Fatigue, Physical Activity, Quality of Life, and Fall Risk in People with Multiple Sclerosis

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Background: *Fatigue, inactivity, and falls are major health issues for people with multiple sclerosis (MS). We examined the extent to which fatigue and low walking activity are associated with quality of life and increased fall risk in people with MS.*

Methods: *People with MS (N = 210, aged 21–74 years) were categorized as having either high or low reported fatigue and walking activity levels and were then followed up for falls using monthly fall diaries for 6 months.*

Results: *A high level of fatigue was significantly associated with higher MS Disease Steps scores, worse balance, high composite physiological (Physiological Profile Assessment) fall risk scores, greater fear of falling, lower World Health Organization Disability Assessment Schedule (WHODAS) quality of life scores, and more prospectively recorded falls. Low walking activity was significantly associated with higher MS Disease Steps scores, reduced proprioception, worse standing and leaning balance, slow stepping, slow gait speed, worse fine motor control, high Physiological Profile Assessment fall risk scores, more fear of falling, and lower WHODAS quality of life scores.*

Conclusions: *Increased fatigue and low walking activity levels were significantly associated with increased fall risk and lower quality of life in people with MS. Interventions aimed at addressing fatigue and inactivity may have multiple benefits for this group.* ***Int J MS Care.*** **2017;19:91–98.**

Fatigue is one of the most common and disabling symptoms experienced by people with multiple sclerosis (MS).[1] Fatigue affects approximately 75% of people with MS and heavily influences mental health, general health status, employment levels, and quality of life.[2] People with MS are also less physically active than their peers without MS. This is evident from a recent meta-analysis that indicated a nearly 1 SD lower level of physical activity in people with MS compared with controls.[3] However, evidence is indicating that physical activity improves or maintains walking mobility, muscle strength, fatigue, depression, cognition, and health-related quality of life.[4]

Falls represent a major mobility-related health issue for people with MS, as demonstrated by an epidemiologic study showing that approximately 60% of people with MS fall one or more times over 3 months.[5] Recent studies have identified a range of neuropsychological, physical, health, and lifestyle risk factors for falls in people with MS.[6,7] Although fatigue and physical activity levels have been extensively investigated in people with MS, few studies have examined relationships between fatigue and falls in this group. Some studies have documented that people with MS are likely to attribute their falls to fatigue.[8,9] However, risk factor studies have produced inconsistent findings. Coote et al.[7] found that Fatigue Severity Scale (FSS) scores were significantly increased in past fallers compared with past nonfallers. In contrast, Nilsagård et al.[10] found no significant difference in FSS scores between those who did and did not

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fall in a 3-month follow-up period. Research in this area has also been limited by relatively small sample sizes, heterogeneity of patient populations, and a restricted range of important associated cognitive, psychological, physical functioning, and quality of life measures.

To address these issues, we conducted a large prospective cohort study using a comprehensive battery of validated measures to examine interrelationships among these important health and lifestyle factors. The main aims were 1) to document levels of fatigue and physical activity in a large community-living sample of people with MS and 2) to determine associations between fatigue, planned exercise, and walking activity and MS disease severity, cognitive functioning, functional ability, health-related quality of life, fear of falling, and falls in this group.

Methods

Participants

Participants (N = 210), recruited from among outpatients of an MS clinic in Sydney, Australia, were included if they were 18 years or older, had received a definite diagnosis of MS (any type) by a neurologist, and were able to stand unsupported for 30 seconds and walk 10 m with or without a mobility aid. The sole exclusion criterion was an inability to understand instructions relating to the study questionnaires and fall diaries due to impaired cognitive function or insufficient English. The study was approved by the Human Research Ethics Committee, University of New South Wales, Sydney, Australia. Participation was voluntary, and informed consent was obtained from all the participants before assessment.

