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Associations between fatigue impact and physical and neurobehavioural factors: An exploration in people with progressive multiple sclerosis☆

L Connolly [a,*], S Chatfield [a], J Freeman [a], A Salter [b], MP Amato [c,d], G Brichetto [e,f], J Chataway [g,h], ND Chiaravalloti [i,j], G Cutter [k], J DeLuca [i,j], U Dalgas [l], R Farrell [g,h], P Feys [m], M Filippi [n,o,p,q,r], M Inglese [s,t], C Meza [u], NB Moore [i], RW Motl [v], MA Rocca [n,o,r], BM Sandroff [i,v], A Feinstein [u]

[a] Faculty of Health, School of Health Professions, University of Plymouth, Devon, UK
[b] Department of Neurology, University of Texas Southwestern Medical Center, Dallas, TX, USA
[c] Department NEUROFARBA, Section Neurosciences, University of Florence, Largo Brambilla 3, 50134 Florence, Italy
[d] IRCCS Fondazione Don Carlo Gnocchi, Florence, Italy
[e] Scientific Research Area, Italian Multiple Sclerosis Foundation (FISM), via Operai 40, 16149 Genoa, Italy
[f] AISM Rehabilitation Service, Italian Multiple Sclerosis Society, Genoa, Italy
[g] Department of Neuroinflammation, UCL Queen Square Institute of Neurology, Faculty of Brain Sciences, Queen Square Multiple Sclerosis Centre, University College London, London WC1B 5EH, UK
[h] National Institute for Health Research, University College London Hospitals, Biomedical Research Centre, London, UK
[i] Kessler Foundation, 120 Eagle Rock Avenue, Suite 100, East Hanover, NJ 07936, USA
[j] Department of Physical Medicine and Rehabilitation, Rutgers New Jersey Medical School, Newark, NJ, USA
[k] Department of Biostatistics, University of Alabama At Birmingham, Birmingham, USA
[l] Exercise Biology, Department of Public Health, Aarhus University, Dalgas Avenue 4, 8000 Aarhus, Denmark
[m] REVAL, Faculty of Rehabilitation Sciences, Hasselt University, Diepenbeek, Belgium
[n] Neuroimaging Research Unit, Division of Neuroscience, IRCSS San Raffaele Scientific Institute, Milan, Italy
[o] Neurology Unit, IRCSS San Raffaele Scientific Institute, Milan, Italy
[p] Neurorehabilitation Unit, IRCSS San Raffaele Scientific Institute, Milan, Italy
[q] Neurophysiology Unit, IRCSS San Raffaele Scientific Institute, Milan, Italy
[r] Vita-Salute San Raffaele University, Milan, Italy
[s] Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, and Center of Excellence for Biomedical Research, University of Genoa, Genoa, Italy
[t] Ospedale Policlinico San Martino-IRCCS, Genoa, Italy
[u] Department of Psychiatry, University of Toronto and Sunnybrook Health Sciences Centre, Toronto, ON M5R 3B6, Canada
[v] Department of Kinesiology and Nutrition, University of Illinois Chicago, Chicago, IL, USA

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ABSTRACT

Background: Fatigue is common in people with multiple sclerosis (MS). Understanding the relationship between fatigue, physical and neurobehavioural factors is important to inform future research and practice. Few studies explore this explicitly in people with progressive MS (pwPMS).
Objective: To explore relationships between self-reported fatigue, physical and neurobehavioural measures in a large, international progressive MS sample of cognitively impaired people recruited to the CogEx trial.
Methods: Baseline assessments of fatigue (Modified Fatigue Impact Scale; MFIS), aerobic capacity (VO_{2peak}), time in moderate-vigorous physical activity (MVPA; accelerometery over seven-days), walking performance (6-minute walk test; 6MWT), self-reported walking difficulty (MS Walking Scale; MSWS-12), anxiety and depression (Hospital Anxiety and Depression Scale; HADS and Beck Depression Inventory-II; BDI-II), and disease impact (MS Impact Scale-29, MSIS-29) were assessed. Participants were categorised as fatigued ($MFIS_{Total}$ >=38) or non-fatigued ($MFIS_{Total}$ $\leq$38).
Statistical Analysis: Differences in individuals categorised as fatigued or non-fatigued were assessed (*t*-tests, chi square). Pearson's correlation and partial correlations (adjusted for EDSS score, country, sex, and depressive

☆ On behalf of the CogEx Research Team

* Corresponding author at: School of Health Professions, Faculty of Health, University of Plymouth, InterCity Place, Plymouth PL4 6AB, UK.
E-mail address: Luke.connolly@plymouth.ac.uk (L. Connolly).

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symptoms) determined associations with $MFIS_{Total}$, $MFIS_{Physical}$, $MFIS_{Cognitive}$ and $MFIS_{Psychosocial}$, and the other measures. Multivariable logistic regression evaluated the independent association of fatigue (categorised $MFIS_{Total}$) with physical and neurobehavioural measures.

