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Brief Communication

Is there a threshold or dose-response association between physical activity and cognitive function in multiple sclerosis?

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Abstract

Objective: Cognitive impairment is prevalent, disabling, and poorly managed in multiple sclerosis (MS). Physical activity, often expressed as steps/day, has been associated with cognitive function in this population. This brief report examined the possibility of a (1) steps/day threshold associated with absence of cognitive impairment or (2) dose-response relationship between steps/day and cognitive function in MS. **Method:** The sample included 358 persons with MS who provided demographic (age, sex, race) and clinical (MS type, disease duration, disability status) information, and completed the Symbol Digit Modalities Test (SDMT) and California Verbal Learning Test-Second Edition (CVLT-II). Participants wore an ActiGraph GT3X+ accelerometer above the non-dominant hip during waking hours of the day over a 7-day period for measuring steps/day. **Results:** The receiver operating characteristic (ROC) curve analysis did not identify a steps/day threshold associated with cognitive impairment on SDMT (area under the curve [AUC] ranged between 0.606 and 0.691). The ROC curve analysis further did not identify a threshold of steps/day associated with cognitive impairment based on CVLT-II (AUC range 0.606 to 0.691). The regression analysis indicated significant linear relationships between steps/day and SDMT ($R^2 = .06$; β=.251; $p < .001$) and CVLT-II ($R^2 = .06$; β=.247; $p < .001$) z-scores. **Conclusion:** The observed linear relationship suggests that focusing on increasing steps/day across all levels of physical activity might have benefits for cognitive function in MS.

Keywords: Multiple sclerosis; exercise; cognition

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Introduction

Cognitive impairment is prevalent, disabling, and sub-optimally managed in multiple sclerosis (MS), and further associated with worse fatigue, anxiety, depression, pain, and quality of life (Chiaravalloti & DeLuca, 2008). There has been interest in physical activity, including exercise training, and cognition in MS. The effects of exercise training on cognition in MS have been inconsistent and inconclusive, but there is evidence linking physical activity with cognition (Sandroff et al., 2016). One study reported a significant positive association between steps/day and cognitive processing speed in 33 persons with MS (Motl et al., 2011). Another study reported a small, but positive association between steps/day and cognitive processing speed in a sample of 212 persons with MS (Sandroff, Dlugonski, et al., 2014). Other research has further reported similar associations in persons with MS who presented with cognitive impairment, even after controlling for covariates such as age and disability status (Motl et al., 2022; Sandroff & Motl, 2020). Some research has examined the association between steps/day and learning and memory, but reported no significant relationship in 60 persons with MS who had cognitive impairment (Motl et al., 2022). Such cross-sectional data has been supported by the results of a randomized controlled trial (RCT) whereby there was a clinically meaningful improvement in cognitive processing speed after a behavioral intervention focusing on steps/day compared with waitlist control in persons with MS (Sandroff, Klaren, et al., 2014).

There are multiple reasons steps/day could be a correlate of cognitive impairment. Conceptually, steps/day may result in activation of central nervous system (CNS) structural networks, and these networks are involved in the regulation of steps/day – this ongoing bidirectional process results in CNS adaptations that manifest as improved cognition (Sandroff et al., 2018). Steps/day represents a marker of ambulatory physical activity, and there is strong evidence of cognitive motor-coupling in MS (Benedict et al., 2011). Steps/day represents an ideal target of behavior change interventions, as it represents a simple, cogent physical activity behavior for change by research participants and perhaps is readily interpretable, actionable, and available for public health (Tudor-Locke & Bassett, 2004).

