Longitudinal relationships among posturography and gait measures in multiple sclerosis

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ABSTRACT

Objective: Gait and balance dysfunction frequently occurs early in the multiple sclerosis (MS) disease course. Hence, we sought to determine the longitudinal relationships among quantitative measures of gait and balance in individuals with MS.

Methods: Fifty-seven ambulatory individuals with MS (28 relapsing-remitting, 29 progressive) were evaluated using posturography, quantitative sensorimotor and gait measures, and overall MS disability with the Expanded Disability Status Scale at each session.

Results: Our cohort's age was 45.8 ± 10.4 years (mean $\pm$ SD), follow-up time 32.8 ± 15.4 months, median Expanded Disability Status Scale score 3.5, and 56% were women. Poorer performance on balance measures was related to slower walking velocity. Two posturography measures, the anterior-posterior sway and sway during static eyes open, feet apart conditions, were significant contributors to walk velocity over time (approximate $R^2 = 0.95$), such that poorer performance on the posturography measures was related to slower walking velocity. Similarly, the anterior-posterior sway and sway during static eyes closed, feet together conditions were also significant contributors to the Timed 25-Foot Walk performance over time (approximate $R^2 = 0.83$).

Conclusions: This longitudinal cohort study establishes a strong relationship between clinical gait measures and posturography. The data show that increases in static posturography and reductions in dynamic posturography are associated with a decline in walk velocity and Timed 25-Foot Walk performance over time. Furthermore, longitudinal balance measures predict future walking performance. Quantitative walking and balance measures are important additions to clinical testing to explore longitudinal change and understand fall risk in this progressive disease population. *Neurology*® 2015;84:2048-2056

GLOSSARY

AIC = Akaike information criterion; **AP** = anterior-posterior; **ECFA** = eyes closed, feet apart; **ECFT** = eyes closed, feet together; **EDSS** = Expanded Disability Status Scale; **EOFA** = eyes open, feet apart; **EOFT** = eyes open, feet together; **ICC** = intraclass correlation coefficient; **ML** = medial-lateral; **MS** = multiple sclerosis; **RMSE** = root-mean-square error; **T25FW** = Timed 25-Foot Walk; **WAD** = weaker side ankle dorsiflexion; **WGT** = worse great toe; **WHE** = weaker side hip extension; **WHF** = weaker side hip flexion; **WV** = walking velocity.

Individuals with multiple sclerosis (MS) experience balance impairments that contribute to unsteady gait and increased fall risk.¹ Many factors influence walking and balance, including strength,²⁻⁴ sensation,^{5,6} and cerebellar atrophy.^{7,8} Recent data from our laboratory showed that anterior-posterior (AP) sway and hip extension strength explained greater than 70% of the variance in walking speed in individuals with MS.⁹ Of note, postural deficits existed even when no differences were present on the Timed Up and Go or Timed 25-Foot Walk (T25FW),¹⁰ suggesting that postural testing may be a useful addition to clinical measures to detect early changes in balance. Gait and balance dysfunction frequently occurs early in the MS disease course; thus, measurement of postural dysfunction may detect clinical deterioration sooner than the average clinical trial time period and improve on the precision of current clinical measures,¹¹ especially as they relate to falls.

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Despite well-documented deficits in balance in MS, longitudinal monitoring across multiple years is lacking. As new interventions and assessment tools are developed for MS, knowledge of the longitudinal relationship among gait and balance measures would be useful. The purpose of this study was to understand the relationship among walking and balance measures over time.

We hypothesized that the relationship between posturography and walking velocity (WV) would be maintained over time, suggesting that these measures offer a practical way to monitor functional decline, which places individuals at greater risk of disability and falls, and may be lessened by tailored rehabilitation.

METHODS Ambulatory participants were included in the study if they had a diagnosis of MS using the 2010 McDonald Criteria.¹² All participants were recruited from the MS Center at Johns Hopkins Medical Institutions between 2005 and 2009, and demonstrated full understanding of the study and study-related tests. Participants were excluded if they had experienced an MS relapse within 3 months of testing or reported a history of peripheral neuropathy or any other orthopedic, neurologic, or cognitive condition that might interfere with study procedures. Balance, walking, strength, sensation, and overall MS disability using the Expanded Disability Status Scale (EDSS)¹³ were assessed at each annual or semiannual session.

