Cognitive Function in Frail Older Adults With Multiple Sclerosis: An Exploratory Study Using Secondary Data Analysis

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ABSTRACT

BACKGROUND: Studies addressing frailty in the context of multiple sclerosis (MS) are emergent. This study explores cognitive function in older adults with MS as a function of frailty status.

METHODS: This cross-sectional study used baseline data from a feasibility randomized controlled trial of a home-based exercise program for older adults with MS. Frailty was verified using performance scores from the Short Physical Performance Battery (SPPB) and cut points available in the literature. Cognitive function was assessed using the Brief International Cognitive Assessments for Multiple Sclerosis (BICAMS). Data were analyzed using inferential statistics adopting a significance of $P < .05$.

RESULTS: Data from 26 older adults with MS (≥60 years) were analyzed. The majority of the participants were women, and over 85% of the sample had the relapsing-remitting form of MS. Participants reported a mean of more than 20 years of disease and a moderate level of disability (Expanded Disability Status Scale score = 4). Nearly 58% of the sample was classified as frail based on SPPB scores. Univariate analysis demonstrated that frail older adults performed significantly worse ($P < .05$) on all 3 BICAMS tests. However, after controlling for age and disability level, only visuospatial memory remained significant between frailty groups ($P = .043$).

CONCLUSIONS: Our findings suggest reduced cognitive function in frail older adults with MS compared with their nonfrail counterparts. This highlights the need to develop interventions to improve cognitive function and to reverse frailty for older adults with MS.

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Frailty is a common and important geriatric syndrome characterized by impaired stress tolerance due to age-associated declines in physiological reserve and function across different organs and systems, thereby increasing vulnerability to adverse health outcomes.[1-3] As a clinical state (not a disease), frailty is associated with an increased risk of falls, disability (dependency), hospitalization, institutionalization, and mortality in older adults from the general population.[4,5]

There is a solid body of knowledge on frailty and its consequences in older adults for the general population,[5,6] yet few studies have addressed frailty in the context of multiple sclerosis (MS). In one recent study, researchers compiled data from more than 490,000 adults (aged 37-73 years) and observed that MS was among the leading conditions associated with frailty, such that people with MS were 15 times more likely to be classified as frail than age-matched individuals without MS.[7] Researchers in another study reported that 91% of participants with MS (wheelchair and scooter users) met the objective criteria for severe frailty and 9% for moderate frailty, and frailty index scores were associated with falls during the previous 6 months.[8]

There is increasing evidence that older adults represent the fastest-growing segment of individuals with MS,[9,10] and frailty increases with age in all older adults.[5] The effect of aging on frailty is likely more pronounced in older adults with MS as a consequence of their worsening disability. Several studies indicate that older adults with MS further develop concomitant pathologies that could worsen the disease's prognosis[11] and their frailty. Collectively, the above underscores the need to explore the impact of frailty on known MS-related outcomes in older adults with MS, as this is a fast-growing subpopulation.

Cognitive impairment is a ubiquitous symptom of MS. This highly prevalent and life-changing outcome occurs in 45% to 65% of those with the disease[12,13] and is more common in older

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TABLE 1. General Demographic and Clinical Characteristics of the Sample

	Overall (N = 26)	Frail (n = 15)	Nonfrail (n = 11)	*P*
Age, mean (SD)	64.30 (4.52)	65.93 (5.35)	62.10 (1.30)	.016
Female, n (%)	23 (88.5)	14 (93.3)	9 (81.8)	.364
RRMS/SPMS, n	24/2	13/2	11/0	-
EDSS, median (IQR)	4.00 (2.50)	5.50 (1.50)	3.50 (1.00)	<.001
Disease duration, mean (SD)	21.11 (10.73)	22.00 (10.94)	19.90 (10.83)	.838

EDSS, Expanded Disability Status Scale; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

TABLE 2. Cognitive Function of Overall Sample and by Frailty Status

	Overall (N = 26)	Frail (n = 15)	Nonfrail (n = 11)	*d*	*P*
SDMT, mean (SD)	47.38 (13.80)	41.93 (13.47)	54.81 (10.79)	1.05	.012
CVLT-II, mean (SD)	52.34 (11.85)	47.93 (10.50)	58.36 (11.31)	0.95	.026
BVMT-R, mean (SD)	22.88 (5.57)	20.33 (5.53)	26.36 (3.41)	1.31	.002

BVMT-R, Brief Visuospatial Memory Test; CVLT-II, California Verbal Learning Test; SDMT, Symbol Digit Modality Test.

than younger adults with MS.[14] Researchers have focused on 3 domains when studying cognitive function in older adults with MS: processing speed, verbal learning, and visuospatial memory. The present study explores cognitive function in those 3 domains in a sample of older adults with MS as a function of frailty status.