Results: The sample comprised 308 pwPMS (62 % female, 27 % primary progressive, 73 % secondary progressive), mean age 52.5 ± 7.2 yrs, median EDSS score 6.0 (4.5–6.5), mean $MFIS_{Total}$ 44.1 ± 17.1, with 67.2 % categorised as fatigued. Fatigued participants walked shorter distances (6MWT, $p = 0.043$), had worse MSWS-12 scores ($p < 0.001$), and lower average % in MVPA ($p = 0.026$). The magnitude of associations was mostly weak between $MFIS_{Total}$ and physical measures ($r = 0.13$ to 0.18), apart from the MSWS-12 where it was strong ($r = 0.51$). The magnitude of correlations were strong between the $MFIS_{Total}$ and neurobehavioural measures of anxiety ($r = 0.56$), depression ($r = 0.59$), and measures of disease impact (MSIS-physical $r = 0.67$; MSIS-mental $r = 0.71$). This pattern was broadly similar for the MSIF subscales. The multivariable model indicated a five-point increase in MSWS-12 was associated with a 14 % increase in the odds of being fatigued (OR [95 %CI]: 1.14 [1.07–1.22], $p < 0.0001$)

Conclusion: Management of fatigue should consider both physical and neurobehavioural factors, in cognitively impaired persons with progressive MS.

1. Introduction

Fatigue is reported to be one of the most common and debilitating symptoms in multiple sclerosis (MS) ranging from 36 – 90 % of those affected (Ramirez et al., 2021; Picariello et al., 2022; Marchesi et al., 2022). The prevalence of fatigue has demonstrated to be significantly higher in people with progressive MS (pwPMS) in comparison to those with non-progressive subtypes (Rooney et al., 2019b) although fatigue severity and fatigue interference have shown to be similar (Herring et al., 2021).

MS-related fatigue is defined as 'a lack of physical and/ or mental energy that is perceived by the individual or the caregiver to interfere with usual and desired activities' (MSCCP, 1998). This can have detrimental effects on a person's physical (Dalgas et al., 2018) and cognitive abilities (Guillemin et al., 2022), exacerbated by the impact of fear and anxiety (Power et al., 2021). Fatigue often limits social and daily activities and occupational status (Penner et al., 2020; Vitturi et al., 2022), impacts quality of life (QoL), and has a negative impact on mood and emotional well-being (van den Akker et al., 2017). Despite the profound effects of fatigue, the cause of fatigue remains unclear (Rooney et al., 2019a; Langeskov-Christensen et al., 2015).

Factors secondary to the disease process (secondary fatigue), such as mood, physical impairments, and physical activity levels (which may include exercise (Mansoubi et al., 2023)), have been noted to reinforce already present primary related mechanisms, thus potentially further increasing fatigue levels in people with MS. The impact of low mood and greater physical disability, for example, has been associated with a decreased odds of engaging in physical activity (Tyszka et al., 2022); this spiral of deconditioning can further affect fatigue and QoL (Moss-Morris et al., 2021). Patient perceptions can also influence people's participation in exercise and physical activity (Learmonth and Motl, 2016). In recognition of this, the evidence-based National Institute for Health and Care Excellence Guidelines (NICE, 2022) [NG220]) recommend exercise and behavioural interventions for MS-fatigue, however there is little indication of how this should be best managed. Moss-Morris et al. (2021) suggest a holistic and multi-disciplinary team approach is required to address physical activity components alongside the more traditional energy conservation and cognitive behavioural therapy (CBT) methods.

Despite the profound effects of fatigue, little research focuses exclusively on pwPMS. Moreover, the prevalence of fatigue, and its relationship with various demographic, disease-related, and health-related characteristics exclusively in a progressive MS population may identify ways to personalise fatigue interventions for this subgroup of people (Penner et al., 2020; Watson et al., 2022; Marchesi et al., 2020). Therefore, this study explores the relationship between fatigue, physical and neurobehavioural factors in a discrete and large sample of pwPMS and considers the clinical relevance of the findings.

2. Methods

2.1. Study design

This study presents data collected at baseline from all eleven sites involved in the CogEx study (across Canada, United States of America, United Kingdom, Italy, Denmark, and Belgium). The study was approved by each site's research ethics board. CogEx is a multi-arm, randomised, blinded, sham-controlled trial of cognitive rehabilitation and aerobic exercise training for pwPMS and cognitive impairment, to improve cognition. The CogEx study protocol (Feinstein et al., 2020) and results (Feinstein et al., 2023) have been described in full elsewhere. We report here on the baseline associations of this large cohort of pwPMS.

2.2. Participants

Potential participants were recruited through MS clinics, databases of previous participants and media advertising in the community. Initial screening took place via telephone for demographic and clinical inclusion/exclusion criteria followed by in-person screening. In all, participants were considered for in-person screening if they (1) had a clinical diagnosis of primary or secondary progressive MS; (2) were between 25 and 65 years of age; (3) had an Expanded Disability Status scale (EDSS) score of < 7.0 (ambulatory with or without assistance); (4) were relapse-free without acute steroid use within the past three months; (5) had no history of neurological disorders besides MS; (6) did not have severe mental illness; (7) did not use drugs that could affect cognition (excluding cannabis); (8) demonstrated low risk for contraindications for exercise; and (9) were insufficiently active based on a Health Contribution Score of the Godin Leisure-Time Exercise Questionnaire <23 units (Motl et al., 2018b).