Researchers have not focused on the nature of the association between physical activity and cognition in MS, and this has implications for the design of RCTs and public health promotion of

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Table 1. Demographic and clinical characteristics of the sample of 358 persons with MS

Characteristic	Statistic
Age (years)	53 (22 – 77)
Sex (*n*, %)	
Female	271, 76%
Male	87, 24%
Race (*n*, %)	
Caucasian	265, 74%
Black/African American	82, 23%
Other	10, 3%
MS type (*n*, %)	
Relapsing-remitting	304, 87%
Progressive	46, 13%
Disease duration (years)	15 (1 – 48)
PDDS score (0 – 8)	2 (0 – 7)

Note: Data are presented as mean (range), number, or percentage. MS = multiple sclerosis, PDDS = Patient Determined Disease Steps.

physical activity behavior. There is existing evidence that steps/day has been associated with cognition in the general population (Ars et al., 2024) and persons with MS (Sandroff, Dlugonski, et al., 2014; Sandroff & Motl, 2020), yet the association might follow either a dose-response or threshold pattern. The dose-response pattern would indicate the accumulation of benefits with increasing steps/day across all levels of physical activity, whereas the threshold pattern would indicate the accumulation of benefits with an optimal number of steps/day, yet no additional benefit associated with increasing steps/day beyond this threshold.

This brief report examined the possibility of a (1) steps/day threshold associated with absence of cognitive impairment or (2) dose-response relationship between steps/day and cognitive function in persons with MS. The results may inform the target of future RCTs involving physical activity behavior change and provide public health guidelines for the promotion of physical activity directed toward improving cognitive function in MS.

Method

Participants

This study involved analysis of data combined from multiple studies for a larger sample size to address our study aims (Baird et al., 2019; Baird & Motl, 2021; Bollaert et al., 2019; Cederberg et al., 2021; Motl et al., 2022; Sandroff et al., 2021). Data from three of the six studies involved cross-sectional designs, and data from the other three were from baseline of clinical trials; there was no overlap in participants across studies. Persons in those studies had the following common inclusion criteria: diagnosis of MS; no relapse in the last 30 days; 18+ years of age; ability to walk with or without assistive devices; and willingness to complete study procedures.

Measures

Physical Activity. Steps/day were measured by the ActiGraph GT3X+ accelerometer (ActiGraph LLC, Pensacola, Florida, USA). The accelerometer was placed in a pouch on an elastic belt, and the belt was worn around the waist with the accelerometer above the non-dominant hip during the waking hours of the day, except during water-based activities, for 7 days. We asked that participants not deviate from normal activities during the 7-day period while wearing the accelerometer, and while we cannot assure that this was always the case, there are published data arguing against reactivity as a source bias with motion sensors (Motl et al., 2012). The procedure for the accelerometer being worn over 7 days permits capture of weekdays and weekends, and the duration of assessment represents standard practice in the field (Arvidsson et al., 2019). Participants recorded the date that the accelerometer was worn in a log; this log was inspected for verifying wear time per day during data processing. We downloaded and processed the data into one-minute epochs without the low frequency extension, as we identified this filter inaccurately over inflated steps in MS (Feito et al., 2015). We have further observed in our laboratory that the inclusion of the low frequency extension when processing step data overestimates the number of steps two-fold. The analyses only included days with valid data based a minimum of 10 h of total wear time, and participants with 1 or more valid days of data were included in the analyses. We based our protocol on procedures and processes applied for the National Health and Nutrition Examination Survey cohort study (Troiano et al., 2008).

Cognitive Function. The Symbol Digit Modalities Test (SDMT) and California Verbal Learning Test-Second Edition (CVLT-II) are standard cognitive outcomes in MS and were the two neuropsychological tests that overlapped across the different studies. The oral version of the SDMT assessed cognitive processing speed (Smith, 1982). We recorded the total number of correct responses in 90 s. The CVLT-II assessed verbal learning and memory (Delis et al., 2000). We summed only the number of correct responses from the five trials for a total possible score out of 80. We calculated z-scores using regression-based norms for persons with MS adjusting for age and sex (Parmenter et al., 2010).

Procedure

The study protocols were approved by University Institutional Review Boards, and de-identified data from those studies were used for the analysis. All participants provided written informed consent prior to data collection. Participants came into the laboratory for standardized in-person assessments of cognitive function, and further reported demographic (age, sex, race) and clinical (MS type, disease duration) information. Disability status was assessed using the Patient Determined Disease Steps (PDDS) (Learmonth et al., 2013). We then provided all participants with an accelerometer on a belt, along with instructions in-person, to wear starting the day after the visit for a measure of physical activity over a 7-day, free-living period. Participants were provided with a log as well as a pre-addressed and pre-stamped envelope for return service through the United States Postal Service.