METHODS

Study Design

This cross-sectional study is a secondary data analysis of the baseline data of a randomized controlled trial (feasibility study) investigating the effects of a home-based exercise program for older adults with MS.[15] The study protocol was approved by the Institutional Review Board of the University of Illinois Urbana-Champaign and conducted according to the Declaration of Helsinki. All participants signed an informed consent document prior to data collection.

Participants

Complete information recruitment and inclusion and exclusion criteria for the original study have been reported elsewhere.[15] Briefly, participants were recruited from the Midwest region of the United States using targeted recruitment through the North American Research Committee on Multiple Sclerosis and MS-specific support and other groups. Inclusion criteria for the study included factors such as age (≥60 years), a definitive diagnosis of MS, relapse-free status, and the ability to walk.

Measures

Frailty

Frailty was categorized using the Short Physical Performance Battery (SPPB).[16] The SPPB has been found to be a valid and objective assessment tool for evaluating lower extremity functioning in older adults with and without MS.[17,18] Previous work demonstrated that the SPPB has good levels of sensitivity (92%) and specificity (80%) in discriminating between frail and nonfrail older adults[19] and the ability to detect early stages of frailty, even among high-functioning older adults with normal mobility.[20] The battery consists of 3 subcomponents/assessments: standing balance, gait speed, and lower extremity strength. Performance scores for each SPPB subcomponent range from 0 to 4, with a total SPPB score ranging from 0 to 12 (higher scores reflect better performance). For this study, the total SPPB score was used to categorize participants into frail or nonfrail categories based on established cut points (ie, 9 points) for older adults available in the literature.[19] Fifteen participants had a score less than or equal to 9 and were classified as frail, and 11 had an SPPB score greater than 9 and were classified as nonfrail.