Standard protocol approvals, registrations, and patient consents. All participants gave written informed consent before participation, and the institutional review boards at Johns Hopkins Medical Institutes and Kennedy Krieger Institute approved all procedures.

Posturography. Posturography data were acquired as previously described by our group.^{9,14,15} Balance was assessed with dynamic and static posturography under 6 conditions using a Kistler 9281 force plate (Kistler Instrumente, Winterthur, Switzerland). Static conditions included the following: (1) eyes open, feet apart (EOFA); (2) eyes open, feet together (EOFT); (3) eyes closed, feet apart (ECFA); and (4) eyes closed, feet together (ECFT). Static posturography is a reliable measure of static balance in persons with MS.¹⁶ Dynamic balance conditions included self-generated perturbations of (1) medial-lateral (ML) sway, and (2) AP sway. To analyze static and dynamic balance conditions, we calculated sway amplitude as described by our group.^{9,14}

Walking. Two distinct measures of walking, one laboratory (WV) and one clinical (T25FW), were chosen to account for walking speed and walking function. WV was assessed with an Optotrak 3020 Motion Capture System (Northern Digital Inc., Waterloo, Canada) as previously described by our group.⁹ Gait parameters were computed using a custom MATLAB program (The MathWorks Inc., Natick, MA). All participants wore their own shoes and those who used bracing or assistive devices for safety during gait used them during all walking trials.

Walking performance was also assessed using the T25FW. This measure was chosen for its ease of administration and common usage in MS clinical trials.¹⁷ The T25FW is not influenced by practice effects¹⁸ and has excellent intrarater (intraclass

correlation coefficient [ICC] = 0.99) and interrater (ICC = 1.0) reliability.¹⁹

Strength. Bilateral hip flexion, hip extension, and ankle dorsiflexion strength were assessed using a MicroFET2 handheld dynamometer (Hoggan Health Industries, West Jordan, UT). Quantitative strength testing is valid and objective in MS.² Two study team members (K.Z. and S.N.) performed all strength testing and demonstrated excellent interrater reliability at the hip (ICC = 0.98) and ankle (ICC = 0.97), and test-retest reliability at the hip (ICC = 0.95) and ankle (ICC = 0.77).² The weaker and stronger sides for each measure were determined using an average of the 2 trials for each muscle for each subject. Measurements for the weaker side for each muscle (hip flexion [WHF], hip extension [WHE], and ankle dorsiflexion [WAD]) were used in the analyses.

Sensation. Vibration thresholds at the great toe were quantified bilaterally with a Vibratron II device (Physitemp, Clifton, NJ). Using a 2-alternative forced choice procedure,²⁰ participants were required to determine which of 2 rods was vibrating. The Vibratron is a valid and objective measure of sensation in MS.² Two study team members (K.Z. and R.M.) performed sensation testing and demonstrated excellent interrater (ICC = 0.96) and test-retest (ICC = 0.91) reliability.² Measurement of the less sensitive (worse) great toe (WGT) was used for analyses.

Statistical analysis. To accommodate longitudinal data over multiple visits, a mixed model with random effects²¹ for each subject was used to account for the differences in within- and between-subject variability over time. To objectively choose the best predictors of WV, we used the Akaike information criterion (AIC) in a backward selection procedure and selected the model with the minimum AIC value. AIC is a measure of the goodness of fit of the statistical model (i.e., how well the model fits the observed data) and aims to maximize the likelihood function for the model while penalizing the number of predictor variables.²² For the final model, suppose Y_{ij} is the WV for subject i at visit j , thus WV for each subject at each visit. The number of months to visit j since the baseline visit is defined as t_j , and X_{pij} are the static or dynamic balance measures for subject i at visit j , where $p = (EOFA, EOFT, ECFA, ECFT, AP\ sway, ML\ sway)$. EDSS score, sex, diagnosis, and age were used to control for the effect of the covariates denoted by the vector C_{ij} for subject i at visit j . The random variability for subject i is u_i and the error associated with each observation for subject i at visit j is ε_{ij} . Thus, the model can be written as follows: $Y_{ij} = \beta_0 + \beta_1 t_j + \beta_2 X_{pij} + \beta_3 C_{ij} + u_i + \varepsilon_{ij}$.