Data analysis

Data were analyzed using IBM SPSS software version 29 (IBM Corp, Armonk, New York, USA). Descriptive statistics were calculated for demographic and clinical information, physical activity, and cognitive function. Values were presented as mean (SD), unless otherwise specified. We conducted analyses focusing on a steps/day threshold associated with absence of cognitive impairment defined by a range of z-score cut-points from of −1.28 through −2.33 SD units and evaluated the classification threshold using receiver operating characteristic (ROC) curve analyses, sensitivity and specificity. The cutoff was selected using the Youden criteria (Youden, 1950). We further performed linear regression analyses wherein we regressed SDMT and CVLT-II z-scores on steps/day in Step 1, followed by PDDS scores as a

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Table 2. Outcomes of physical activity and cognitive function for the sample of 358 persons with MS

Outcome	Mean (Range)	Z-Score (Range)
Steps/day	5,462 (279, 17,273)	N/A
SDMT score	47 (6, 84)	−1.02 (−3.82, 2.32)
CVLT-II score	46 (17, 75)	−1.10 (−2.83, 2.62)

Note: MS = multiple sclerosis, SDMT = Symbol Digit Modalities Test, CVLT-II = California Verbal Learning Test-Second Edition.

Table 3. Results of the receiving operating characteristic curve analyses for identifying possible steps/day thresholds and other z-score values for SDMT and CVLT-II

Z-Score cut-point	Test	Area under curve	Sensitivity	Specificity	Youden's index
−1.28	SDMT	.620	.430	.766	.191
	CVLT-II	.636	.826	.402	.228
−1.50	SDMT	.604	.557	.620	.177
	CVLT-II	.620	.765	.441	.207
−1.65	SDMT	.619	.550	.651	.202
	CVLT-II	.608	.760	.438	.197
−1.96	SDMT	.636	.540	.683	.223
	CVLT-II	.606	.756	.415	.171
−2.33	SDMT	.685	.541	.774	.315
	CVLT-II	.691	.652	.690	.342

Note: SDMT = Symbol Digit Modalities Test, CVLT-II = California Verbal Learning Test-Second Edition.

potential predictor in Step 2. Using the linear regression models, we calculated z-score values for SDMT and CVLT-II associated with various steps/day thresholds. We then provided estimates of the improvement that might be achieved by increasing steps/day using normative data (Kramer et al., 2020; Strober et al., 2020).

Results

Descriptive characteristics

We provided demographic and clinical characteristics for the sample in Table 1. The descriptive statistics of the physical activity and cognitive function outcomes are presented in Table 2. Of note, the sample overall had below average performance on the SDMT and CVLT-II with z-scores of −1.02 and −1.10, respectively.

Receiving operating characteristic curve analysis: threshold value

Results of the ROC curve analyses for steps/day and other z-score values for SDMT and CVLT-II are presented in Table 3. We examined various definitions of cognitive impairment from −1.28 to −2.33 SD units below the mean for assessing if the poor performance in the ability to discriminate between impaired and unimpaired cognitive results was associated with the value of the z-score. The ROC curve analysis did not identify a highly predictive steps/day threshold associated with cognitive impairment based on SMDT z-scores. The area under the curve (AUC) ranged between 0.619–0.685. The analysis further did not identify a predictive number of steps/day associated with cognitive impairment based on CVLT-II z-scores (AUC range 0.606–0.691). Regardless of the definition of impairment used, the AUCs and classification results in terms of sensitivity and specificity were at best marginal.