Assessment Measures

The questionnaire and assessment measures used in this study encompassed health, sensorimotor, balance, and neuropsychological factors required for safe mobility. They were administered at one time point by trained therapists and took approximately 1.5 hours to complete.

Demographic, Health, and Disability Measures

Participants completed a structured questionnaire to provide information about age, sex, previous falls and fall injuries in the past year, number of years diagnosed as having MS, type of MS, and walking aids used. Participants' level of disability was assessed using the validated Disease Steps scale.[11]

Fatigue

Fatigue was assessed using the FSS,[12] a commonly used self-report questionnaire for measuring fatigue in people with MS. Participants were asked to rate their level of agreement on nine fatigue-related statements, ranging from 1 (strongly disagree) to 7 (strongly agree). Participants were classified into two groups with respect to their fatigue levels: low fatigue (mean FSS item scores <5) and high fatigue (mean FSS item scores ≥5). This criterion was used because Valko et al.[12] reported mean (SD) FSS item scores of 4.66 (1.64) in patients with MS, and Lerdal et al.[13] indicated that FSS item scores greater than 4 are indicative of fatigue.

Planned Exercise and Walking Activity

Physical activity was assessed using items from the Incidental and Planned Exercise Questionnaire (IPEQ).[14] This self-report questionnaire covers the frequency and duration of planned and incidental physical activities and has high reported test-retest repeatability (intraclass correlation coefficient = 0.84). The IPEQ consists of ten questions about physical activity pertaining to an average week in the past 3 months. Participants were classified into two groups with respect to their planned activity levels: taking part in no planned activities per week or taking part in 1 or more planned activities per week. Planned exercises were defined as physical exercises aimed at improving and maintaining balance, strength, flexibility, and coordination. Excluded activities were walking (included in a separate question), routine activities such as gardening and house cleaning, and seated activities such as bingo and piano playing. Participants were also classified with respect to walking activity: low walking activity (≤1 h/wk) or high walking activity (>1 h/wk).

Sensorimotor Function

Visual contrast sensitivity was assessed using the Melbourne Edge Test.[15] Proprioception was measured with participants sitting using a lower-limb–matching task.[15] Maximal isometric quadriceps strength was included as an outcome measure because it is a major lower-limb muscle group important for sit-to-stand, transfers, gait, and stair climbing. It was measured in both legs while participants were seated on a high chair with the hips and knees flexed to 90°. A strain gauge was fixed horizontally with straps on the lower shin, after which the participant was given a total of three attempts for each leg to push against the strap as forcefully as possible.

The timed Nine-Hole Peg Test (NHPT)[16] was administered to gain a measure of the extent of disease affecting complex upper-extremity function. Performance on the NHPT was examined by asking seated participants to pick up nine pegs from a shallow container one at a time as quickly as possible, place them in nine holes, and then remove them again as quickly as possible, one at a time, replacing them in the container. Simple Reaction Time was measured with a light as a stimulus and a finger press as the response.[15]

Balance

Postural sway was assessed using a sway meter with demonstrated high external validity and reliability.[17] Testing was performed with participants standing on the floor and on a medium-density foam rubber mat (65 × 65 × 15 cm thick) with eyes open and closed. Controlled leaning balance was measured using two tests with demonstrated validity and reliability: the maximal balance range and coordinated stability tests.[18] In these tests, the sway meter was attached anteriorly to the participant. In the maximal balance range test, participants were required to lean as far forward and as far back as possible without moving the feet or bending at the hips. The coordinated stability test required participants to adjust balance by leaning or rotating the body without moving the feet so that the pen followed and remained within the borders of a 1.5-cm-wide convoluted track marked on an A4 size paper sheet.

