collected with patient-reported questionnaires delivered to each participant online and filled in electronically. Via a study specific questionnaire, data on age, sex, living situation, having children < 18 years of age living at home, education level, and work status were collected. Further questions were related to height, weight, status of tobacco smoking, alcohol intake, and physical activity level. Furthermore, information on time since diagnosis, MS type, and disease modifying treatment was obtained by the neurologist. Disease severity was scored by the neurologist using the EDSS (Kurtzke, 1983). Mood was assessed using the Beck Depression Inventory II (Beck et al., 1996).

The Modified Fatigue Impact Scale (MFIS) (Multiple Sclerosis Council for Clinical Practice Guidelines 1998) was used as a measure of impact of fatigue on common daily activities. The MFIS was created by shortening the 40-item original Fatigue Impact Scale (Fisk et al., 1994). The MFIS items were selected by the National Multiple Sclerosis Society and resulted in 21 of the original items, which can be aggregated into a total sum score, and into subscales for physical (nine items), cognitive (ten items), and psychosocial (two items) functioning (Multiple Sclerosis Council for Clinical Practice Guidelines 1998). Good psychometric properties of the MFIS scale have been reported across several European

translations of the MFIS scale (Kos et al., 2005). The Danish version of the MFIS has not been formally validated but is widely accepted in the medical community and frequently used in Danish MS fatigue studies.

Analyses

Statistical analyses were carried out using Stata, version 14.2 (StataCorp LP, Texas, USA).

Descriptive statistics were in the first part (i.e. when presenting participants in Table 1) used to present demographics (sex, age, living situation, children < 18 years of age at home, work status and education level), and to present disease-related characteristics (time since diagnosis, MS type, disease severity, disease modifying treatment), and depressive symptoms. Data non-normally distributed are presented as median (interquartile range).

In the second part (i.e. when comparing subgroups in Table 2), a linear mixed model was used to compare MFIS *total, physical, cognitive*, and *psychosocial* scores across subgroups of selected characteristics (sex, age, body mass index, time since diagnosis, MS type, disease severity, tobacco smoking, alcohol intake, and physical activity) with subject set as a random effect and subgroup as a fixed effect. The a priori defined selection of variables included as possible adjustors in the regression analyses was partly based on existing literature on plausible associations with fatigue and fatigue impact (Lerdal et al., 2007; Strober et al., 2020), and partly on our clinical experience on plausible associations.

In the third part (i.e. when evaluating adjusted associations in Table 3), simple regression analyses along with multivariate regression analyses were used to examine associations between lifestyle factors and MFIS *total, physical, cognitive*, and *psychosocial* scores. In the simple regression analyses associations between each lifestyle factor separately (tobacco smoking, alcohol intake, physical activity) and MFIS scores were examined. In the multivariate regression analyses associations between the lifestyle factors combined and the different MFIS scores were examined (Model 1), along with adjustments for age and sex (Model 2) and with adjustments for time since diagnosis, MS type, disease severity and disease modifying treatment (Model 3). Prior to the second and third parts of the analyses, data were shown to be normally distributed (histograms and q-q-plots of residuals) and absent of heteroscedasticity (Breusch Pagan test) and multicollinearity (variance inflation factor). These data are presented as R^2-values and p-values for the overall models, along with coefficients (representing how much the variable can alter MFIS scores), standardized beta values (representing how much each variable contribute to influencing MFIS scores), and p-values for variables included in each model. The statistical significance levels were set at $p<0.01$ to account for multiple analysis, while a $p-$level of $0.05>p>0.01$ was considered a trend. Data are presented as mean ± standard deviation (SD) or mean (95% confidence interval [CI]).

Table 1
Demographics and disease-related characteristics in patients with MS who completed the Modified Fatigue Impact Scale ($n = 417$).