Following in-person screening, to enter CogEx participants had to (1) be cognitively impaired as defined by a Symbol Digit Modalities Test (SDMT) score of ≥ 1.282 standard deviation (SD) below the age-, sex- and education-adjusted normative data, specific to each participating country (Benedict et al., 2012; Boringa et al., 2001; Costers et al., 2017; Goretti et al., 2014; Parmenter et al., 2010; Walker et al., 2016); (2) demonstrate corrected visual acuity better than 20/70; (3) were not severely depressed, scoring <29 on the BDI-II, and (4) demonstrate intact language comprehension, scoring >28 on the Token Test (De Renzi and Faglioni, 1978).

2.3. Clinical measures

Demographic and diagnostic data, collected at baseline, included age, sex, body mass index, education status, type of MS and disease duration. EDSS scores were provided by the participating centres. This study focusses on physical, neurobehavioural, and fatigue parameters, measured at baseline and collected in a standardised manner. Please see

Feinstein et al. (2020) for the full assessment battery.

2.4. Fatigue

Fatigue impact was assessed using the self-report Modified Fatigue Impact Scale (MFIS), which comprises a total score $MFIS_{Total}$ and three subscales ($MFIS_{Physical}$, $MFIS_{Cognitive}$ and $MFIS_{Psychosocial}$). Higher scores indicate more fatigue impact. The $MFIS_{Total}$ score (available range 0 – 84) was dichotomised at 38 to create two categories of participants, fatigued and non-fatigued (Flachenecker et al., 2002).

2.5. Cardiorespiratory fitness

Cardiorespiratory fitness was measured as peak oxygen consumption (VO_{2peak}; ml/kg/min) and peak work rate (WR_{peak}; W) utilising an incremental exercise test (IET) to exhaustion on a recumbent cross trainer (NuStep TX5R, NuStep, Inc., Ann Arbor, MI, USA) and an open-circuit spirometry system for analysing expired gases. Prior to starting the IET, participants were read scripted, standardised procedures for the IET and reporting of ratings of perceived exertion (RPE). Following an initial one-minute rest period on the cross trainer, the IET commenced with a one-minute warm-up at 15 W and a step rate of 60 steps/minute. Watt Rate (WR) was then increased by 5 or 10 W/minute (dependent on EDSS score). A metronome was utilised to assist participants with prescribed step rate. The IET ceased when participants reached volitional exhaustion or steps fell by >15 steps below the prescribed step rate for 30 s. VO_2, respiratory exchange ratio (RER) and heart rate (HR) were continuously monitored during the IET and averaged across 20-second intervals. The criteria used to determine VO_{2peak} included satisfying two of the following four criteria: (1) a plateau in VO_2 toward the end of the test despite an increase in WR; (2) RER ≥1.10; (3) peak HR (HR_{peak}) within 10 beats per minute of age-predicted maximum; or (4) RPE ≥17. VO_{2peak}, HR_{peak} and WR_{peak} were determined as the peak value reached in a 20-second period during the IET.

2.6. Free-living physical activity

Free-living moderate to vigorous physical activity (MVPA) was measured during the waking hours over a 7-day period prior to the intervention period using the Actigraph GT3x+ accelerometer (Actigraph, Inc., Pensacola, FL, USA). The accelerometer was positioned on the participant's non-dominant hip and a patient-reported wear-time log was recorded for compliance. Raw data were downloaded to the software package Actilife (ActiGraph Corporation) and processed using the low-frequency extension into 60-second epochs. Data were scored for wear time and time spent (minutes/day) in sedentary, light, and MVPA domains using MS-specific cut-points (Sandroff et al., 2012). Data were considered valid and subsequently analysed only for those days consisting of ≥10 h of wear time (≥600 min) and cases of ≥1 valid days (Klaren et al., 2016). Free-living activity was expressed in percent of total wear time across valid days.

2.7. Exercise behaviour

Exercise behaviour was measured based on a Health Contribution Score (HCS) of the patient-reported Godin Leisure Time Exercise Questionnaire (Godin and Shephard, 1985). Recommended for use in physical activity research, the HCS has a score range of 0–98, with higher scores indicating higher levels of physical activity (Sikes et al., 2019). To be eligible for inclusion, participants scored <23 on the HCS, indicating they had spent less than two days per week (30 mins or more at a time) in moderate to strenuous exercise (Motl et al., 2018a).

2.8. Walking capacity

Walking performance was determined using the 6-minute walk test; 6MWT which entails measuring the distance covered, whilst walking on a flat, indoor surface (metres) over a time of 6-minutes, performed at maximal speed according to standardised instructions (Goldman et al., 2019). The impact of MS on the individual's walking ability was measured using the self-report Multiple Sclerosis Walking Scale-12 (MSWS-12; range 0–100) (Hobart et al., 2003).

2.9. Neurobehavioural measures

Participants were screened for depression prior to recruitment using the 21-item self-report BDI-II (score range 0–63) (Sacco et al., 2016). Those scoring above 29, indicating severe depressive symptoms, did not meet the eligibility criteria and were excluded. The Hospital Anxiety and Depression Scale (HADS), a self-report measure of anxiety and depression was undertaken at baseline. A score of 0–7 is considered normal, 8–10 borderline, and 11–21 abnormal (Zigmond and Snaith, 1983).