Stepping and Mobility

Stepping was assessed with a test of choice stepping reaction time.[19] Participants stood on a nonslip black mat (0.8 × 1.2 cm) marked with four rectangular panels (32 × 13 cm), one in front of each foot and one to the side of each foot. Participants were instructed to step onto specific rectangle panels in sequence as quickly as possible. Mobility was assessed by walking speed over 10 m with and without a secondary cognitive task (counting backward by threes starting at 100). To allow for acceleration and deceleration, 2 m was provided at either end of a 10-m marked course. The secondary cognitive task was included because it has been established that such tasks significantly affect balance and gait in people with MS.[20]

Neuropsychological Assessment

Cognitive processing was assessed using the Trail Making Test (TMT),[21] including Part A (TMT-A) testing simple attention and Part B (TMT-B) testing complex attention. In the TMT-A, participants were asked to draw lines connecting numbered circles in numerical order. The TMT-B included a similar task but the circles contained numbers and letters (eg, 1-A-2-B). Total time to complete each test was recorded. The difference between parts A and B (TMT-B-A) was calculated to remove the motor speed element from the test evaluation, leaving an estimate of executive function. This test was chosen because it has consistently been found to discriminate significantly between fallers and nonfallers in samples of older people and people with MS.[6,22]

Physiological Profile Assessment Fall Risk Score

The Physiological Profile Assessment (PPA) provides a fall risk index score composed of weighted values from five of the previously mentioned sensorimotor and balance measures: visual contrast, lower-limb proprioception, quadriceps strength, reaction time, and sway on the foam mat with eyes open. In studies of older people, PPA fall risk index scores discriminate between multiple and nonmultiple fallers with accuracies up to 75%, with scores less than 0 indicating a low risk of falling; 0 to 1, a moderate risk of falling; and 2 or greater, a high risk of falling.[15]

Quality of Life

Quality of life was measured using the cross-culturally validated 12-item version of the World Health Organization Disability Assessment Schedule (WHODAS) 2.0 questionnaire. The questionnaire captures an individual's level of functioning in six major life domains: cognition, mobility, self-care, getting along, life activities, and participation in society.[23]

Falls and Fear of Falling

A fall was defined as "unintentionally coming to the ground or some lower level and other than as a consequence of sustaining a violent blow, loss of consciousness, sudden onset of paralysis as in stroke, or an epileptic seizure."[24] Falls were monitored by using monthly postal fall diaries prospectively over 6 months, with monthly telephone follow-up if required. Fear of falling was examined with the Falls Efficacy Scale-International.[25]

Statistical Analysis

Data were analyzed using a statistical software program (IBM SPSS Statistics for Windows, version 22.0; IBM Corp, Armonk, NY). For continuously scaled variables with right-skewed distributions, log-transformations were used before analysis. Associations between the ordinally scaled Disease Steps measure and continuously

scored variables were calculated using Spearman correlation coefficients. Independent *t* tests and Mann-Whitney *U* tests were used as appropriate to compare the neuropsychological, sensorimotor, balance, gait, quality of life, Disease Steps, and fall measures with dichotomized (high and low levels) measures of fatigue, planned exercise, and walking activity as the dependent variables. Complementary χ^2 tests for contingency tables were also used to assess associations among the dichotomized measures of fatigue, planned exercise, and walking activity between these variables and faller group status. Additional variables, such as disease duration, disability levels, and treatments, were not included in the analyses as possible confounders because the underlying premise is to identify functional/physiological predictors,[15] and the inclusion of medical conditions may result in overadjusting and dilution of important explanatory findings.[26]

Results

Participants

The mean (SD) age of participants was 50.8 (11.1) years, and 152 were women (72.4%). Table 1 shows the demographic and MS-specific disease characteristics of the sample.

Fatigue

The FFS was completed by 203 (96.7%) participants. Mean FSS scores were weakly but significantly associated with MS Disease Steps scores (Spearman rho = 0.164, $P = .019$). Overall, 126 participants (60.0%) reported a high level of fatigue (mean FSS item scores ≥5). Participants categorized as having a high level of fatigue ranged from 40.7% in those with a Disease Steps score of 0 to 73.1% in those with a Disease Steps score of 5 (Figure 1). Participants with a high level of fatigue were also significantly more likely to have a low level of walking activity ($\chi^2 = 5.210$, $df = 1$, $P = .030$) but not more likely to do no planned exercise ($\chi^2 = 2.423$, $df = 1$, $P = .132$).