Regression analysis: dose-response curve

The regression analysis indicated a significant linear relationship between steps/day and SDMT z-scores ($R^2 = .06; \beta = .251; p < .001$) and CVLT-II z-scores($R^2 = .06$; $\beta = .247$; $p < .001$), and this was unchanged when disability status (PDDS scores) was included in the model (SDMT: $R^2 = .08$; $p < .001$ & CVLT-II: $R^2 = .06$; $p < .001$). We presented the results of the regression analyses in Table 4. We further calculated SDMT and CVLT-II z-scores associated with steps/day and provided estimates of raw SDMT and CVLT-II scores associated with meeting 10,000 steps/day in Table 5. Of note, this is an estimated change based on cross-sectional data from our regression models.

Discussion

This study examined the possibility of a (1) steps/day threshold being associated with absence of cognitive impairment or (2) dose-response relationship between steps/day and cognitive function in persons with MS. The ROC curve analyses did not identify a steps/day cut-point associated with cognitive impairment, but the linear regression analyses indicated significant positive associations between levels of steps/day and cognition function, albeit relatively weak based on 6–8% of shared variance. These results may inform future RCTs of physical activity behavior change and public health guidelines for the promotion of physical activity directed toward improving cognitive function in MS. We do recognize that the association is fairly weak, and that this might support the examining of multifaceted interventions for improving cognition in MS.

Based on the poor specificity and sensitivity from the ROC curve analysis, we were unable to identify a clear steps/day threshold associated with cognitive impairment. By comparison, there was a weak positive association between steps/day and cognition based on the linear regression analysis, and this suggests that higher levels of steps/day were associated with better cognitive function based on both SDMT and CVLT-II z-scores. After adjusting for disability level, the associations were still significant. This may suggest that physical activity-related adaptations in neuroplasticity may occur regardless of ambulatory disability status (Sandroff et al., 2018). Although the results were not surprising per se, we note the importance of determining the nature of the relationship between steps/day and cognitive function so that future physical activity programs can be better informed to promote the likelihood of improved cognitive function. Of note, there is evidence for dose and/or threshold associations for steps/day and outcomes in the general population (Paluch et al., 2022; Shibukawa et al., 2024; Sofi et al., 2011), and we focused on this for cognition in MS.

Our findings generally align with the existing evidence that physical activity is associated with cognitive function in MS. Researchers have reported that steps/day were moderately associated with cognitive processing speed in MS (Motl et al., 2011; Sandroff, Dlugonski, et al., 2014), and further reported a weaker relationship between steps/day and verbal learning and memory (Motl et al., 2011). When we controlled for disability level based on PDDS scores, steps/day remained a significant, independent correlate of both cognitive functions, thereby suggesting that ambulatory disability level does not totally confound the relationship between physical activity and cognitive function. The relationship between steps/day and cognitive function, independent of disability level, would support a general recommendation that the wider population with MS can increase steps/day and reap additional benefits. We have replicated the results of previous research in a larger sample of persons with MS,

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Table 4. Linear regression analyses of associations between steps/day and cognitive function z-scores for processing speed and learning/memory outcomes

Step	Variable	*B*	*SE B*	*β*	*p*-value
a. SDMT z-score					
Step 1	Steps/day	0.00009896	0.000	0.251	<0.001
Step 2	Steps/day	0.00008269	0.000	0.209	<0.001
	PDDS score	−0.079	0.036	−0.120	0.029
Note: $R^2 = 0.063$ for Step 1; $R^2 = 0.075$ for Step 2.					
b. CVLT-II z-score					
Step 1	Steps/day	0.00008068	0.000	0.247	<0.001
Step 2	Steps/day	0.00007153	0.000	0.218	<0.001
	PDDS score	−0.043	0.030	−0.078	0.157
Note: $R^2 = 0.061$ for Step 1; $R^2 = 0.065$ for Step 2.					

Note: SDMT = Symbol Digit Modalities Test, CVLT-II = California Verbal Learning Test-Second Edition, PDDS = Patient Determined Disease Steps.