Variables and instruments	Criteria for categorization	$N = 417$
Age[a]	Years, median (IQR)	51 (44, 57)
Sex	Female / Male, n (%)	286 (69) / 131 (31)
Living situation ($n = 414$)	Co-habiting / Living alone, n (%)	289 (70) / 125 (30)
Children < 18 years at home ($n = 414$)	Yes / No, n (%)	118 (29) / 296 (71)
Education level ($n = 414$)	7 to 9 years, n (%)	68 (16.5)
	10 to 11 years, n (%)	150 (36.5)
	11 to 12 years, n (%)	100 (24)
	> 12 years, n (%)	96 (23)
Work status ($n = 414$)	Working full time, n (%)	14 (3.5)
	Working part time, n (%)	70 (17)
	Job applicant	22 (5.5)
	Retirement[b] (n (%)	265 (64)
	Sickness absence, n (%)	43 (10)
Time since diagnosis[a]	Years, median (IQR)	8 (3, 15)
MS type	Relapsing remitting, n (%)	169 (41)
	Secondary progressive, n (%)	181 (43)
	Primary progressive, n (%)	67 (16)
Disease severity	EDSS[c], median (IQR); mean (SD)	4.5 (3.5, 6.5); 4.8 (1.5)
	EDSS[c] 0 − 3.5, n (%)	121 (29)
	EDSS[c] 4 − 5.5, n (%)	136 (32.5)
	EDSS[c] 6 − 6.5, n (%)	144 (34.5)
	EDSS[c] 7 − 7.5, n (%)	16 (4)
Disease modifying treatment	Yes / No, n (%)	222 (53) / 195 (47)
Depressive symptoms	Yes / No, n (%)	185 (44) / 232 (56)

[a] Continuous data are presented as median (IQR).
[b] Retirement –due to disability, ($n = 254$); due to age, ($n = 8$); being housewife/-husband, ($n = 3$).
[c] EDSS = Expanded Disability Status Scale.

Results

From March 2012 to May 2014, 427 MS patients were included for participation in the pragmatic randomized controlled trial forming the main study of the present investigation ((Sorensen et al., 2012); (Boesen et al., 2018)). Of those, 417 MS patients completed the MFIS at study entry and were subsequently included in the present study. Demographics and disease-related characteristics of this sample are presented in Table 1. Median age was 51 years, 69% were female, median time since diagnosis was 8 years with 41% having relapsing remitting MS. A total of 29% had no serious walking limitation (EDSS ≤4.0), 32.5% could walk 100 m without walking aid (EDSS ≤5.5), 34.5% were dependent of walking aid (EDSS 6 − 6.5) and 4% primarily used a wheelchair when moving around (EDSS 7 − 7.5).

In the whole sample, the mean MFIS *total* score was 39.7 points, whereas the mean scores on *cognitive, physical* and *psychosocial* functioning were 16.8, 19.6 and 3.3 points, respectively (Table 2).

Subgroup comparisons

As shown in Table 2, higher MFIS *total* scores were observed in patients with shorter time since diagnosis, being a tobacco smoker, and not undertaking regular physical activity. Somewhat similar findings were observed for the different MFIS sub-scores (*physical, cognitive, psychosocial*), especially MFIS *physical scores*.

Simple and multivariate regression analyses

The simple regression analysis revealed that tobacco smoking and physical activity were both associated with the MFIS *total* score, *physical* score, and *psychosocial* score (Table 2). Tobacco smoking showed a trend towards being associated with MFIS *cognitive* score, whereas alcohol intake was not associated with any MFIS scores (Table 2).

Overall, the multivariate analyses (Model 1, 2, and 3) with MFIS *total, physical* and *psychosocial* scores as dependent variables, respectively, were all significant, i.e. revealing that the chosen lifestyle factors (without/with adjustment for age and gender in Model 2, and addition of without/with adjustment for disease-related characteristics in Model 3) were associated with the MFIS *total, physical* and *psychosocial* scores (with 5% to 12% of the variance explained). Only physical activity was consistently and significantly associated with the MFIS *total* and *physical* scores, while physical activity and tobacco smoking consistently were significantly associated with the MFIS *psychosocial* scores. Also, tobacco smoking showed a trend towards associations with the MFIS *total* and *physical* scores. In the multivariate analyses with the MFIS *cognitive* score as the dependent variable, only Model 3 was significant, with no lifestyle factor significantly associated (Table 3).