Table 2 shows the mean (SD) scores for the continuously scored test measures for people with mean FSS item scores above and below the cut-point score of ≥5. Participants with high levels of reported fatigue had significantly increased sway with eyes closed while standing on the floor, high PPA fall risk scores, greater concern about falling, and worse scores on the WHODAS 2.0. The Spearman correlation coefficient for the association between mean FSS item scores and the summed WHODAS 2.0 score was 0.57 ($P < .001$), and greater fatigue levels were significantly associated with worse function in all of the individual WHODAS 2.0 items (Spearman rho = 0.22–0.58, $P < .01$); relationships are presented in Supplementary Figure 1, which is published in the online version of this article at ijmsc.org.

Complete fall follow-up was achieved with the system of diaries and follow-up telephone calls. One hundred twenty-six participants (60%) reported at least one fall

Table 1. Demographic and disease-specific characteristics of the 210 study participants

Characteristic	Value
Age, mean (SD) [range], y	50.8 (11.1) [21–74]
Sex, F/M, No. (%)	152 (72.4)/58 (27.6)
Disease duration, mean (SD) [range], y	9.9 (7.0) [0.2–31.1]
Disease type, No. (%)	
Primary progressive	26 (12.4)
Relapsing-remitting	121 (57.6)
Secondary progressive	27 (12.9)
Unknown[a]	36 (17.1)
Disease Steps score, No. (%)	
0	28 (13.3)
1	57 (27.1)
2	25 (11.9)
3	37 (17.6)
4	37 (17.6)
5	26 (12.4)
Mobility aids, No. (%)	
No aids	108 (51.4)
Walking stick	58 (27.6)
Frame or rollator	18 (8.6)
Crutches	7 (3.3)
Ankle brace	5 (2.4)
Others (wheelchair, scooter, etc.)	14 (6.7)
Disease-modifying therapy, No. (%)	
None	73 (34.8)
Interferon beta-1a	48 (22.9)
Interferon beta-1b	21 (10.0)
Natalizumab	21 (10.0)
Glatiramer acetate	38 (18.1)
Not sure	9 (4.3)
Antispasticity medication, No. (%)	
None	165 (78.6)
Baclofen	30 (14.3)
Valium	6 (2.9)
Botulin toxin	2 (1.0)
Not sure	7 (3.3)
Falls and fall-related injuries in the past 12 mo	
Falls, mean (SD) [range], No.	2.5 (2.1) [0–6]
≥1 fall injuries, No. (%)	71 (33.8)
≥1 fall-related fractures, No. (%)	34 (16.2)

[a]Participants did not report what type of multiple sclerosis they had.