Table 5. Calculation of z-score values for SDMT and CVLT-II associated with steps/day based on the linear regression analyses and changes in raw SDMT and CVLT-II scores associated with meeting 10,000 steps/day

Steps/Day	SDMT z-score	Score†	CVLT-II z-score	Score‡
1,000	−1.46	4 – 10	−1.46	8 – 10
2,000	−1.36	4 – 9	−1.36	7 – 9
3,000	−1.26	4 – 8	−1.26	6 – 8
4,000	−1.16	3 – 6	−1.16	5 – 7
5,000	−1.06	4 – 5	−1.06	5 – 6
6,000	−0.96	2 – 4	−0.96	4
7,000	−0.86	1 – 3	−0.86	3
8,000	−0.76	1 – 2	−0.76	2
9,000	−0.67	0 – 1	−0.67	1
10,000	−0.57	–	−0.57	–

Note: SDMT = Symbol Digit Modalities Test, CVLT-II = California Verbal Learning Test-Second Edition.
†scores calculated using normative SDMT data from Strober et al., 2020.
‡scores calculated using normative CVLT-II data from Kramer et al., 2020.

such that our findings identified a small, but positive dose-response relationship between physical activity and cognitive processing speed. However, unlike previous research, we further identified a significant relationship between physical activity and verbal learning and memory. The small amount of variance shared between physical activity and cognition (R^2 of 6–8%) suggests that future research should consider other parameters of physical activity or other health behaviors such as diet for improving cognitive function.

There has been substantial interest in designing RCTs that target physical activity, including exercise training, for the improvement of cognitive function in persons with MS (Sandroff et al., 2016). To date, the evidence has been conflicting for exercise training effects on cognition, as the trials have limitations including poor methodological quality, the recruitment of the general sample of persons with MS rather than those with cognitive impairment, and the inclusion of cognitive function as a secondary outcome (Sandroff et al., 2016). There is one RCT of a behavioral intervention focusing on walking for increasing steps/day as part of daily life that reported clinically meaningful improvements in SDMT score compared with a waitlist control (Sandroff, Klaren, et al., 2014). This suggests that promoting physical activity as part of daily life through increasing steps/day may represent a meaningful avenue for improving both cognitive processing speed and verbal learning and memory in MS. To that end, future trials should consider using age-adjusted z-scores for pre-post testing in the context of an intervention for avoiding change as a confound of changes in z-scores when there is a prolonged intervention period.

There are limitations that should be considered when interpreting the results of our study. One limitation was the cross-sectional design of this study, which does not permit an understanding of steps/day and clinically meaningful change in cognition, or order effects that steps/day are a result of lesser disability since PDDS is a broad categorization and may not capture the full range of disability affecting steps/day even at the same PDDS level. The strength of the relationship between physical activity and cognitive function may vary over time and have lesser strength earlier in the disease course. We did not account for education, mood, or depressive symptoms, and these factors may influence or be influenced by physical activity and cognition. We further assessed a narrow set of cognitive functions and did not assess other cognitive domains such as attention, visuospatial ability, working memory, or abstract reasoning.

This brief report did not identify an optimal threshold of steps/day associated with cognitive function in MS, but there was evidence of a dose-response association. Physical activity (steps/day) was positively and linearly associated with cognitive outcomes, independent of disability, and increasing physical activity levels may be beneficial for the management of cognitive impairment in MS. This suggests that accumulating more steps/day through walking as part of daily life might be a pragmatic approach for improving cognitive function in MS.

Author contribution. Brenda Jeng: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft. Gary R. Cutter: Conceptualization, Methodology, Formal analysis, Supervision, Writing – review & editing. Robert W. Motl: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Supervision, Writing – review & editing.

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Competing interests. None.

References

Ars, J., Calderón-Larrañaga, A., Beridze, G., Laukka, E. J., Farrés-Godayol, P., Pérez, L. M., Inzitari, M., & Welmer, A. K. (2024). Association between accelerometer-assessed physical activity and cognitive function in older adults: A cross-sectional study. *The American Journal of Geriatric Psychiatry*, *S1064-7481*(24), 00481-0.

Arvidsson, D., Fridolfsson, J., & Börjesson, M. (2019). Measurement of physical activity in clinical practice using accelerometers. *Journal of Internal Medicine*, *286*(2), 137–153.