2.10. Disease impact

The impact of MS on physical and psychological functioning was measured using the Multiple Sclerosis Impact Scale (MSIS-29), a 29-item self-report scale, comprised of two scales: the physical and psychological scales (Hobart et al., 2005). Higher scores indicate a greater impact of MS.

2.11. Statistical analyses

Across the 11 CogEx study sites, data were entered using REDCap®. The baseline data analysed for this study was undertaken by the study biostatistician (AS) using SAS v9.4 software (SAS Inc., Cary, NC, USA). Differences in fatigue categories were assessed using a *t*-test or Wilcoxon rank-sum test for continuous variables, as appropriate, and chi square or Fisher's exact test for categorical variables. Data are reported as mean (standard deviation (SD)) unless otherwise stated. Associations with $MFIS_{Total}$ and its three subscales ($MFIS_{Physical}$, $MFIS_{Cognitive}$ and $MFIS\text{-}_{Psychosocial}$) and physical and neurobehavioural measures were assessed using a Pearson correlation coefficient. Values for correlation coefficients of 0.1, 0.3, and 0.5 were interpreted as weak, moderate, and strong, respectively (Cohen, 1988). Additionally, the partial correlation between the MFIS and the physical and neurobehavioural measures was evaluated adjusting for EDSS score, country, sex, and depressive symptoms using the HADS. The partial correlations for the HADS depression and BDI total adjusted for EDSS score, country, and sex.

Multivariable logistic regression was conducted to evaluate the independent association of fatigue (categorised $MFIS_{Total}$ score) with the physical and neurobehavioural measures. Variable selection was conducted using a stepwise selection method and the Bayesian Information Criterion for inclusion. The odds ratios and 95 % confidence intervals [95 %CI] are reported.

3. Results

3.1. Participant characteristics

Three hundred and eleven pwPMS satisfied the inclusion/exclusion criteria. Of these, baseline data were obtained and analysed for 308 individuals (3 participants did not have an MFIS score and were excluded). Demographic and clinical characteristics are reported in Tables 1 and 2, and further divided by the presence of fatigue. In summary, 62 % of the participants were female, 45 % educated to college/university level, and 73 % presented with secondary progressive MS. The overall mean (SD) MFIS total score was 44 (17) and 209 (68 %) of participants were considered having fatigue. Greater disability (higher EDSS score), higher use of an assistive device, greater symptoms of depression and anxiety, and a lower physical and mental disease impact were reported in those persons fatigued compared to participants who

Table 1
Participant demographic and clinical characteristics overall and by fatigue group.

	Total (N = 308)	Non–Fatigued (N = 99)	Fatigued (N = 209)	p-value
Age (yrs)	52.5(7.2)	53.1(7.0)	52.3(7.2)	0.33[a]
Sex:				0.41[c]
Male (n)	116(37.7)	34(34.3)	82(39.2)	
Female (n)	192(62.3)	65(65.7)	127(60.8)	
Total years of schooling (yrs)	14.0(3.3)	13.7(3.5)	14.1(3.3)	0.41[a]
Highest level of education completed:				0.36[c]
Primary (n)	25(8.1)	10(10.1)	15(7.2)	
Secondary (high school) (n)	145(47.1)	50(50.5)	95(45.5)	
College/ University (n)	138(44.8)	39(39.4)	99(47.4)	
SDMT z-score	−2.1(0.75)	−2.0(0.72)	−2.2(0.75)	*0.017*
BMI (kg/m^2)*	27.3(33.1)	27.4(33.4)	27.2(33.1)	0.97[a]
EDSS score*	6.0 [4.5,6.5]	5.0[4.0,6.5]	6.0[4.8,6.5]	*0.017*[b]
Disease Duration (yrs)*	14.6(9.6)	13.7(10.6)	15.0(9.2)	0.29[a]
Age at onset (yrs)*	37.9(11.1)	39.4(12.1)	37.2(10.5)	0.11[a]
Type of MS				0.10[c]
Primary progressive (n)	84(27.3)	33(33.3)	51(24.4)	
Secondary progressive (n)	224(72.7)	66(66.7)	158(75.6)	
Assistive Device				*0.001*[c]
None (n)	111(36.0)	50(50.5)	61(29.2)	
Unilateral (n)	86(27.9)	19(19.2)	67(32.1)	
Bilateral (n)	111(36.0)	30(30.3)	81(38.8)	

BMI: Body mass index; EDSS: Expanded Disability Status scale; MS: Multiple sclerosis; 6MWT: 6-minute walk test. *Data not available for all subjects. Missing values: BMI = 2, EDSS score = 1, Disease Duration = 2, Age at onset =2.
Values presented as Mean ± SD, Median [P25, P75], Median (min, max) or N (column%).
p-values: *a* = *t*-test, *b*=Wilcoxon rank-sum test, *c*=Pearson's chi-square test.

were non-fatigued ($p < 0.05$).

Table 2 highlights that fatigued participants reported a shorter distance covered in the 6MWT, lower peak watts as part of the IET, slightly lower percentage of time spent in MVPA, and higher MSWS-12 scores compared to those who were non-fatigued ($p < 0.05$). There was no significant difference in VO_{2peak} between fatigued and non-fatigued groups.