Physical activity (β=0.18, $p<0.01$) was significantly associated with the MFIS *total* score in the unadjusted model (r^2=0.05, $p<0.01$). The contribution of physical activity to the MFIS *total* score remained in both

Table 2
Impact of fatigue in different MS subgroups.

Variables	Modified Fatigue Impact Scale Total impact *mean (95% CI[1])*	*p value*	Physical impact *mean (95% CI[1])*	*p value*	Cognitive impact *mean (95% CI[1])*	*p value*	Psychosocial impact *mean (95% CI[1])*	*p value*
All (n = 417)	39.7 (38.3 – 41.1)		19.6 (19.0 – 20.3)		16.8 (15.9 – 17.6)		3.3 (3.1 – 3.5)	
Demographic and physical characteristics								
Sex (n = 417)								
Female	39.0 (37.3 – 40.6)	0.118	19.2 (18.4 – 20.0)	0.052	16.6 (15.6 – 17.6)	0.493	3.2 (3.0 – 3.4)	0.109
Male	41.3 (38.8 – 43.8)		20.6 (19.4 – 20.8)		17.2 (15.8 – 18.6)		3.5 (3.2 – 3.8)	
Age (n = 417)								
< 51 years of age	40.5 (38.4 – 42.6)	0.262	19.2 (18.2 – 20.3)	0.265	17.9 (16.7 – 19.1)	0.007	3.3 (3.1 – 3.6)	0.694
≥ 51 years of age	39.0 (37.2 – 40.8)		20.0 (19.2 – 20.9)		15.7 (14.6 – 16.8)		3.3 (3.0 – 3.5)	
Body mass index (n = 414)								
Normal (< 25.0) (n = 226)	39.2 (37.4 – 41.1)	0.538	19.6 (18.7 – 20.5)	0.976	16.3 (15.2 – 17.4)	0.321	3.3 (3.0 – 3.5)	0.967
Overweight (≥25.0) (n = 188)	40.1 (38.0 – 42.1)		19.6 (18.6 – 20.6)		17.2 (15.9 – 18.4)		3.3 (3.0 – 3.5)	
Disease-related characteristics								
Time since diagnosis (n = 417)								
< 8 years	42.4 (40.5 – 44.4)	0.000	20.7 (19.7 – 21.6)	0.003	18.2 (17.0 – 19.4)	0.000	3.5 (3.2 – 3.8)	0.046
≥ 8years	37.2 (35.4 – 39.1)		18.7 (17.8 – 19.6)		15.4 (14.3 – 16.5)		3.1 (2.9 – 3.4)	
Type (n = 417)								
Relapsing remitting (n = 169)	40.1 (38.0 – 42.3)	0.835	18.8 (17.7 – 19.8)	0.079	18.3 (17.0 – 19.5)	0.010	3.1 (2.8 – 3.4)	0.138
Secondary progressive(n = 181)	39.2 (37.0 – 41.4)		20.2 (18.1 – 21.2)		15.8 (14.5 – 17.1)[a]		3.3 (3.0 – 3.6)	
Primary progressive (n = 67)	39.8 (37.0 – 42.7)		20.6 (19.3 – 21.8)		15.6 (13.9 – 17.4)[e]		3.7 (3.2 – 4.1)	
Disease severity (n = 417)								
EDSS[2] 0–3.5 (n = 121)	39.7 (37.1 – 42.3)	0.066	17.6 (16.4 – 18.9)	0.001	19.1 (17.7 – 20.6)	0.000	2.9 (2.6 – 3.3)	0.091
EDSS[2] 4.0–5.5 (n = 136)	41.8 (39.4 – 44.2)		20.5 (19.4 – 21.6)[a]		17.8 (16.4 – 19.2)		3.5 (3.2 – 3.8)	
EDSS[2] 6.0–6.5 (n = 144)	38.4 (36.1 – 40.7)		20.6 (19.5 – 21.7)[a]		14.4 (13.0 – 15.8)[a,b]		3.4 (3.1 – 3.8)	
EDSS[2] 7.0–7.5 (n = 16)	33.5 (25.9 – 41.1)		18.9 (14.4 – 23.4)		11.3 (7.8 – 14.8)[a,b]		3.3 (2.5 – 4.1)	
Lifestyle factors								
Tobacco smoking (n = 414)								
No (n = 302)	38.4 (36.8 – 40.0)	0.003	19.1 (18.3 – 19.8)	0.007	16.2 (15.2 – 17.2)	0.049	3.1 (2.9 – 3.3)	0.000
Yes (n = 112)	43.0 (40.4 – 45.5)		21.1 (19.9 – 22.3)		18.0 (16.6 – 19.6)		3.8 (3.5 – 4.2)	
Alcohol intake (n = 414)								
No (n = 176)	39.6 (37.4 – 41.8)	0.902	19.2 (18.2 – 20.2)	0.313	17.1 (15.8 – 18.4)	0.204	3.4 (3.1 – 3.6)	0.807
1–2 times per week (n = 153)	39.9 (37.8 – 42.0)		19.6 (18.5 – 20.7)		17.1 (15.8 – 18.3)		3.2 (2.9 – 3.5)	
≥ 3 times per week (n = 85)	39.0 (35.8 – 42.2)		20.5 (19.0 – 22.1)		15.3 (13.3 – 17.2)		3.2 (2.8 – 3.7)	
Physical activity[4] (n = 414)								
≥ 3 times per week (n = 119)	36.3 (34.0 – 38.7)	0.001	17.9 (16.6 – 19.2)	0.000	15.6 (14.2 – 17.1)	0.232	2.8 (2.5 – 3.1)	0.000
1–2 times per week (n = 186)	39.8 (37.7 – 41.9)[a]		19.4 (18.5 – 20.3)		17.2 (16.0 – 18.4)		3.2 (2.9 – 3.5)[a]	
Not regularly[5] (n = 109)	43.4 (40.7 – 46.1)[a,b]		22.1 (20.8 – 23.4)[a,b]		17.2 (15.5 – 18.9)		4.1 (3.7 – 4.4)[a,b]	