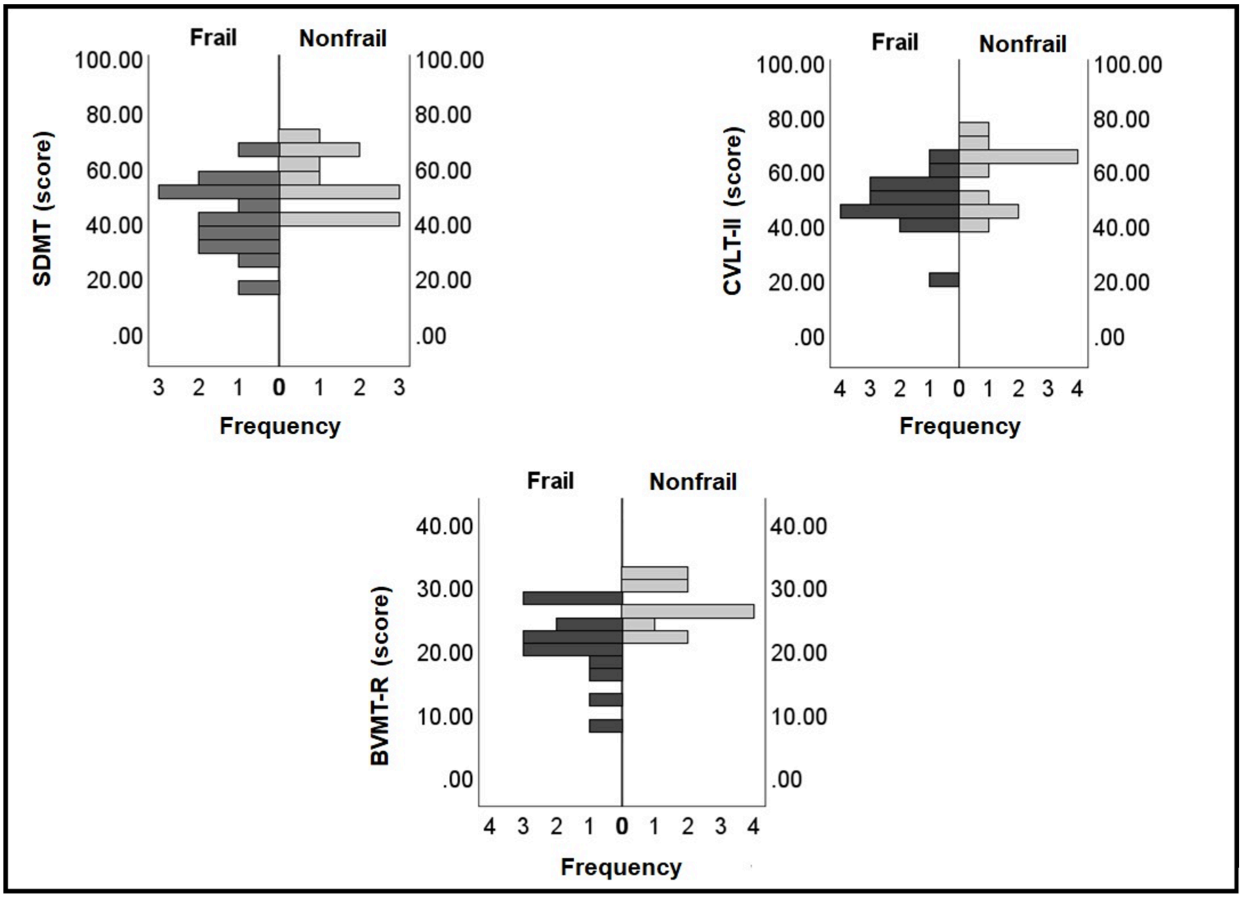
Cognitive Function

Cognitive function was measured using the Brief International Cognitive Assessment for MS (BICAMS).[21,22] BICAMS includes the oral version of the Symbol Digit Modalities Test (SDMT) as a measure of processing speed, the California Verbal Learning Test (CVLT-II) as a measure of verbal learning, and the Brief Visuospatial Memory Test-Revised (BVMT-R) as a measure of visuospatial learning and memory.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics, version 26, and significance was set at *P* less than .05. We first used descriptive statistics (ie, mean, median, and percentage) to describe the overall sample. An independent *t* test was then used to compare performance on the selected cognitive function tests between frail and nonfrail individuals. Effect sizes based on Cohen *d* were calculated and interpreted as small (ie, 0.2), moderate (ie, 0.5), or

FIGURE. Frequency Analysis of the 3 Cognitive Function Tests by Frailty Status



BVMT-R, Brief Visuospatial Memory Test; CVLT-II, California Verbal Learning Test; SDMT, Symbol Digits Modality Test.

large (ie, 0.8). Because age and disability level were significantly different between frail categories, we conducted a covariance analysis controlling for age and disability level.

RESULTS

TABLE 1 displays the demographic and clinical characteristics of the overall sample and subsamples by frailty status. Briefly, data from 26 adults with MS aged 60 years or older were analyzed, with 15 individuals in the frail group and 11 individuals in the nonfrail group. The mean age of the participants was 64.3 years with the frail group being significantly older than the nonfrail group ($P = .016$). Additionally, a majority of the sample was women (~88%), and approximately 92% of the participants had the relapsing-remitting form of MS. Overall, participants presented with a moderate level of disability, with the frail group demonstrating higher disability scores than their nonfrail counterparts ($P < .001$).

TABLE 2 depicts the mean and standard deviation values, along with effect sizes (Cohen *d*) for all 3 BICAMS tests. Independent sample *t* tests indicated that scores observed for the SDMT (ie, processing speed), CVLT-II (ie, verbal learning), and BVMT-R (ie, visuospatial memory) were significantly higher ($P<.05$) for older adults with MS classified as nonfrail than those classified as frail. The frequency of performance scores for the 3 tests employed in the study, separated by frailty status in older adults with MS, is in the **FIGURE**.