To understand the unique contribution of strength and sensation impairments, these variables (WHF, WHE, WAD, WGT) were added to the model, and the same process of using AIC criterion in a backward selection procedure was used to select the model with the minimum AIC value. This process was then repeated with Y_{ij} as the T25FW for subject i at visit j in both the balance-only model and the model with the addition of strength and sensation measures. Approximate R^2 values were calculated to enhance clinical relevance of the models.

To identify the improvement of a model with balance and strength measures to demographics alone using exact adjusted R^2 values, a multiple linear regression model was used. When WV was the outcome, the model with demographics alone had an adjusted R^2 value of 62%; inclusion of balance measures improved the adjusted R^2 value to 67%. Addition of strength measures further improved the adjusted R^2 value to 75%; thus, the addition of balance and strength measures to demographics improved the model. To accommodate the variability of longitudinal data over multiple visits, a mixed

Table	Baseline characteristics		
	Relapsing MS (n = 28)	Progressive MS (n = 29)	Total (n = 57)
Age, y	39.3 (8.5)	52.0 (7.9)	45.8 (10.4)
Sex, F/M	18/10	14/15	32/25
Symptom duration, mo	7.7 (5.9)	18.1 (20.5)	13.0 (15.9)
EDSS score	2.5 (0–5)	5.5 (2.5–7)	3.5 (0–7)
Disease-modifying therapy use	23/28	15/29	38/57
No therapy	5/28	14/29	19/57
Interferon β	13/23	8/15	21/38
Glatiramer acetate	8/23	5/15	13/38
Natalizumab	1/23	0/15	1/38
Other	1/23	2/15	3/38
Walk velocity, m/s	1.7 (0.43)	1.1 (0.55)	1.4 (0.57)
T25FW, s	5.1 (4.4)	9.2 (6.6)	7.0 (5.9)
Static balance measures, mm			
EOFA	5.1 (2.1)	8.2 (4.0)	6.7 (3.6)
EOFT	9.4 (5.6)	12.2 (4.3)	10.8 (5.2)
ECFA	6.3 (3.4)	11.6 (6.4)	10.8 (5.2)
ECFT	11.7 (7.0)	15.7 (6.5)	9.1 (5.8)
Dynamic balance measures, mm			
AP sway	62.2 (11.2)	51.3 (12.2)	56.7 (12.8)
ML sway	105.3 (27.2)	88.6 (25.9)	97.0 (27.6)
Vibration sensation, vu	3.1 (2.1)	7.8 (5.1)	5.4 (4.5)
Strength measures, lb			
Hip flexion	41.7 (12.7)	23.1 (16.1)	32.4 (17.1)
Hip extension	33.4 (11.8)	19.3 (16.3)	26.5 (15.8)
Ankle dorsiflexion	41.5 (11.3)	28.3 (17.9)	34.9 (16.3)
No. of visits	4.0 (1.5)	4.3 (1.5)	4.1 (1.5)
Baseline to final visit duration, mo	31.1 (14.0)	34.4 (16.7)	32.8 (15.4)

Abbreviations: AP = anterior-posterior; ECFA = eyes closed, feet apart; ECFT = eyes closed, feet together; EDSS = Expanded Disability Status Scale; EOFA = eyes open, feet apart; EOFT = eyes open, feet together; ML = medial-lateral; MS = multiple sclerosis; T25FW = Timed 25-Foot Walk; vu = vibration unit.

All values are mean (SD) with the exception of EDSS score, which is median (range), and disease-modifying therapies, which reports number of participants.

model with random effects²¹ for each subject was required as described above.

Based on the modeling of the relationship of balance and strength measures with the outcome, the longitudinal prediction performance of these measures was examined. To build the model, the longitudinal data for each patient excluding their last visit were used as a training set. After estimating the parameters in the random-effects model above using the training data, we predicted the outcome for each patient for their last visit. We then computed the root-mean-square error (RMSE) of the predicted value with the true walking performance of the patient at their last visit. The correlation of the estimated values with the true values is shown as an indication of prediction accuracy.

RESULTS Study population. Fifty-seven individuals participated in this study. Participants were subgrouped

by diagnosis, and baseline characteristics are presented in the table.