[1]CI = Confidence interval
[2]EDSS = Expanded Disability Status Scale.
[3]Retirement – this category included Retirement due to disability, (n = 254); due to age, (n = 8); being Housewife/-husband, (n = 3).
[4]Physical activity reported as number of occasions per week performing physical activity with moderate intensity for at least 30 min.
[5]Not regularly – this category contain n = 39 persons with MS that reported 'cannot exercise' due to disability.
Statistics: significance level set at $p<0.01$, trend level (shown in italic) set at $0.05>p>0.01$.
Post hoc analysis were carried out if p-level < 0.05. Post hoc analysis; relative to reference group (most active):
[a]= different from 1st (reference) group, [b]= different from 2nd group, [c]= different from 3rd group, [d]different from 3rd group.
[e]Despite a lower mean value the analysis showed only a trend due to the greater variability.

model 2 (β=0.18, $p<0.01$) (r^2=0.05, $p<0.01$) and model 3 (β=0.20, $p<0.01$) (r^2=0.09, $p<0.01$). However, in model 3 time since diagnosis (β=–0.22, $p<0.01$) also was significantly associated (Table 3).

Physical activity (β=0.23, $p<0.01$) was significantly associated with the MFIS *physical* score in the unadjusted model (r^2=0.07, $p<0.01$), which remained (β=0.23, $p<0.01$) in model 2 (r^2=0.07, $p<0.01$). Physical activity was still associated (β=0.21, $p<0.01$) in model 3 (r^2=0.12, $p<0.01$). Furthermore, time since diagnosis (β=–0.22, $p<0.01$) and disease severity (β=0.16, $p<0.01$) were significantly associated with the MFIS *physical* score in Model 3. Tobacco smoking showed a trend towards association in all three models (Table 3).