3.2. Associations between fatigue, physical, and neurobehavioural measures

Table 3 presents the correlations between fatigue impact ($MFIS_{Total}$, $MFIS_{Physical}$, $MFIS_{Cognitive}$ and $MFIS_{Psychosocial}$) and the physical and neurobehavioural measures. Correlations between the $MFIS_{Total}$ and the physical measures were typically weak in magnitude (r = −0.13 to –0.18) apart from self-reported walking impact (MSWS-12, r = 0.52), which was strong. Correlations between the $MFIS_{Total}$ and neurobehavioural measures were all strong in magnitude (r = 0.56 to 0.72).

The magnitude of correlations between scores on the physical fatigue impact subscale ($MFIS_{Physical}$) and the physical measures were weak (cardiorespiratory fitness, r = −0.21 to −0.25; physical activity −0.23 to –0.28) to moderate (6MWT total distance, r = −0.3) apart from the MSWS-12 where the correlation was strong (MSWS-12, r = 0.64). The magnitude of correlations between scores on the $MFIS_{Psychosocial}$ subscale and neurobehavioural measures were consistently moderate to strong (r = 0.44 – 0.6).

Following adjustments for depressive symptoms, EDSS score, sex and country, the partial correlations were determined between fatigue impact ($MFIS_{Total}$, $MFIS_{Physical}$, $MFIS_{Cognitive}$ and $MFIS_{Psychosocial}$) and the

Table 2
Baseline clinical measures for the total group, and when categorised as fatigued or non-fatigued.

	Total (N = 308)	Non-Fatigued (N = 99)	Fatigued (N = 209)	p-value
Physical measures				
Walking:				
6MWT total distance (m)	266.5 (141.0)	290.1(152.1)	255.3 (134.3)	*0.043*
MSWS-12*	63.1 (26.5)	46.3(29.0)	71.1(21.0)	*<0.001*
Cardiorespiratory Fitness:				
VO_{2peak} (mL/kg/min)*	17.4(6.4)	18.0(6.8)	17.1(6.2)	0.24
WR_{peak} (W)*	81.0 (33.8)	86.6(37.3)	78.4(31.7)	*0.047*
Physical Activity:				
Num Accelerometer Days (n)*	6.2(1.9)	6.0(1.5)	6.3(2.1)	0.28
Wear time in Sedentary (%)*	66.4 (11.7)	65.0(12.8)	67.1(11.1)	0.16
Wear time in Light (%)*	32.2 (10.5)	33.2(11.2)	31.7(10.1)	0.28
Wear time in MVPA (%)*	1.7(2.3)	2.1(2.8)	1.5(2.1)	*0.026*
Avg minutes/day of MVPA*	13.2 (18.1)	17.0(22.1)	11.3(15.5)	*0.012*
Health Contribution Score	4.8(6.5)	5.4(6.9)	4.5(6.3)	0.28
Neurobehavioural measures				
Anxiety and Depression:				
HADS anxiety score	6.5(4.5)	3.6(3.2)	7.9(4.4)	*<0.001*
HADS depression score	6.2(4.0)	3.4(3.0)	7.5(3.7)	*<0.001*
$BDI\text{-}II_{Total}$ score	11.9(7.8)	7.0(5.3)	14.2(7.8)	*<0.001*
Disease Impact:				
MSIS-29 physical score	46.6 (22.7)	28.8(18.5)	55.1(19.4)	*<0.001*
MSIS-29 mental score	37.2 (24.2)	17.4(14.9)	46.6(22.0)	*<0.001*

Health Contribution score from the Godin Leisure Time Exercise Questionnaire; 6MWT: 6-minute walk test; MSWS-12: Multiple sclerosis walking scale; VO_{2peak}: Peak oxygen consumption; WR_{peak}: Peak work rate; MVPA (minute/day): Minutes per day of moderate-to-vigorous physical activity; HADS: Hospital anxiety and depression scale; BDI: Beck depression inventory; MSIS: Multiple sclerosis impact scale.
*Data not available for all subjects. Missing values: MSWS-12 = 3, VO_{2peak} = 1, Peak Watts = 1, Num Accelerometer Days = 25, Avg% in Sedentary = 25, Avg% in Light = 26, Avg% in MVPA = 25, Avg Total MVPA = 25.
Values presented as Mean ± SD, Median [P25, P75], Median (min, max) or N (column %), p-values = *t*-test.

physical and neurobehavioural measures. Table 3 demonstrates that the magnitude of the partial correlations was generally consistent but attenuated. Correlations between fatigue impact and the physical measures that were typically significant but weak in magnitude were no longer significant.

3.3. Multivariable logistic regression model

The predictors of being fatigued in the multivariable logistic model included MSWS-12 total score and MSIS-mental. A 5-point increase in MSWS-12 total score was associated with a 14 % increase in the odds of being fatigued (OR [95 %CI]: 1.14 [1.07–1.22], $p < 0.0001$). For the MSIS-mental, a 5-point increase in the score was associated with a 53 % increase in the odds of being fatigued (OR [95 %CI]: 1.53 [1.36–1.73], $p < 0.0001$).