Assessing walking performance over time. To understand the relationship over time among measures of walking and balance, we built several regression models. The models focus on the examination of 2 measures of walking: (1) WV, a quantitative measure, and (2) T25FW, a clinical measure, and evaluate the influence of balance (static and dynamic), lower extremity impairments (strength and sensation), and demographic information (age, sex, symptom duration, disease subtype, and EDSS score) on walking. All participants remained ambulatory over the course of the study; during the study, 7 of 47 individuals transitioned from no assistive device to unilateral support, 2 of 47 from no device to bilateral support, and 3 of 5 from unilateral support to bilateral support. The average change in WV over time was -0.012 m/s, and in T25FW performance was 0.48 seconds, indicating that participants walked slower at the final visit compared with baseline testing.

Factors best explaining WV over time. In figure 1A, the progression from initial to final model is presented showing the influence of balance and demographic contributors on WV over time. The final model included EOFA, AP sway, and demographics and explained $>95\%$ of the variance in WV (approximate R^2 of 0.95). Figure 1B includes the same balance measures and demographic data as above with the addition of quantitative strength and sensation measures. The results show that individuals with progressive disease walk slower than those with relapsing disease; EDSS score is a significant contributor to WV in MS, and not surprisingly, strength measures are also significantly related to WV over time. The final model included WHF, WHE, WAD, EOFA, AP sway, and demographic data, and explained $>95\%$ of the variance in WV (approximate R^2 of 0.96). In both final models, EOFA and AP sway were significant contributors to WV over time. Figure 2 shows individual data of the relationship of AP sway (figure 2A) and EOFA (figure 2B) to WV over time.

Factors best explaining T25FW over time. The relationships among T25FW, balance measures, and demographics are described in figure 3A. Figure 3B includes measures of strength and sensation in the model. The results of both models indicate that individuals with progressive disease are slower to complete the T25FW, poorer strength of the hip flexors and ankle dorsiflexors is related to poorer performance on the T25FW over time, and that the T25FW increases (i.e., walking becomes slower) over time, on average 0.041 seconds (figure 3A) and 0.072 seconds (figure 3B) each month depending on the model. EDSS scores did not significantly contribute to the T25FW (i.e., EDSS falls out of the model).

Figure 1 Diagram of 2 regression models exploring the factors best explaining walk velocity over time

(A) The final model included EOFA, AP sway, and demographics with an approximate R^2 of 0.9525. (B) With the addition of measures of strength and sensation, the final model included WHF, WHE, WAD, EOFA, AP sway, and demographics with an approximate R^2 of 0.9548. Demographic information included in both models: age, sex, EDSS score, diagnosis (relapsing vs progressive), and duration of study involvement. AIC = Akaike information criterion; AP = anterior-posterior; ECFA = eyes closed, feet apart; ECFT = eyes closed, feet together; EDSS = Expanded Disability Status Scale; EOFA = eyes open, feet apart; EOFT = eyes open, feet together; ML = medial-lateral; MS = multiple sclerosis; WAD = weaker side ankle dorsiflexion; WGT = worse great toe; WHE = weaker side hip extension; WHF = weaker side hip flexion.

The final model explaining T25FW with balance and demographic measures included ECFT, AP sway, and demographics with an approximate R^2 of 0.83 while the final model that also included strength included WHF, WAD, ECFT, AP sway, and demographics with an approximate R^2 of 0.85. In both models, AP sway is a significant contributor to T25FW performance over time. Figure 4 shows individual data on the relationship of AP sway (figure 4A) and EOFA (figure 4B) to T25FW over time.

Predicting long-term walking performance. As a preliminary exploratory analysis to examine whether balance measures are predictive of WV, we used the relationships identified in our study to build a prediction model, where the longitudinal balance data are used to predict the WV at the subject's last visit. The prediction accuracy was high (RMSE = 0.15); the correlation of the predicted WV values with the true WV was 0.96, implying that longitudinal balance data can accurately predict WV at the subject's final visit. The same model was applied to the T25FW and resulted

Figure 2 Three-dimensional scatterplot indicating the relationship of walking velocity to balance over time

Three-dimensional scatterplot indicating the relationship of walking velocity to (A) AP sway, and (B) EOFA over time. Each point on the figure represents a participant visit and the shade of the point indicates walking velocity, with lighter dots indicating slower walking velocity. Velocity measures were binned into quartiles indicating slowest walking 0%–25%, 26%–50%, 51%–75% (median), 76% to the maximum value. AP = anterior-posterior; EOFA = eyes open, feet apart.

in an RMSE of 0.81; the correlation between the predicted T25FW and the true T25FW was 0.91, implying that longitudinal balance data can also accurately predict T25FW performance at the subject's final visit.

