ORIGINAL RESEARCH

Relationship between physical performance and cognitive performance measures among community-dwelling older adults

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submit your manuscript | www.dovepress.com Dovepress http://dx.doi.org/10.2147/CLEPS62392 **Purpose:** Cognitive impairment is correlated with physical function. However, the results in the literature are inconsistent with cognitive and physical performance measures. Thus, the aim of this study was to determine the association between cognitive performance and physical function among older adults.

Methods: A total of 164 older adults aged \geq 60 years and residing in low-cost housing areas in Kuala Lumpur, Malaysia participated in this study. Cognitive performance was measured using the Mini Mental State Examination, clock drawing test, Rey auditory verbal learning test, digit symbol test, digit span test, matrix reasoning test, and block design test. Physical performance measures were assessed using the ten step test for agility, short physical performance battery test for an overall physical function, static balance test using a Pro.Balance board, and dynamic balance using the functional reach test.

Results: There was a negative and significant correlation between agility and the digit symbol test (r=-0.355), clock drawing test (r=-0.441), matrix reasoning test (r=-0.315), and block design test (r=-0.045). A significant positive correlation was found between dynamic balance, digit symbol test (r=0.301), and matrix reasoning test (r=0.251). The agility test appeared as a significant (R^2 =0.183, R^2 =0.407, R^2 =0.299, P<0.05) predictor of some cognitive performance measures, including the digit span test, clock drawing test, and Mini Mental State Examination.

Conclusion: These results suggest that a decline in most cognitive performance measures can be predicted by poor execution of a more demanding physical performance measure such as the ten step test for agility. It is imperative to use a more complex and cognitively demanding physical performance measure to identify the presence of an overall cognitive impairment among community-dwelling older adults. It may also be beneficial to promote more complex and cognitively challenging exercises and activities among older adults for optimal physical and cognitive function.

Keywords: cognitive performance, physical performance, older adults

Introduction

The aging population in Malaysia has significantly increased in number over the last few decades. It is imperative to perform extensive research to provide evidence-based strategies for successful aging.¹ Aging affects many domains of cognitive performance.² Even though evidence indicates that age-related cognitive decline is related with genetic factors,^{3,4} there is also a strong possibility that cognitive performance declines with a parallel decrease in physical performance.⁵ This is partly due to the common biological changes and underlying age-related decline shared by both physical and cognitive functioning.⁶

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In several prospective studies, it has been demonstrated that maintenance of higher levels of physical fitness helps to protect against cognitive deterioration, even at an advanced age.^{7,8} Maintaining higher levels of physical performance and cardiorespiratory and aerobic fitness may help in mitigating cognitive impairments among older adults.⁹⁻¹¹ In a study by Voss et al,¹² it was reported that aerobic fitness was associated with better average accuracy and mean response time across all levels of spatial memory task among older adults. Poor physical performance among older adults may also lead to more rapid cognitive decline and early onset of dementia.¹³ However, the association between many cognitive measures and physical performance measures is still unclear due to methodological differences in the studies. Muscle strength was found to be associated with cognitive performance.14 Balance ability and mobility were demonstrated to be associated with cognitive performance but these physical performance measures had a sex moderated effect.15 It has also been suggested that the effect of the many physical performance measures on the different domains in cognitive performance may be the same.¹⁵

It is noteworthy that in the previous studies, a predictive physical performance measure was not included in examining the association between cognitive performance and physical performance measures. Thus, the objectives of this study were to determine the association between cognitive performance and physical performance measures that included agility, overall physical performance, and dynamic and static balance among community-dwelling older adults, and to examine whether physical performance can predict cognition in older adults. This study is part of a larger study among older adults in Malaysia (Kuala Lumpur Aging Study [KLAS]).¹⁶