Time since diagnosis (β=-0.16, $p<0.01$) and disease severity (β=-0.21, $p<0.01$) contributed significantly to the MFIS *cognitive* score in Model 3. Physical activity showed a trend towards association (β=0.10, p = 0.03) in Model 3 (r^2=0.09, $p<0.01$). No other variables were associated with the MFIS *cognitive* score (Table 3).

Tobacco smoking (β= 0.15, $p<0.01$) and physical activity (β=0.26, $p<0.01$) were significantly associated with the MFIS *psychosocial* score in the unadjusted model (r^2=0.09, $p<0.01$). The contribution of tobacco smoking (β=0.15, $p<0.01$ in both models) and physical activity (β=0.26, $p<0.01$, and β=0.25, $p<0.01$, respectively) to the MFIS *psychosocial* score remained in model 2 (r^2 =0.09, $p<0.01$) and in model 3 (r^2=0.11, $p<0.01$) (Table 3).

Discussion

This study investigated how potential modifiable lifestyle factors were associated with the fatigue impact in a large sample of well-characterized MS patients. We found that physical activity was significantly associated with and had the highest standardized beta values (compared to alcohol and tobacco smoking) with regard to fatigue impact on total scores of functioning and specifically in terms of physical and psychosocial functioning. Furthermore, tobacco smoking was significantly associated with fatigue impact on psychosocial functioning, while alcohol intake was not associated with fatigue impact. None of the lifestyle factors were significantly associated with fatigue impact on cognitive functioning. In the adjusted regression models time since diagnosis was significantly associated with fatigue impact on total, physical and cognitive functioning, as was disease severity with fatigue impact on physical and cognitive functioning.

Physical deconditioning has previously been linked to MS-related fatigue (Kos et al., 2008; Langeskov-Christensen et al., 2017; Krupp

Table 3
Multivariate regression analysis without (Model 1) and with adjustments for age and sex (Model 2) along with time since diagnosis, course, disease severity and disease modifying treatment (Model 3) of the Modified Fatigue Impact Scale total, physical, cognitive, and psychosocial scores.