DISCUSSION Our models demonstrate a strong relationship between walking and balance performance and that longitudinal monitoring of gait and balance identifies changes in disease progression that may be amenable to rehabilitation.

A recent study from our laboratory⁹ showed that at a single visit, WV in individuals with MS was best explained by AP sway, EOFA, and hip strength. Our longitudinal data reinforce this observation; both AP sway and EOFA were significant contributors to WV, and remained important contributors even in the presence of strength measures. Likewise, measures of strength contributed significantly to both WV and T25FW models (figures 1 and 3), indicating that our strength results were consistent with our cross-sectional data.

There are very few studies examining gait and balance longitudinally in MS. Increasing disability in gait has been noted over a 10-year period²³; however, no declines in balance or gait were observed over 18 months.¹¹ The present study included study visits spanning 32 months on average. WV did not decline over this time period (time is not a significant contributor in figure 1, A and B); however, T25FW did demonstrate a significant increase over time (figure 3, A and B). Of note, the relationship among gait and balance measures over time is consistent; a 1-mm increase in EOFA results in a reduction in WV of

0.018 or 0.017 m/s, depending on the model used (figure 1, A and B). Similarly, a 1-mm increase in AP sway results in an increase in WV of 0.0033 or 0.0024 m/s (figure 1, A and B, respectively). These data suggest that changes in balance will result in yearly declines in WV of 0.03 to 0.22 m/s on average, although some individuals may experience greater declines. The clinical relevance of the change in WV can be indirectly assessed by examining minimal clinically important difference values for WV in MS (0.08–0.14 m/s)²⁴ and other neurologic populations (0.10–0.20 m/s),²⁵ suggesting that accumulated declines in balance over time would result in a clinically meaningful change in WV.

We assessed the relationship between the T25FW and balance measures (ECFT and AP sway) and found that there was a significant relationship of T25FW over time, with T25FW increasing by 0.041 seconds on average per month (p value = 0.017), which was not observed with WV. This may be explained in part by EDSS score, which significantly contributed to WV, but not to T25FW. AP sway significantly contributed to T25FW performance over time; a 1-mm increase in AP sway resulted in a reduction in T25FW performance of 0.058 or 0.049 seconds, depending on the model (figure 3, A and B). The clinical implication of this change in T25FW performance can be indirectly assessed by examining minimal detectable change values for T25FW in MS (2.7 seconds).²⁶ These data suggest that changes in balance will result in clinically meaningful declines in T25FW performance over an average period of 3 to 5 years, although some individuals may experience more rapid declines.

Figure 3 Diagram of 2 regression models exploring the factors best explaining T25FW over time

(A) The final model included ECFT, AP sway, and demographics with an approximate R^2 of 0.8259. (B) With the addition of measures of strength and sensation, the final model included WHF, WAD, ECFT, AP sway, and demographics with an approximate R^2 of 0.8452. Demographic information is the same as in figure 1. AIC = Akaike information criterion; AP = anterior-posterior; ECFA = eyes closed, feet apart; ECFT = eyes closed, feet together; EOFA = eyes open, feet apart; EOFT = eyes open, feet together; ML = medial-lateral; MS = multiple sclerosis; T25FW = Timed 25-Foot Walk; WAD = weaker side ankle dorsiflexion; WGT = worse great toe; WHE = weaker side hip extension; WHF = weaker side hip flexion.

Previous studies exploring longitudinal balance data have used body-worn sensors or accelerometers to collect data.^{11,27,28} In this study, we focused on measuring longitudinal changes using a force plate and a 3-dimensional motion capture system. These tools are known to reliably quantify balance and gait characteristics and can be used to identify impairments modifiable with physical rehabilitation in this heterogeneous population. Studies utilizing portable devices such as accelerometers to measure local dynamic stability during walking have been limited, because 2 trials of 34 continuous steps are required,

and if individuals walk “very slowly or stopped repeatedly,” these trials were excluded.²⁷ In this study, only 18 of 49 participants had data suitable for local dynamic stability calculation.²⁷ Calculating stability during walking has definite functional benefits, but may not be feasible in all patients with MS. AP sway is a useful alternative measure of dynamic stability that mimics gait initiation and can be performed even in those who walk slowly. AP sway measurement would likely generalize to a larger portion of the MS population because it can be performed by those with limited ability to ambulate. Improvements in

Figure 4 Three-dimensional scatterplot indicating the relationship of T25FW to balance over time

Three-dimensional scatterplot indicating the relationship of T25FW to (A) AP sway and (B) EOFA over time. Each point on the figure represents a participant visit and the shade of the point indicates T25FW performance, with lighter dots indicating slower T25FW performance. T25FW measures were binned into quartiles indicating slowest walking 0%–25%, 26%–50%, 51%–75% (median), 76% to the maximum value. AP = anterior-posterior; EOFA = eyes open, feet apart; T25FW = Timed 25-Foot Walk.