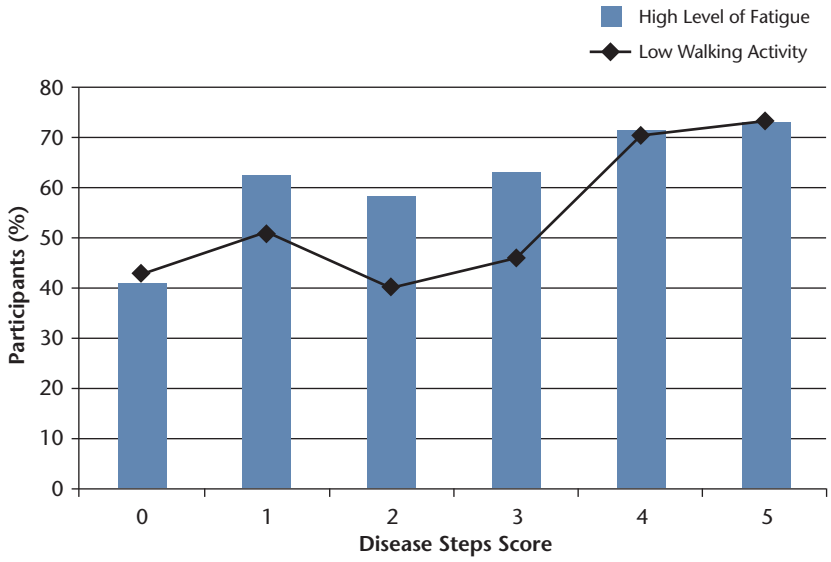

Figure 1. **Combined bar and line graph of high levels of fatigue and low walking activity according to Disease Steps score**

in the 6-month follow-up period. Of those who fell, 32 (25%) fell one time, 25 (20%) fell twice, and 69 (55%) fell three times or more. The median fatigue score for fallers was 5.8 (interquartile range = 4.3–6.8), which was significantly higher than that for nonfallers, that is, 5.1 (interquartile range = 4.0–6.1) (Mann Whitney U = 4114.50, z = 2.06, P = .039). There were also significant associations between individual FSS items and faller status when dichotomized into yes-no variables. Forty of the 82 nonfallers with FFS data (48.8%) reported that exercise brings on fatigue compared with 83 of the 121 fallers with FFS data (68.6%) (χ^2 = 8.04, df = 1, P = .005). Similarly, 48 nonfallers (58.5%) reported that fatigue prevents sustained physical functioning compared with 91 fallers (75.2%) (χ^2 = 6.29, df = 1, P = .014).

Planned Exercise and Walking Activity

Walking activity levels were significantly associated with MS Disease Steps levels (Spearman rho = .225, P = .008). Seventy-two participants (34.3%) did not participate in any planned exercise, and 113 (53.8%) had low walking activity (≤1 h/wk). The percentage of participants with walking activity of 1 h/wk or less ranged from 42.9% in participants with a Disease Steps score of 0 to 73.1% in participants with a Disease Steps score of 5 (Figure 1).

Table 2 shows the mean (SD) scores for the continuously scored test measures for people who did nil or one or more planned exercise activities and who had low or high walking activity. Planned exercise as a dichotomized variable was significantly associated with only one measure: summed WHODAS 2.0 scores. In contrast, low walking activity as a dichotomized variable was significantly associated with several measures: worse proprioception, worse balance as indicated by three of the four sway tests and the coordinated stability test, slow choice stepping reaction times, slow walking speed (with and without the conduct of a secondary cognitive task), worse fine motor control, high PPA fall risk scores, worse scores on the WHODAS 2.0, and greater concern about falling.

No significant differences between the activity measures and falls were evident: 46 of the 122 fallers with planned exercise data (37.7%) and 26 of the 82 nonfallers with planned exercise data (31.7%) reported no planned exercise (χ^2 = 0.77, df = 1, P = .46), and 63 of the 126 fallers with walking activity data (50.0%) and 50 of 83 nonfallers with walking activity data (60.2%) reported low levels of walking activity (χ^2 = 0.15, df = 1, P = .16).

Discussion

The study findings revealed that people with MS with high fatigue levels performed significantly worse on tests of balance and had high composite physiological (PPA) fall risk scores, greater fear of falling, lower WHODAS 2.0 quality of life scores, and more falls in the 6-month period after assessment than people with MS with low fatigue levels. These findings demonstrate the significant and broad range of health and lifestyle factors associated with fatigue, including MS Disease Steps and reduced walking activity, and build on previous studies that have found that people with MS identify fatigue as a contributing factor to their falls[8,9] and reduced quality of life.[27,28]

People with MS rate walking as one of the most important bodily functions and state that mobility is the

Table 2. Test scores for sensorimotor, balance, gait, neuropsychological function, and quality of life measures for participants categorized as having low or high fatigue, 0 or 1 or more planned exercise per week, and less than 1 or 1 or more hours of walking activity per week