Dependent variable	Independent variables	R^2	P value	Coefficient (CI95%)	Standard β value	P value
MFIS total score	Model 1					
	Tobacco smoking	0.05	<0.01	3.99 (0.97:7.00)	0.13	0.01
	Alcohol			−0.26 (−2.00:1.49)	−0.01	0.77
	Physical activity			3.49 (1.69:5.30)	0.18	<0.01
	Model 2					
	Tobacco smoking	0.05	<0.01	3.89 (0.86:6.93)	0.12	0.01
	Alcohol			−0.32 (−2.11:1.47)	−0.02	0.72
	Physical activity			3.42 (1.60:5.23)	0.18	<0.01
	Age			0.01 (−0.15:0.16)	0.00	0.95
	Sex			1.97 (−0.91:4.86)	0.06	0.18
	Model 3					
	Tobacco smoking	0.09	<0.01	3.50 (0.52:6.48)	0.11	0.02
	Alcohol			−0.35 (−2.10:1.40)	−0.02	0.70
	Physical activity			3.77 (1.98:5.57)	0.20	<0.01
	Age			0.11 (−0.07:0.28)	0.07	0.22
	Sex			1.56 (−1.29:4.41)	0.05	0.28
	Time since diagnosis			−0.38 (−0.55:−0.20)	−0.22	<0.01
	Course			−1.85 (−4.36:0.66)	−0,09	0.15
	Disease severity			−0.34 (−1.33:0.66)	−0.04	0.51
	Disease modifying treatment			−3.58 (0.32:6.84)	−0.13	0.03
MFIS physical score	Model 1					
	Tobacco smoking	0.07	<0.01	1.67 (0.22:3.12)	0.11	0.02
	Alcohol			0.62 (−0.22:1.46)	0.07	0.15
	Physical activity			2.11 (1.24:2.98)	0.23	<0.01
	Model 2					
	Tobacco smoking	0.07	<0.01	1.74 (0.29:3.19)	0.11	0.02
	Alcohol			0.41 (−0.44:1.27)	0.05	0.34
	Physical activity			2.11 (1.24:2.98)	0.23	<0.01
	Age			0.08 (0.00:0.15)	0.10	<0.05
	Sex			1.22 (−0.16:2.60)	0.08	0.08
	Model 3					
	Tobacco smoking	0.12	<0.01	1.40 (−0.02:2.82)	0.09	0.05
	Alcohol			0.44 (−0.39:1.28)	0.05	0.30
	Physical activity			1.98 (1.13:2.84)	0.21	<0.01
	Age			0.08 (−0.00:0.16)	0.10	0.05
	Sex			0.89 (−0.47:2.25)	0.06	0.20
	Time since diagnosis			−0.18 (−0.27:−0.10)	−0.22	<0.01
	Course			−0.60 (−1.80:0.59)	−0.06	0.32
	Disease severity			0.75 (0.27:1.22)	0.16	<0.01
	Disease modifying treatment			1.35 (−0.20:2.91)	−0.10	0.09
MFIS cognitive score	Model 1					
	Tobacco smoking	0.01	0.05	1.69 (−0.15:3.53)	0.09	0.07
	Alcohol			−0.80 (−1.87:0.26)	−0.07	0.14
	Physical activity			0.75 (−0.36:1.85)	0.06	0.18
	Model 2					
	Tobacco smoking	0.02	0.05	1.52 (−0.33:3.37)	0.08	0.11
	Alcohol			−0.63 (−1.72:0.46)	−0.06	0.26
	Physical activity			0.67 (−0.43:1.78)	0.06	0.23
	Age			−0.08 (−0.18:0.01)	−0.08	0.10
	Sex			0.52 (−1.24:2.29)	0.03	0.56
	Model 3					
	Tobacco smoking	0.09	<0.01	1.49 (−0.29:3.28)	0.08	0.10
	Alcohol			−0.68 (−1.73:0.37)	−0.06	0.20
	Physical activity			1.18 (0.10:2.26)	0.10	0.03
	Age			0.02 (−0.08:0.12)	0.02	0.71
	Sex			0.52 (−1.19:2.23)	0.03	0.55
	Time since diagnosis			−0.17 (−0.28:−0.06)	−0.16	<0.01
	Course			−1.21 (−2.72:0.29)	−0.10	0.11
	Disease severity			−1.17 (−1.77:−0.57)	−0.21	<0.01
	Disease modifying treatment			1.78 (−0.17:3.74)	−0.11	0.07
MFIS psychosocial score	Model 1					
	Tobacco smoking	0.09	<0.01	0.63 (0.24:1.01)	0.15	<0.01
	Alcohol			−0.07 (−0.30:0.15)	−0.03	0.51
	Physical activity			0.64 (0.41:0.87)	0.26	<0.01
	Model 2					
	Tobacco smoking	0.09	<0.01	0.64 (0.25:1.02)	0.15	<0.01
	Alcohol			−0.11 (−0.33:0.12)	−0.04	0.36
	Physical activity			0.63 (0.40:0.87)	0.26	<0.01
	Age			0.01 (−0.01:0.03)	0.05	0.27
	Sex			0.23 (−0.14:0.59)	0.06	0.23
	Model 3					
	Tobacco smoking	0.11	<0.01	0.61 (0.22:0.99)	0.15	<0.01
	Alcohol			−0.11 (−0.33:0.12)	−0.04	0.35

(*continued on next page*)

Table 3 (*continued*)