Analysis of Covariance

Because age and disability status (ie, EDSS score) were significantly different between groups (Table 1), we conducted an analysis of covariance controlling for those variables. Results indicated that visuospatial memory measured using the BVMT-R remained significantly different between groups (favorable to the nonfrail group; mean [SE], frail, 19.61 [1.78] vs nonfrail, 27.34 [2.27]; $P=.043$). There were no group differences in processing speed (SDMT; mean [SE], frail, 43.22 [4.88] vs nonfrail, 53.05 [6.22]; $P=.329$) or verbal learning (CVLT-II; mean [SE], frail, 48.59 [4.13] vs nonfrail, 57.46 [5.27]; $P=.299$) after controlling for age and disability status.

DISCUSSION

This study explored differences in cognitive function among older adults with MS as a function of frailty status. Univariate analysis revealed that frail older adults with MS had worse performance on all 3 cognitive tests than nonfrail counterparts. However, after controlling for age and disability level (ie, EDSS score), only visuspatial memory via BVMT-R scores remained significantly different between groups such that frail participants had worse performance than nonfrail participants. Because our sample size was small, future research should examine differences in cognition as a function of frailty status controlling for other factors, including age and disability, to replicate and extend our initial results. We were unable to draw definitive inferences regarding cognition and frailty in older adults with MS.

Overall, 57.7% of our sample was classified as frail based on SPPB scores. This number is similar to the upper bound range (59%) observed in studies conducted in older adults of the general population,[5] but different from the 28%[23] and the 100%[8] observed in previous studies with people with MS.

Differences in the prevalence of frailty between populations can be partially attributed to different assessment instruments, different operationalizations, and the setting where the study was conducted.[5] For example, one study classified individuals using a frailty index based on 30 health deficits in 45 people with MS who used a wheelchair or scooter.[8] Another study classified frailty using the Fried criteria and the frailty index in a sample of 80 adults with MS, aged 50 to 74 years, with mild levels of disability (EDSS = 2.8 ± 2).[23] The present study classified individuals based on scores of the widely adopted SPPB. We believe our approach is valid because previous work conducted in older adults demonstrated that the SPPB has good levels of sensitivity (92%) and specificity (80%) in discriminating frail from nonfrail older adults without MS when compared against the widely accepted Fried criteria[24] and the ability to detect early stages of frailty, even among high-functioning older adults with normal mobility.[19,20]

Although the univariate analysis demonstrated that performance in all 3 cognitive function tests was worse in frail than nonfrail older adults with MS, subsequent analysis revealed that only visuospatial memory remained significantly lower for the frail group after controlling for age and disability status. Comparing our findings on cognitive function and frailty in older adults with MS is challenging due to the paucity of studies addressing this topic, particularly studies examining the association between frailty and health-related outcomes in people with MS. A recent study conducted with 80 individuals with MS (mean age, 58.5 years; range, 50-74 years) and 30 controls suggested that frailty (verified by the frailty index) was independently associated with disability status (EDSS), comorbidities, education level, and disease duration.[23] However, no cognitive outcomes were included in that study.

As previously mentioned, although frailty has been heavily studied in older adults of the general population, studies of frailty in the context of MS are few. Nevertheless, it is important to highlight that the prevalence of cognitive impairment in older adults with MS is higher than observed in younger people with MS.[25] For example, in a study describing the prevalence and profile of cognitive impairment in older adults with MS, researchers observed that approximately 77% of older adults with MS (≥55 years) demonstrate impairment in 2 or more cognitive domains.[14] Results from this study demonstrated that information processing speed was the most impaired domain (68.8%), followed by verbal learning (49.5%), executive function (47.7%), and visuospatial learning (26.6%). Similarly, researchers in a recent study examined cognitive impairment in older adults with MS (mean age, 62 years) and observed that approximately 47% presented with cognitive impairment.[26] Researchers have further observed that performance scores on visuospatial memory (eg, BVMT-R) linearly decreased with age in people with MS, with the oldest presenting with the lowest scores.[27] This seems to contrast with other forms of cognitive tests such as those focusing on processing speed (eg, SDMT) and verbal learning (eg, CVLT-II), in which abrupt decreases in those 60 years or older are observed.[27] This suggests that visuospatial memory is affected differently in older adults with MS than other forms of cognition and, therefore, should be given special consideration in comparison with other domains of cognition.[27]

Collectively, the findings of our study added to results from previous work to reinforce the ideas that cognitive impairment is a concern in people with MS, but particularly among older adults with MS, and that frailty may exacerbate such a problem.