	Fatigue		Planned exercise		Walking activity	
Measure	FSS mean score <5 (n = 84)	FSS mean score ≥5 (n = 126)	0/wk (n = 72)	≥1/wk (n = 138)	<1 h/wk (n = 113)	≥1 h/wk (n = 97)
MS Disease Steps score[a]	2.0 (1.0–3.0)	3.0 (1.0–4.0)[b]	2.0 (1.0–3.8)	2.0 (1.0–4.0)	3.0 (1.0–4.0)	2.0 (1.0–3.0)[c]
Visual contrast sensitivity, dB	21.5 (1.7)	21.9 (2.0)	22.0 (1.9)	21.7 (1.9)	21.7 (2.0)	21.7 (1.6)
Proprioception, degree error	4.1 (2.9)	3.9 (2.6)	4.0 (2.4)	4.0 (2.8)	4.4 (3.1)	3.5 (1.9)[b]
Quadriceps strength, kg force	29.2 (11.8)	29.0 (11.1)	29.6 (12.9)	29.0 (10.6)	29.0 (11.6)	29.6 (12.3)
Sway, mm						
Eyes open on floor	136 (100)	180 (144)	173 (147)	157 (121)	168 (116)	160 (150)
Eyes closed on floor	241 (204)	329 (249)[c]	343 (271)	270 (211)	316 (228)	277 (244)[b]
Eyes open on foam	302 (214)	359 (245)	350 (252)	329 (226)	380 (239)	295 (228)[c]
Eyes closed on foam	663 (390)	686 (378)	649 (412)	690 (367)	760 (385)	588 (360)[c]
Coordinated stability, error score	21.7 (20.8)	21.7 (18.0)	20.6 (17.3)	22.1 (20.0)	25.1 (18.7)	18.3 (19.2)[b]
Choice stepping reaction time, s	36.3 (19.0)	41.0 (19.7)	38.1 (20.0)	39.7 (19.3)	44.3 (20.8)	33.8 (16.6)[c]
10 m gait time, s	12.6 (11.8)	13.2 (9.0)	12.7 (10.6)	13.0 (9.9)	15.0 (11.3)	10.5 (7.7)[c]
10 m dual-task gait time, s	17.2 (17.5)	18.6 (13.8)	17.9 (14.9)	18.1 (15.5)	20.9 (16.1)	14.6 (13.3)[c]
NHPT, s	28.4 (11.2)	28.5 (9.6)	28.6 (11.8)	28.4 (9.3)	30.5 (12.7)	26.5 (6.9)[c]
TMT-B-A, s	54.2 (32.5)	66.8 (50.8)	69.3 (52.5)	58.0 (39.9)	70.4 (53.7)	53.5 (32.7)
PPA fall risk (z) score	1.84 (1.38)	2.27 (1.55)[b]	2.10 (1.61)	2.10 (1.45)	2.39 (1.51)	1.78 (1.45)[c]
FES-I score	29.5 (9.0)	38.3 (11.4)[c]	35.8 (11.6)	34.5 (11.3)	37.5 (11.8)	32.2 (10.4)[c]
WHODAS 2.0 score	22.6 (6.6)	31.8 (8.3)[c]	30.0 (10.1)	27.3 (8.1)[b]	30.4 (8.8)	25.9 (8.4)[c]

Abbreviations: FES-I, Falls Efficacy Scale-International; MS, multiple sclerosis; NHPT, Nine-Hole Peg Test; PPA, Physiological Profile Assessment; TMT, Trail Making Test; WHODAS, World Health Organization Disability Assessment Schedule.
Note: Data are given as mean (SD) except where indicated otherwise.
[a]Median (interquartile range) with comparisons assessed by Mann-Whitney *U* tests. All other comparisons assessed with group *t* tests.
[b]Significant at $P < .05$.
[c]Significant at $P < .01$.