Dependent variable	Independent variables	R^2	P value	Coefficient (CI95%)	Standard β value	P value
	Physical activity			0.61 (0.38:0.85)	0.25	<0.01
	Age			0.01 (−0.02:0.03)	0.04	0.59
	Sex			0.15 (−0.22:0.52)	0.07	0.42
	Time since diagnosis			−0.02 (−0.35:−0.00)	−0.11	0.03
	Course			−0.03 (−0.35:0.30)	−0.01	0.87
	Disease severity			0.08 (−0.05:0.21)	0.07	0.20
	Disease modifying treatment			0.44 (0.02:0.86)	0.11	0.04

et al., 2010; Pilutti et al., 2013) and, further, it has been reported that increased physical capacity as a result of exercise training can decrease fatigue in MS patients (Pilutti et al., 2013). However, the previous reported association between physical activity level and fatigue was at best weak (Kos et al., 2008). Our results imply that increased physical activity level contributes to less impact of fatigue on total and physical functioning, which support previous reports of the positive effects of physical activity (Heine et al., 2015). However, rigorous longitudinal studies specifically designed to reduce fatigue in clinically fatigued MS patients are needed to elucidate how the physical activity/exercise programs should be executed (in terms of type, intensity, frequency, duration). According to the results from the present study, where shorter time since diagnosis and/or lower disease severity were significantly associated with higher fatigue impact on total and physical functioning, future studies need to further investigate the potential effect of such characteristics on how physical activity/exercise can influence fatigue. In our study physical activity also contributed to the impact of fatigue on psychosocial functioning, consistent with results from a previous review reporting positive effects of various types of physical activity/exercise interventions on psychological aspects of fatigue (Latimer-Cheung et al., 2013). Also, our results are in line with a recent study (Driehuis et al., 2018), suggesting that MS patients need to adhere to physical activity and stay as physically conditioned as possible to preserve physical health and to allow participation in valued activities in everyday life. Moreover, being physically active contributes to better quality of life (Motl and Gosney, 2008). Importantly, a recent meta-analysis has reported that behavioral interventions are efficacious for potentially sustaining physical activity behavior in MS patients (Kim et al., 2020) which point out the importance for rehabilitation services to include behavioural change support when delivering such interventions for the individual.

A recent meta-analysis showed that physical exercise generally not improve cognition in people with MS (Gharakhanlou et al., 2020). However, most studies have been carried out in patient populations that were not necessarily cognitively impaired at study entry, while at the same time "cognition" being a secondary outcome. Interestingly, a recent study including MS patients being cognitively impaired at baseline reported a beneficial effect on cognition following a physical exercise intervention (Ozkul et al., 2020). In the present multivariate regression analysis, increased physical activity level showed a trend towards an association with less impact of fatigue in the MFIS subdomain of cognitive functioning. Our results therefore (cautiously) suggest that the level of fatigue could be a mechanism explaining potential beneficial effects of physical activity or exercise on cognitive function in people with MS, which need investigation in future studies.

A recent study reported that non-smoking was associated with a lower impact of fatigue on total functioning when assessed by the MFIS (Kahraman et al., 2020). This is in accordance with the results of the present study where current smoking was associated with higher scores of fatigue impact on total, physical and psychosocial functioning (Table 2). However, in the regression analyses the contribution to fatigue impact was significant for psychosocial functioning only. The results from our study and the study by Kahraman et al. (Kahraman et al., 2020) imply that tobacco smoking influences fatigue in MS patients, but the specific aspects that are influenced need to be confirmed. Additionally, the negative influence of tobacco smoking even on disease progression has previously been shown (Hedstrom et al., 2013), which further highlights the importance of supporting smoking cessation.

Use of alcohol did not contribute to fatigue impact in any analysis, which is in line with a previous study (Bombardier et al., 2004). However, the restriction of alcohol use is likely beneficial since it is known to be associated with both lower quality of life and depression (Weiland et al., 2014; Bombardier et al., 2004), which are known as secondary contributors to fatigue.