4. Discussion

This analysis of the baseline data from the CogEx study demonstrates that 63 % of individuals within this progressive MS population were

Table 3
Pearson's (*r*) correlation coefficients and partial correlation coefficients ($r_{Partial}$) of fatigue, physical, and neurobehavioural measures.

Variable	N	MFIS total *r*	p-value	$r_{Partial}$	p-value	MFIS physical *r*	p-value	$r_{Partial}$	p-value	MFIS cognition *r*	p-value	$r_{Partial}$	p-value	MFIS psychosocial *r*	p-value	$r_{Partial}$	p-value
Physical measures																	
Walking:																	
6MWT total distance (m)	308	−0.13	0.02	0.03	0.59	−0.3	<0.0001	−0.12	0.04	0.06	0.31	0.19	<0.01	−0.2	<0.01	−0.12	0.06
MSWS-12 score	305	0.52	<0.0001	0.44	<0.0001	0.64	<0.0001	0.58	<0.0001	0.28	<0.0001	0.17	<0.01	0.51	<0.0001	0.43	<0.0001
Cardiorespiratory Fitness:																	
VO_{2peak} (mL/kg/min)	307	−0.14	<0.01	−0.07	0.22	−0.21	<0.01	−0.15	0.02	−0.04	0.54	0.02	0.77	−0.15	0.01	−0.09	0.13
WR_{peak} (W)	307	−0.18	<0.01	−0.1	0.09	−0.25	<0.0001	−0.14	0.02	−0.06	0.31	−0.01	0.83	0.05	0.42	−0.17	<0.01
Physical Activity:																	
MVPA (min/day)	283	−0.16	0.01	−0.07	0.26	−0.28	<0.0001	−0.16	0.01	−0.02	0.8	0.05	0.42	−0.2	<0.01	−0.14	0.02
Health contribution score	308	−0.16	<0.01	−0.06	0.34	−0.23	<0.0001	−0.14	0.02	−0.06	0.27	0.03	0.67	−0.12	0.02	−0.04	0.53
Neurobehavioural measures																	
Anxiety and Depression:																	
HADS anxiety score	308	0.57	<0.0001	0.32	<0.0001	0.45	<0.0001	0.26	<0.0001	0.53	<0.0001	0.29	<0.0001	0.44	<0.0001	0.15	0.01
HADS depression score	308	0.59	<0.0001	0.59	<0.0001	0.48	<0.0001	0.47	<0.0001	0.54	<0.0001	0.54	<0.0001	0.55	<0.0001	0.54	<0.0001
BDI-II$_{Total}$ score	308	0.56	<0.0001	0.57	<0.0001	0.44	<0.0001	0.47	<0.0001	0.52	<0.0001	0.52	<0.0001	0.47	<0.0001	0.47	<0.0001
Disease Impact:																	
MSIS-29 physical score	308	0.67	<0.0001	0.53	<0.0001	0.71	<0.0001	0.6	<0.0001	0.46	<0.0001	0.29	<0.0001	0.66	<0.0001	0.52	<0.0001
MSIS-29 mental score	308	0.72	<0.0001	0.57	<0.0001	0.58	<0.0001	0.46	<0.0001	0.66	<0.0001	0.5	<0.0001	0.6	<0.0001	0.37	<0.0001

MFIS: modified fatigue impact scale; 6MWT: 6-minute walk test; MSWS: multiple sclerosis walking scale-12; VO_{2peak}: peak oxygen consumption; WR_{peak}: peak work rate; MVPA (minute/day): minutes per day of moderate-to-vigorous physical activity; HADS: hospital anxiety and depression scale; BDI: beck depression inventory; MSIS: multiple sclerosis impact scale.
*Partial Correlation is adjusted for EDSS score, country, sex and HADS depression score (except for the HADS depression and BDI measures).
**Statistical significance at Benjamini–Hochberg corrected *p*-value of 0.015 for multiple comparisons.

categorised as fatigued, according to established cut-offs for the MFIS. We explored the relationship between self-reported fatigue and a range of physical and neurobehavioural outcomes, some of which were observer-rated and others of which were self-reported.

Our key findings were that people who were categorised according to the MFIS as being fatigued had significantly higher levels of depressive and anxiety symptoms, reduced walking distances over a 6-minute timed test, reduced perceived walking ability, and spent less time undertaking MVPA compared to those who were non-fatigued.

A statistically significant difference was identified between the fatigued and non-fatigued groups in terms of walking distance, but not for the IET to volitional exhaustion regarding VO_{2peak} achieved. Whilst acknowledging that these tests (6MWT, IET) are measuring two different constructs, nevertheless both require physical performance to be sustained over at least 6 min. One might expect a significant difference to be seen between fatigued and non-fatigued individuals in both the 6MWT and the IET measures. For instance, findings from Sebastiao et al. (2017) found VO_{2peak} to be significantly lower in the fatigued group compared with the non-fatigued group of people with MS. Sebastiao et al. (2017) highlight that the difference, in part, could be due to the difference in disability level (fatigued group EDSS = 4.5; non-fatigued group EDSS = 3.5). Notably, in the current sample, EDSS scores were 5.0 and 6.0 for non-fatigued and fatigued groups, respectively. Additionally, compared to the sample of Sebastiao et al. (2017) which included people with RRMS (>75 %), the current sample consisted only of individuals with progressive MS whom, by way of inclusion criteria on to the CogEx trial, were insufficiently active based on a Health Contribution Score of the Godin Leisure-Time Exercise Questionnaire (< 23 units). Taken together, it could be argued that, regardless of fatigue level, overall cardiorespiratory fitness (VO_{2peak}) is unlikely to differ for insufficiently active pwPMS.