As a potentially reversible state, frailty is a complex concept based mainly on physical vulnerability, but it also encompasses mental/psychological and social vulnerabilities.[28] Thus, interventions aimed at reverting this clinical state in older adults with MS could revolve around a multidisciplinary approach that includes physical activity. This is based on a recent review focusing on older adults from the general population indicating that physical activity/exercise alone or in combination with other interventions (eg, nutrition, cognitive, social, pharmaceutical, or behavior) may result in frailty reversal.[29] This aligns with the multidisciplinary approach to patient care observed in MS.[30] Although the type of physical activity normally varies, evidence suggests that resistance exercise performed over a minimum of 12 weeks has the most beneficial effect on physical frailty.[31,32] This is reinforced by a recent review suggesting that resistance exercise performed regularly over the course of 6 months has the potential to improve both the physical and physiological aspects of frailty.[33] The emphasis on physical activity and/or exercise to reverse different aspects of frailty in previous studies relies on the fact that such behavior is essential for individuals across their life span, is highly recommended for general health and well-being for people with MS, and is key to helping manage numerous MS symptoms such as physical and cognitive function.[34]

In the past, frailty was used to assess mortality risk in adults 65 years or older[35]; more recently, the concept of frailty has been broadened to include physical, cognitive, social, emotional, and even economic components.[36] Given the well-known benefits of physical activity and exercise training in different dimensions (eg, physical, emotional, social), older adults with MS across the disability spectrum can benefit from such activities. In fact, physical activity and exercise training are highly recommended for people with MS[34,37] of all ages and levels of disability and constitute effective rehabilitation therapy.

Our study has notable strengths. First, this study is one of the few to investigate health-related outcomes in older adults with MS in the context of frailty. Second, an assessment of cognitive function was done using the valid and widely accepted BICAMS. However, interpretation of our findings warrants caution due to some limitations. Although there are different methods to identify frailty—with the Fried method[24] being the most accepted—we used scores from the SPPB to classify participants as frail or nonfrail using cut points validated for a sample of community-dwelling older adults.[19] Results of previous studies demonstrated that the SPPB can detect early stages of frailty with good levels of sensibility and sensitivity in community-dwelling older adults[19,20] and that SPPB scores are strongly associated with frailty.[38,39] However, the validity of the SPPB scores to categorize older adults with MS as frail has not been verified. The SPPB weighs heavily on lower-extremity function. Therefore, people with MS with significant spinal cord involvement would be more likely to score as frail, likely accounting for the significantly higher EDSS in the frail group. On the other hand, people with MS with predominant spinal cord disease may present with lower disease burden in the brain, potentially resulting in better cognitive preservation.

It is important to note that none of the existing methods to identify frailty in community-dwelling older adults without MS have been validated or developed for those with MS. Further, this secondary analysis study involved the data of only 26 older adults with MS, which can arguably be considered a small sample. Despite the limitations, we were able to gather preliminary evidence of reduced cognitive function in frail older adults with MS.

CONCLUSIONS

Our findings suggest that nonfrail older adults with MS with certain levels of preserved mobility (ie, no more than unilateral assistive device) present with better cognitive processing speed, verbal learning, and visuospatial memory than frail counterparts. However, after controlling for age and disability, only visuospatial memory remained significantly different between frail and nonfrail participants, but this may be the result of small sample size and low statistical power. Coupled with findings from previous work, the results of the present study highlight the need to develop interventions for frailty, a reversible clinical state, in older adults with MS. As a concept that involves physical, psychological, and social aspects, a multidisciplinary approach to reverse frailty is warranted, potentially one that includes physical activity and/or exercise training. Evidence in older adults of the general population suggests that physical activity alone or in combination with other interventions (eg, nutrition, cognitive, social, pharmaceutical, or behavior) may result in frailty reversal.[29] In fact, physical activity and exercise training are highly recommended for people with MS of all ages and levels of disability as a key to rehabilitation and to improving overall health and well-being.[34,37]