Results on which variables that influence fatigue in MS patients are inconsistent, which might reflect the complexity of the underlying causes of fatigue (Kos et al., 2008). Another explanation might relate to the application of different self-reporting scales when assessing fatigue. In this study we used the MFIS, where more specific aspects of fatigue impact can be explored. In the multivariate regression models, variables selected based on existing literature and clinical experience – age, sex, and disease-related characteristics – were included as potential contributors to the studied lifestyle factors. We found that higher disease severity is associated with increased fatigue impact on physical functioning which might result from the physical limitations upcoming with a more severe disease, a finding also recently reported in a prevalence study of fatigue in MS (Rzepka et al., 2020). It was, however, also observed that a lower disease severity was associated with increased fatigue impact on cognitive functioning. This may be explained by awareness of upcoming cognitive problems and a lowered mood level early in the disease due to worries about the future. Also, we found that shorter time since diagnosis significantly adjusted for increased fatigue impact, on total, physical and cognitive functioning, which might reflect that patients with longer disease duration have learned strategies to manage their fatigue in order to reduce the fatigue impact (e.g. reduce their activities). An additional variable included in the multivariate regression models was MS type, where no significant association with fatigue impact was found. Our result therefore contrasts the results from a recent study (Rooney et al., 2019), which reported that fatigue was more prevalent in those with progressive MS. Data on objectively collected disease-related characteristics extracted from patient records in the present study compared to self-reported data collected online confirmed by the participants themselves in the study by Rooney et al. (Rooney et al., 2019) may explain this discrepancy between studies.

Clinical implications

The present study adds further evidence to the beneficial effects of physical activity/exercise for people with MS. Moreover, undertaking regular physical activity is associated with less fatigue impact on total, physical and psychosocial functioning in this group. Although future longitudinal studies outlining the optimal physical activity/exercise program are still warranted, introducing physical activity and exercise does seem like a useful approach for rehabilitation services in management of fatigue. Also, the observed association between tobacco smoking and fatigue impact on total, physical and psychosocial functioning suggest that smoking cessation is a potential target in fatigue management.

Methodological considerations

Strengths of this study were the inclusion of a large sample of well-

characterized patients with mild to moderate/severe MS severity who had a cognitive function that allowed independent completion of the included questionnaires. Another strength was that data on disease-related characteristics were extracted from patient records, i.e., they were objectively assessed unlike the study by Fitzgerald et al. The main limitation is the cross-sectional evaluation which limit conclusions on causal relationships. Furthermore, some data was based on patient reported outcomes, which could not be validated objectively. Also, a majority of the participants were on retirement which might have influenced the generalizability of the results, but it also mirrors the fact that retirement is common in this group. Also, the influence of important secondary pathways that likely influence fatigue impact on functioning, such as depressive symptoms and sleep disturbance, was not included as possible contributors/adjustors to the lifestyle factors impact – inclusion of these pathways in the analyses would have contributed to even more stringent results. A limitation of the study is also the use of the Danish version of the MFIS since this version has not been formally validated. Further, the psychometrics of the psychosocial MFIS subscale has previously been questioned (Kos et al., 2005) which needs to be considered.

Conclusion

In conclusion, several modifiable life-style factors were associated with fatigue impact on functioning of which physical activity showed the most pronounced associations with fatigue impact on physical and psychosocial functioning, while the impact on cognitive functioning only showed a trend. Tobacco smoking contributed significantly to fatigue impact on psychosocial functioning, while alcohol intake did not contribute to fatigue impact in any domains. Time since diagnosis significantly contributed to fatigue impact on total, physical and cognitive functioning, as did disease severity on physical and cognitive functioning. Introducing or supporting maintenance of physical activity/exercise and cessation of tobacco smoking seems to be a useful approach for rehabilitation services to help patients with MS manage fatigue.

Credit author statement

The authors have contributed to this research paper as follows:

Sverker Johansson: Data analysis, writing - original draft;

Anders G Skjerbaek: Conceptualization, methodology, data collection, writing - original draft;

Michael Norgaard: Conceptualization, methodology, data collection, writing - original draft;

Finn Boesen: Conceptualization, methodology, data collection, writing - original draft;

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Declaration of Competing Interest

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The authors report no declarations of interest.

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