It is also speculated that the lack of difference in VO_{2peak} between fatigued and non-fatigued groups could be due to the use of the recumbent cross-trainer for the IET which allows the individual to use all four limbs to exercise while in a seated, secured position compared to the bipedal nature of the 6MWT, in which fatigability of foot dorsiflexors can often be problematic, particularly in those with moderate to severe disability (Coca-Tapia et al., 2021). Therefore, when assessing pwPMS, it seems advisable to include the use of both measures to be able to assess absolute cardiorespiratory fitness (IET) with an exercise modality which utilises all limbs (recumbent cross-trainer) as well as walking ability whilst undertaking a walking task (6MWT).

Another potential reason for the IET and 6MWT findings could be the effect of active and passive encouragement (Edwards et al., 2018). The test procedure for the 6MWT is performed in an environment with minimal distraction. The tester is required to adhere to a standardised script where no encouragement is provided other than informing the participant, at one-minute intervals, as to how many minutes have passed. In contrast, the standardised IET protocol is designed to ensure participants achieve their maximal aerobic capacity with active encouragement throughout the testing procedure. Here motivational components include the use of a metronome to keep to pace, and verbal active praise from the researchers to encourage the individual to reach volitional exhaustion.

We explored the relationship between subjective impact of fatigue, walking capacity and subjective walking ability. Our findings align closely with those of Dalgas (2017) whose multi-centre mixed sample study of 180 people with MS (88 of whom were in the progressive phase) also demonstrated weak negative correlations with the 6MWT (walking velocity) and $MFIS_{Total,}$ and a stronger relationship with subjective walking ability. This was despite our sample being more physically disabled (median EDSS 6.0 [4.5, 6.5] versus EDSS 4.1 [SD 1.8, range 0 – 6.5) and comprising only of pwPMS. Both studies lend support to the notion that the weaker correlation between fatigue impact and objectively rated walking distance compared to the self-rated measure of walking ability (MSWS-12) may be, at least in part, accounted for by the broader conceptual nature of the MSWS-12 which incorporates perceived effort and concentration rather than solely on walking distance.

Several mixed sample studies have reported correlation coefficients between fatigue impact and measures of depressive and anxiety symptoms in people with MS (Sparasci et al., 2022; Tarasiuk et al., 2021; Hanna and Strober, 2020; Greeke et al., 2017). In line with our study findings, strong, statistically significant correlations between fatigue and measures of depressive symptoms and anxiety have been found by some (Sparasci et al., 2022; Tarasiuk et al., 2021), with others identifying moderate statistically significant correlations with depressive symptoms (AlSaeed et al., 2022; Hanna and Strober, 2020). Together, these findings underline the importance of assessment and awareness of neurobehavioural factors when supporting individuals to best manage fatigue, by addressing aspects such as motivation, attitudes, beliefs, and behaviours (Fidao et al., 2021). The combined use of a CBT approach to address unhelpful thoughts and behaviours (Thomas et al., 2013), with a structured, graduated exercise programme and fatigue management education holds promise (Harrison et al., 2021). Further research is required to investigate the effectiveness of combining all modalities.

Few studies to date have explored the relationship between fatigue and physical and neurobehavioural factors in pwPMS. A strength of this analysis is its large multinational sample size, and inclusion of people with a broad range of disability levels, exclusively in the progressive phase. The rigorous standardisation of outcome measures employed in the trial supports the validity of the results and provides a sound scientific base of evidence. The study should also be viewed in the light of its limitations. The restriction of range in the outcomes, as a direct consequence of the inclusion criteria relating to physical activity and cognition, narrows the population characteristics which may have downwardly biased the correlations. The generalisability of this sample is therefore not representative of progressive MS overall. Furthermore, it is acknowledged that in this analysis of baseline data the outcomes are only described at one time point which means causality of assumptions cannot be assessed. A post hoc analysis of the impact of the CogEx interventions on fatigue looking specifically at those fatigued at baseline and post active- or sham-exercise would allow further investigation of potential causal relationships.

5. Conclusion

Fatigue is a prevalent symptom of MS, which can be influenced by many factors. Our data suggest that both physical and neurobehavioural factors should be considered when supporting pwPMS to manage fatigue, underlining the need for a coordinated and holistic multidisciplinary approach to management. This should routinely include assessment and management of neurobehavioural symptoms, and the patient's perspective on disease impact, which were demonstrated in this cross-sectional analysis to be more strongly associated with fatigue. Longitudinal studies are warranted that further investigate the assessment and management of these elements in fatigued pwPMS.