Comment: A better measuring stick for walking in multiple sclerosis

A hallmark of the later stages of multiple sclerosis (MS) is the gradual decline in walking, which both limits mobility and increases risk of injury from falling. Walking is a complex task, involving strength, coordination, and sensation. Like many complex neurologic functions, walking is easy to observe, but difficult to measure. While early characterization of walking dysfunction in MS focused on maximum walking distance and need for assistive devices (i.e., a cane or walker), more recent metrics target walking speed and distance walked within a period of time (i.e., 3-minute walk).

Fritz et al.¹ have taken this characterization of walking in people with MS to a new level. In this report, they used a force plate posturography platform to measure postural sway in 57 people with MS, both while the participants were standing still (static) and after perturbations of the platform (dynamic). As expected, poorer balance performance was associated with slower walking velocity. More importantly, a combination of static and dynamic balance performance, along with clinical demographics, accounted for the vast majority (95%) of the variance in the change in walking velocity over about 3 years. Impaired strength and sensation predicted change in walking velocity as well.

This study advances our ability to characterize walking impairment in MS and highlights the clinical relevance of measurement tools such as those utilized in the Zackowski laboratory.² Future efforts should focus on whether these tools can measure improvement following rehabilitative intervention, and whether the improvements measured by posturography are associated with increased mobility, decreased injury from falls, and increased patient-reported quality of life. Although an attractive outcome measure for phase II, proof-of-concept trials, posturography will need more widespread availability before it could be potentially utilized in rehabilitative trials.

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ML and AP sway measures have been noted following a training program,²⁷ suggesting that dynamic balance is amenable to rehabilitation training and holds promise as an outcome measure in future studies.

There are several limitations in this study. Cognitive status of the participants was not formally tested at any study visit; however, all participants were able to follow study directions. We used handheld dynamometry to measure strength, which can be variable between testers. Two raters performed strength testing (K.Z. and S.N.) and demonstrated excellent interrater reliability (ICC > 0.97). While additional factors such as spasticity or proprioceptive loss could contribute to walking dysfunction, these factors are more subjective and were therefore excluded from this quantitative analysis. Finally, all posturography measures were recorded on a force plate, which is rarely available in clinical settings. However, force plate data are reliable in MS and may generalize to a greater portion of the MS population, as use of portable devices has been hampered by the inability to assess individuals with limited ambulation.²⁷ Furthermore, use of clinical measures developed to quantify dynamic leaning balance is not yet widespread.^{29,30}

Use of baseline function to predict future walking status is an exciting area of study; the model presented here is preliminary and shows the use of longitudinal balance data to build models for predicting future walking performance. To make claims about the predictive power of baseline balance and strength measures on the change in walking performance over time, more systematic baseline and follow-up visits for a larger number of patients are required.

These data suggest that quantitative measures of dynamic and static balance contribute important information to longitudinal walking performance in MS. While AP sway and EOFA are important contributors to WV, AP sway and ECFT may be more important contributors to T25FW performance. When strength measures are considered, WHF and WAD strength were associated with both WV and T25FW over time. Future work should link these quantitative measurements to fall risk, because balance and strength are important indicators of fall risk in MS. Rigorous evaluation of balance may lead to a more quantitative means of determining fall risk and the development of rehabilitative strategies to decrease that risk and predict future function.

AUTHOR CONTRIBUTIONS

Nora E. Fritz: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, statistical analysis. Scott D. Newsome: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, contribution of patients. Ani Eloyan: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, statistical analysis. Rhul Evans R. Marasigan: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, statistical analysis, study supervision. Peter A. Calabresi: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, study supervision, obtaining funding. Kathleen M. Zackowski: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, contribution of vital reagents/tools/patients, acquisition of data, statistical analysis, study supervision, obtaining funding.

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