Baird, J. F., Cederberg, K. L. J., Sikes, E. M., Silveira, S. L., Jeng, B., Sasaki, J. E., Sandroff, B. M., & Motl, R. W. (2019). Physical activity and walking performance across the lifespan among adults with multiple sclerosis. *Multiple Sclerosis and Related Disorders*, *35*, 36–41.

Baird, J. F., & Motl, R. W. (2021). Cognitive function and whole-brain MRI metrics are not associated with mobility in older adults with multiple sclerosis. *International Journal of Environmental Research and Public Health*, *18*(8), 4232.

Benedict, R. H. B., Holtzer, R., Motl, R. W., Foley, F. W., Kaur, S., Hojnacki, D., & Weinstock-Guttman, B. (2011). Upper and lower extremity motor function and cognitive impairment in multiple sclerosis. *Journal of the International Neuropsychological Society*, *17*(4), 643–653.

Bollaert, R. E., Marsh, A. P., Cutter, G. R., & Motl, R. W. (2019). The virtual short physical performance battery: Psychometric properties and validation in older adults with multiple sclerosis. *Journal of Applied Gerontology*, *38*(10), 1492–1505.

Cederberg, K. L. J., Walters, A. S., Amara, A. W., Braley, T. J., Schuetz, M. L., Mathison, B. G., & Motl, R. W. (2021). Validity and reliability of the suggested immobilization test for measurement of restless legs syndrome severity in adults with multiple sclerosis. *Sleep Medicine*, *84*, 343–351.

Chiaravalloti, N. D., & DeLuca, J. (2008). Cognitive impairment in multiple sclerosis. *Lancet Neurology*, *7*(12), 1139–1151.

Delis, D. C., Kramer, J. H., Kaplan, E., & Ober, B. A. (2000). *California Verbal Learning Test: Second edition, adult version*. Psychological Corporation.

Feito, Y., Garner, H. R., & Bassett, D. R. (2015). Evaluation of ActiGraph's low-frequency filter in laboratory and free-living environments. *Medicine & Science in Sports & Exercise*, *47*(1), 211–217.

Kramer, A. O., Casaletto, K. B., Umlauf, A., Staffaroni, A. M., Fox, E., You, M., & Kramer, J. H. (2020). Robust normative standards for the California Verbal earning Test (CVLT) ages 60-89: A tool for early detection of memory impairment. *Clinical Neuropsychologist*, *34*(2), 384–405.

Learmonth, Y. C., Motl, R. W., Sandroff, B. M., Pula, J. H., & Cadavid, D. (2013). Validation of patient determined disease steps (PDDS) scale scores in persons with multiple sclerosis. *BMC Neurology*, *13*(1), 37.

Motl, R. W., Gappmaier, E., Nelson, K., & Benedict, R. H. B. (2011). Physical activity and cognitive function in multiple sclerosis. *Journal of Sport and Exercise Psychology*, *33*(5), 734–741.

Motl, R. W., McAuley, E., & Dlugonski, D. (2012). Reactivity in baseline accelerometer data from a physical activity behavioral intervention. *Health Psychology*, *31*(2), 172–175.

Motl, R. W., Sandroff, B. M., & Benedict, R. H. B. (2022). Moderate-to-vigorous physical activity is associated with processing speed, but not learning and memory, in cognitively impaired persons with multiple sclerosis. *Multiple Sclerosis and Related Disorders*, *63*, 103833.

Paluch, A. E., Bajpai, S., Bassett, D. R., Carnethon, M. R., Ekelund, U., Evenson, K. R., Galuska, D. A., Jefferis, B. J., Kraus, W. E., Lee, I. M., Matthews, C. E., Omura, J. D., Patel, A. V., Pieper, C. F., Rees-Punia, E., Dallmeier, D., Klenk, J., Whincup, P. H., Dooley, E. E., & Fulton, J. E. (2022). Daily steps and all-cause mortality: A meta-analysis of 15 international cohorts. *The Lancet Public Health*, *7*(3), e219–e228.