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REFERENCES

1. Chen X, Mao G, Leng SX. Frailty syndrome: an overview. *Clin Interv Aging*. 2014;9:433-441. doi:10.2147/CIA.S45300
2. Xue QL. The frailty syndrome: definition and natural history. *Clin Geriatr Med*. 2011;27(1):1-15. doi:10.1016/j.cger.2010.08.009
3. Ahmed N, Mandel R, Fain MJ. Frailty: an emerging geriatric syndrome. *Am J Med*. 2007;120(9):748-753. doi:10.1016/j.amjmed.2006.10.018
4. Morley JE, Vellas B, van Kan GA, et al. Frailty consensus: a call to action. *J Am Med Dir Assoc*. 2013;14(6):392-397. doi:10.1016/j.jamda.2013.03.022
5. Rohrmann S. Epidemiology of frailty in older people. *Adv Exp Med Biol*. 2020;1216:21-27. doi:10.1007/978-3-030-33330-0_3
6. Ofori-Asenso R, Chin KL, Mazidi M, et al. Global incidence of frailty and prefrailty among community-dwelling older adults: a systematic review and meta-analysis. *JAMA Netw Open*. 2019;2(8):1-18. doi:10.1001/jamanetworkopen.2019.8398
7. Hanlon P, Nicholl BI, Jani BD, et al. Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of 493 737 UK Biobank participants. *Lancet Public Health*. 2018;3(7):e323-e332. doi:10.1016/S2468-2667(18)30091-4
8. Zanotto T, Rice LA, Sosnoff JJ. Frailty among people with multiple sclerosis who are wheelchair users. *PLoS One*. 2022;17(7):e0271688. doi:10.1371/journal.pone.0271688
9. Capasso N, Virgilio E, Covelli A, et al. Aging in multiple sclerosis: from childhood to old age, etiopathogenesis, and unmet needs: a narrative review. *Front Neurol*. 2023;14:1207617. doi:10.3389/fneur.2023.1207617
10. Hittle M, Culpepper WJ, Langer-Gould A, et al. Population-based estimates for the prevalence of multiple sclerosis in the United States by race, ethnicity, age, sex, and geographic region. *JAMA Neurol*. 2023;80(7):693-701. doi:10.1001/jamaneurol.2023.1135
11. Ostolaza A, Corroza J, Ayuso T. Multiple sclerosis and aging: comorbidity and treatment challenges. *Mult Scler Relat Disord*. 2021;50:102815. doi:10.1016/j.msard.2021.102815
12. Kalmar JH, Gaudino EA, Moore NB, Halper J, DeLuca J. The relationship between cognitive deficits and everyday functional activities in multiple sclerosis. *Neuropsychology*. 2008;22(4):442-449. doi:10.1037/0894-4105.22.4.442
13. Benedict RHB, Zivadinov R. Risk factors for and management of cognitive dysfunction in multiple sclerosis. *Nat Rev Neurol*. 2011;7(6):332-342. doi:10.1038/nrneurol.2011.61
14. Branco M, Ruano L, Portaccio E, et al. Aging with multiple sclerosis: prevalence and profile of cognitive impairment. *Neurol Sci*. 2019;40(8):1651-1657. doi:10.1007/s10072-019-03875-7
15. Sebastião E, McAuley E, Shigematsu R, et al. Home-based, square-stepping exercise program among older adults with multiple sclerosis: results of a feasibility randomized controlled study. *Contemp Clin Trials*. 2018;73:136-144. doi:10.1016/j.cct.2018.09.008
16. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol*. 1994;49(2):M85-M94. doi:10.1093/geronj/49.2.m85
17. Motl RW, Learmonth YC, Wójcicki TR, et al. Preliminary validation of the short physical performance battery in older adults with multiple sclerosis: secondary data analysis. *BMC Geriatr*. 2015;15:157. doi:10.1186/s12877-015-0156-3

18. Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. *N Engl J Med*. 1995;332(9):556-561. doi:10.1056/NEJM199503023320902
19. da Câmara SM, Alvarado BE, Guralnik JM, Guerra RO, Maciel AC. Using the Short Physical Performance Battery to screen for frailty in young-old adults with distinct socioeconomic conditions. *Geriatr Gerontol Int*. 2013;13(2):421-428. doi:10.1111/j.1447-0594.2012.00920.x
20. Verghese J, Xue X. Identifying frailty in high functioning older adults with normal mobility. *Age Ageing*. 2010;39(3):382-385. doi:10.1093/ageing/afp226
21. Langdon DW, Amato MP, Boringa J, et al. Recommendations for a Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). *Mult Scler*. 2012;18(6):891-898. doi:10.1177/1352458511431076
22. Benedict RHB, Amato MP, Boringa J, et al. Brief International Cognitive Assessment for MS (BICAMS): international standards for validation. *BMC Neurol*. 2012;12:55. doi:10.1186/1471-2377-12-55
23. Ayrignac X, Larochelle C, Keezer M, et al. Frailty in ageing persons with multiple sclerosis. *Mult Scler*. 2021;27(4):613-620. doi:10.1177/1352458520923945
24. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56(3):M146-M156. doi:10.1093/gerona/56.3.m146
25. Chiang HS, Khera A, Stopschinski BE, et al. Cognitive decline in older people with multiple sclerosis—a narrative review of the literature. *Geriatrics (Basel)*. 2022;7(3):61. doi:10.3390/geriatrics7030061
26. Jakimovski D, Weinstock-Guttman B, Roy S, et al. Cognitive profiles of aging in multiple sclerosis. *Front Aging Neurosci*. 2019;11:105. doi:10.3389/fnagi.2019.00105
27. Baird JF, Cederberg KLJ, Morghen Sikes E, et al. Changes in cognitive performance with age in adults with multiple sclerosis. *Cogn Behav Neurol*. 2019;32(3):201-207. doi:10.1097/WNN.0000000000000200
28. Takatori K, Matsumoto D. Social factors associated with reversing frailty progression in community-dwelling late-stage elderly people: an observational study. *PLoS One*. 2021;16(3):e0247296. doi:10.1371/journal.pone.0247296
29. Kolle AT, Lewis KB, Lalonde M, Backman C. Reversing frailty in older adults: a scoping review. *BMC Geriatr*. 2023;23(1):751. doi:10.1186/s12877-023-04309-y
30. Wallin MT, Campea S, Haselkorn JK. Multidisciplinary management of a patient with multiple sclerosis: part 1. neurologists' and physiatrists' perspectives. *Fed Pract*. 2015;32(suppl 3):14S-17S.
31. Fiatarone MA, O'Neill EF, Ryan ND, et al. Exercise training and nutritional supplementation for physical frailty in very elderly people. *N Engl J Med*. 1994;330(25):1769-1775. doi:10.1056/NEJM199406233302501
32. Marcos-Pardo PJ, Orquin-Castrillón FJ, Gea-García GM, et al. Effects of a moderate-to-high intensity resistance circuit training on fat mass, functional capacity, muscular strength, and quality of life in elderly: a randomized controlled trial. *Sci Rep*. 2019;9(1):7830. doi:10.1038/s41598-019-44329-6
33. Saragih ID, Yang YP, Saragih IS, et al. Effects of resistance bands exercise for frail older adults: a systematic review and meta-analysis of randomised controlled studies. *J Clin Nurs*. 2022;31(1-2):43-61. doi:10.1111/jocn.15950
34. Kalb R, Brown TR, Coote S, et al. Exercise and lifestyle physical activity recommendations for people with multiple sclerosis throughout the disease course. *Mult Scler*. 2020;26(12):1459-1469. doi:10.1177/1352458520915629
35. Vaupel JW, Manton KG, Stallard E. The impact of heterogeneity in individual frailty on the dynamics of mortality. *Demography*. 1979;16(3):439-454.
36. Thurn M, Gustafson DR. Faces of frailty in aging with HIV infection. *Curr HIV/AIDS Rep*. 2017;14(1):31-37. doi:10.1007/s11904-017-0348-x
37. Sebastião E, Wood T, Motl RW, et al. The importance of promoting physical activity and exercise training as adjuvant therapy for people with multiple sclerosis. *Motriz*. 2022;28:1-5. doi:10.1590/S1980-657420220016021
38. Tieland M, Brouwer-Brolsma EM, Nienaber-Rousseau C, van Loon LJC, De Groot LC. Low vitamin D status is associated with reduced muscle mass and impaired physical performance in frail elderly people. *Eur J Clin Nutr*. 2013; 67(10):1050-1055. doi:10.1038/ejcn.2013.144
39. Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. *J Nutr Health Aging*. 2012;16(7):601-608. doi:10.1007/s12603-012-0084-2