CRediT authorship contribution statement

L Connolly: Investigation, Visualization, Writing – original draft, Writing – review & editing. **S Chatfield:** Investigation, Writing – original draft, Writing – review & editing. **J Freeman:** Conceptualization, Investigation, Methodology, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing. **A Salter:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Visualization. **MP Amato:** Conceptualization, Investigation, Methodology, Writing – review & editing. **G Brichetto:** Conceptualization, Funding acquisition, Investigation, Methodology, Writing – review & editing. **J Chataway:** Formal analysis, Investigation, Methodology, Writing – review & editing. **ND Chiaravalloti:** Conceptualization, Investigation, Methodology, Writing – review & editing. **G Cutter:** Conceptualization, Investigation, Writing – review & editing. **J DeLuca:** Conceptualization, Funding acquisition, Investigation, Methodology, Writing – review & editing. **U Dalgas:** Conceptualization, Funding acquisition, Investigation, Methodology, Writing – review & editing. **R Farrell:** Conceptualization, Investigation, Methodology, Writing – review & editing. **P Feys:** Conceptualization, Investigation, Methodology, Writing – review & editing. **M Filippi:** Project administration. **M Inglese:** Conceptualization, Investigation, Methodology, Writing – review & editing. **C Meza:** Conceptualization, Funding acquisition, Investigation, Methodology, Writing – review & editing. **NB Moore:** Conceptualization, Investigation, Methodology, Writing – review & editing. **RW Motl:** Formal analysis, Investigation, Methodology, Writing – review & editing. **MA Rocca:** Formal analysis, Investigation, Methodology, Writing – review & editing. **BM Sandroff:** Investigation, Methodology, Writing – review & editing. **A Feinstein:** Conceptualization, Funding acquisition, Investigation, Methodology, Writing – review & editing.

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Amber Salter receives research funding from Multiple Sclerosis Society of Canada, National Multiple Sclerosis Society, CMSC and the US Department of Defense and is a member of the editorial board for Neurology. She serves as a consultant for Gryphon Bio, LLC. She is a member of the Data and Safety Monitoring Board for Premature Infants Receiving Milking or Delayed Cord Clamping (PREMOD2), Central Vein Sign: A Diagnostic Biomarker in Multiple Sclerosis (CAVS-MS), and Ocrelizumab for Preventing Clinical Multiple Sclerosis in Individuals With Radiologically Isolated Disease (CELLO).

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Nancy Chiaravalloti is on an Advisory Board for Akili Interactive and is a member of the Editorial Boards of Multiple Sclerosis Journal and Frontiers in NeuroTrauma.

Gary Cutter is a member of Data and Safety Monitoring Boards for Astra-Zeneca, Avexis Pharmaceuticals, Biolinerx, Brainstorm Cell Therapeutics, Bristol Meyers Squibb/Celgene, CSL Behring, Galmed Pharmaceuticals, Horizon Pharmaceuticals,Hisun Pharmaceuticals, Mapi Pharmaceuticals LTD, Merck, Merck/Pfizer, Opko Biologics, OncoImmune, Neurim, Novartis, Ophazyme, Sanofi Aventis, Reata Pharmaceuticals, Teva pharmaceuticals, VielaBio Inc, Vivus, NHLBI (Protocol Review Committee), NICHD (OPRU oversight committee). He is on Consulting or Advisory Boards for BioDelivery Sciences International, Biogen, Click Therapeutics, Genzyme, Genentech, GW Pharmaceuticals, Klein-Buendel Incorporated, Med- immune, Medday, Neurogenesis LTD, Novartis, Osmotica Pharmaceuticals, Perception Neurosciences, Recursion/Cerexis Pharmaceuticals, Roche, TG Therapeutics. Dr. Cutter is employed by the University of Alabama at Birmingham and President of Pythagoras, Inc. a private consulting company located in Birmingham AL.

John DeLuca is an Associate Editor of the Archives of Physical Medicine and Rehabilitation, and Neuropsychology Review; received compensation for consulting services and/ or speaking activities from Biogen Idec, Celgene, MedRhythms, and Novartis; and receives research support from Biogen Idec, National Multiple Sclerosis Society, Consortium of Multiple Sclerosis Centers, and National Institutes of Health.

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Peter Feys is editorial board member of NNR and MSJ, provides consultancy to NeuroCompass and was board of advisory board meetings for BIOGEN.

Massimo Filippi is Editor-in-Chief of the Journal of Neurology and Associate Editor of Human Brain Mapping, Neurological Sciences, and Radiology, received compensation for consulting services and/or speaking activities from Alexion, Almirall, Bayer, Biogen, Celgene, Eli Lilly, Genzyme, Merck-Serono, Novartis, Roche, Sanofi, Takeda, and Teva Pharmaceutical Industries, and receives research support from Biogen Idec, Merck-Serono, Novartis, Roche, Teva Pharmaceu tical Industries, the Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, and ARiSLA (Fondazione Italiana di Ricerca per la SLA). Matilde Inglese is Co-Editor for Controversies for Multiple Sclerosis Journal; received compensation for consulting services and/or speaking activities from Biogen Idec, Merck-Serono, Novartis, Roche, Sanofi Genzyme; and received research support from NIH, NMSS, the MS Society of Canada, the Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, H2020 EU Call.

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