Parmenter, B. A., Testa, S. M., Schretlen, D. J., Weinstock-Guttman, B., & Benedict, R. H. (2010). The utility of regression-based norms in interpreting the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). *Journal of the International Neuropsychological Society*, *16*(1), 6–16.

Sandroff, B. M., Dlugonski, D., Pilutti, L. A., Pula, J. H., Benedict, R. H., & Motl, R. W. (2014). Physical activity is associated with cognitive processing speed in persons with multiple sclerosis. *Multiple Sclerosis and Related Disorders*, *3*(1), 123–128.

Sandroff, B. M., Klaren, R. E., Pilutti, L. A., Dlugonski, D., Benedict, R. H., & Motl, R. W. (2014). Randomized controlled trial of physical activity, cognition, and walking in multiple sclerosis. *Journal of Neurology*, *261*(2), 363–372.

Sandroff, B. M., & Motl, R. W. (2020). Device-measured physical activity and cognitive processing speed impairment in a large sample of persons with multiple sclerosis. *Journal of the International Neuropsychological Society*, *26*(8), 798–805.

Sandroff, B. M., Motl, R. W., Reed, W. R., Barbey, A. K., Benedict, R. H. B., & DeLuca, J. (2018). Integrative CNS plasticity with exercise in MS: The PRIMERS (PRocessing, Integration of Multisensory Exercise-Related Stimuli) conceptual framework. *Neurorehabilitation and Neural Repair*, *32*(10), 847–862.

Sandroff, B. M., Motl, R. W., Scudder, M. R., & DeLuca, J. (2016). Systematic, evidence-based review of exercise, physical activity, and physical fitness effects on cognition in persons with multiple sclerosis. *Neuropsychology Review*, *26*(3), 271–294.

Sandroff, B. M., Wylie, G. R., Baird, J. F., Jones, C. D., Diggs, M. D., Genova, H., Bamman, M. M., Cutter, G. R., DeLuca, J., & Motl, R. W. (2021). Effects of walking exercise training on learning and memory and hippocampal neuroimaging outcomes in MS: A targeted, pilot randomized controlled trial. *Contemporary Clinical Trials*, *110*, 106563.

Shibukawa, T., Fujiyoshi, A., Moniruzzaman, M., Miyagawa, N., Kadota, A., Kondo, K., Saito, Y., Kadowaki, S., Hisamatsu, T., Yano, Y., Arima, H., Tooyama, I., Ueshima, H., & Miura, K. (2024). Association of step counts with cognitive function in apparently healthy middle-aged and older Japanese men. *Preventive Medicine Reports*, *38*, 102615.

Smith, A. (1982). *Symbol Digit Modalities Test: Manual*. Western Psychological Services. Los Angeles

Sofi, F., Valecchi, D., Bacci, D., Abbate, R., Gensini, G. F., Casini, A., & Macchi, C. (2011). Physical activity and risk of cognitive decline: A meta-analysis of prospective studies. *Journal of Internal Medicine*, *269*(1), 107–117.

Strober, L. B., Bruce, J. M., Arnett, P. A., Alschuler, K. N., Lebkuecher, A., Di Benedetto, M., Cozart, J., Thelen, J., Guty, E., & Roman, C. (2020). A new look at an old test: Normative data of the symbol digit modalities test - Oral version. *Multiple Sclerosis and Related Disorders*, *43*, 102154.

Troiano, R. P., Berrigan, D., Dodd, K. W., Mâsse, L. C., Tilert, T., & McDowell, M. (2008). Physical activity in the United States measured by accelerometer. *Medicine & Science in Sports & Exercise*, *40*(1), 181–188.

Tudor-Locke, C., & Bassett, D. R. (2004). How many steps/day are enough? Preliminary pedometer indices for public health. *Sports Medicine*, *34*(1), 1–8.

Youden, W. J. (1950). Index for rating diagnostic tests. *Cancer*, *3*(1), 32–35.

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