most valued activity of daily living.[29] We examined two measures of physical activity from the IPEQ: planned exercise and total walking activity; of these, walking activity was more strongly associated with physical performance, functional activity, and fall efficacy. Low walking activity (<1 h/wk) was significantly associated with reduced proprioception, worse standing and leaning balance, slow stepping, slow gait speed, worse fine motor control, high PPA fall risk scores, high levels of fear of falling, and worse WHODAS 2.0 quality of life scores, whereas no planned exercise was associated with only reduced total WHODAS 2.0 quality of life scores. Self-reported walking activity over a 1-week period seems to be a simple and appropriate marker of disability, Disease Steps score, and disease progression.[30] In contrast, it seems that the construct of planned exercise as used in the present questionnaire was too broad and ill-defined, leading to study participants interpreting it in different ways and rendering it less useful as a screening tool. This construct may be more accurately measured with questionnaires or interview items that more tightly specify physical activities.

Not unexpectedly, participants with higher fatigue levels were also more likely to have low activity levels. This finding is consistent with a report of a survey of 417 individuals with MS that identified fatigue, along with impairment and lack of time, as among the top three barriers to exercise.[31] Several nonsignificant findings warrant discussion. Higher levels of fatigue were not significantly associated with reduced quadriceps strength, slow stepping, slower gait speed (with or without a secondary cognitive task), poor NHPT coordination, and reduced executive function assessed using the TMT. Previous studies have found that fatigue is associated with impaired cognition and less functional cerebral activation in several regions involved in motor planning and execution.[32,33] It may be that the present participants performed the tests in an unfatigued state, minimizing any variance on this measure, and that significant associations may become more readily apparent after participants undertake a fatiguing activity. Previous studies

have also documented that reduced muscle strength is significantly associated with low levels of physical activity in people with MS,[4] but such an association was not apparent herein. It is possible that the isometric measure of strength did not sufficiently represent functional strength or that Disease Steps and the wide age range (21–73 years) may have confounded the association. The inclusion of a measure of knee flexion strength may also have been instructive because knee extension strength often remains greater than flexion strength, even at an advanced stage of walking disability, in part due to spasticity.

We also acknowledge other limitations. We used questionnaires to measure fatigue and physical activity because this is the most practical method for gaining this information in studies requiring large sample sizes.[34] These self-report assessments have advantages in that they have demonstrated validity[12,13] and reflect participants' symptom descriptions[12] and activity types, but self-report assessments also have disadvantages regarding subjectivity and recall bias. Future studies could use simple clinical fatigue routines, such as balance assessment before and after a 6-minute walk[35] and remote activity monitoring using accelerometers, to assess physical activity over extended periods.[36] Second, cognitive status was based on the clinical judgment of the assessing physiotherapist, and no formal cognitive screen was administered. However, because no participants had difficulties completing the TMTs or following other test instructions, it is evident that the sample was without significant cognitive impairment. Third, we did not include variables such as disease duration, disability levels, or disease type in the analyses owing to the functional/physiological approach used. Further studies could include these variables as covariates or in mediational analyses to further elucidate fall risk in people with MS. Finally, the inclusion of other signs and symptoms, such as joint contractures and spasticity, depression, education, and social status, may have revealed additional information regarding physical activity and fall risk in people with MS.

In conclusion, the study findings indicate that increased fatigue and low walking activity levels are significantly associated with increased fall risk and lower quality of life in people with MS. High fatigue levels were additionally associated with prospectively measured falls. Interventions aimed at addressing fatigue and inactivity may have multiple benefits for this group. □

PracticePoints

- Fatigue, reduced physical activity, and falls are major health problems for people with MS.
- Increased fatigue and low walking activity levels are significantly associated with increased fall risk and lower quality of life in people with MS.
- Interventions addressing fatigue and inactivity may have multiple benefits for this group.

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