Methods

A total of 164 older adults aged \geq 60 years and residing in low-cost housing areas, ie, Kuala Lumpur City Hall Flat Housing Area, Zone 1, Cheras, were invited to participate in this cross-sectional study using advertisements and flyers. Older adults who 1) had severe vision, hearing, and speech problems; 2) had difficulty in getting around without assistance from another person or device; 3) had difficulty in walking 6 m; 4) had severe medical conditions and were on antipsychotics, antidepressants, hormone replacement therapy, and drugs affecting the dopaminergic system or had severe osteoarticular pathologies with functional limitations, vertebral stenosis, primitive and minor neuroradicular diseases, invalidating neurological diseases, former acute cerebral vascular events, cognitive deficit, diabetic neuropathy, Parkinson's disease and minor parkinsonism, vertigo syndromes (labyrinthine disease, dizziness), stroke, or under active therapy for life-threatening cancers; 5) were unable to be contacted or refused to participate in the study; and 6) had a Geriatric Depression Scale¹⁷ score greater than five; were excluded. Informed consent was obtained after providing both written and verbal information to the participants. Ethical approval was obtained from the Secretariat for Research and Ethics of Universiti Kebangsaan Malaysia (KLAS-NN-135-2011). Participants gathered at respective community centers and were interviewed for sociodemographic and neuropsychological status. Then, physical performance was assessed by trained final year physiotherapist undergraduates.

Demographic information and physical assessment

Age, sex, ethnicity, marital status, education level, and medical conditions were obtained using a pretested questionnaire. The presence of hypertension, diabetes, stroke, heart disease, asthma, osteoporosis, hip fracture, and arthritis were defined as a self-reported condition based on diagnosis by the participant's physician. Functional status (instrumental activities of daily living)¹⁸ was also obtained using pretested questionnaires.

Physical performance measures

Agility was measured using the ten step test (TST),¹⁹ in which participants were asked to step one foot up and down onto a 10 cm height block followed by the other foot, as fast as possible. The time taken by the participant to perform ten repetitions was recorded. The shorter the time the participant used to complete the ten repetitions, the better their agility. TST has been reported to be highly reliable (r=0.960) in individuals ranging in age from 20–99 years.¹⁹ TST, which includes quickness and repetition, is suitable to use for agility testing.

The short physical performance battery (SPPB)²⁰ was used to measure physical performance. SPPB consists of three tests that include walking speed, chair stands, and standing balance. Each test is scored from zero (inability to complete the task) to four (highest level of performance). The sum of the score (zero to 12) was used as a measurement of level of physical performance. In the standing balance test, participants were required to maintain tandem, semi-tandem, and side-by-side standing for 10 seconds. For the timed chair test, participants were instructed to sit and stand five times as quickly as possible on a straight back chair with their arms crossed over their chest and back leaning on the chair. In the

Physical performance measure is associated with cognitive performance

walking speed test, participants were instructed to walk a standard distance of a 12 foot pathway (2 feet of acceleration, 8 feet of usual speed steady walk, and 2 feet of deceleration). Participants were allowed to use their walking aids in this test and walk at their usual pace. High reliability (r=0.89) was reported for SPPB in a population aged 64–75 years.²¹

Static balance was tested using a Pro.Balance board (Lab Rehab Pte Ltd, Singapore), which has an intraclass correlation coefficient of r=0.92.^{22,23} Participants were requested to stand on the Pro.Balance board with their eyes open while maintaining their balance for 30 seconds. Overall balance performance was calculated using the Pro.Balance software. This method has been used among older adults in a previous study.²⁴

Dynamic balance was measured using the functional reach test (FRT).²⁵ In FRT, participants were asked to stand barefooted while maintaining an upright position and to reach forward with an outstretched arm without moving their feet. The distance of reaching was represented by the difference between the starting and ending position of the third knuckle. Participants who were able to reach farther indicated better dynamic balance. High reliability (r=0.92) using FRT was reported in an elderly population aged 69–104 years.²⁶

Cognitive performance tests

Cognitive function was assessed using seven cognitive domains: global cognitive function (Mini Mental State Examination [MMSE]),²⁷ executive control function (the clock drawing test),²⁸ verbal memory (Rey auditory verbal learning test [RAVLT]),²⁹ and subtests of Wechsler Adult Intelligent Scale III,³⁰ ie, digit symbol, digit span, matrix reasoning, and block design. Depression was assessed using the Geriatric Depression Scale questionnaire.³¹

MMSE is composed of 13 components which are divided into five sections: orientation, registration, attention and calculation, recall, and language and copying.²⁷ The maximum possible score is 30 points. Cronbach's α of 0.76 was obtained from a Malaysian elderly population aged 57–75 years old.³² In the clock drawing test, participants were given blank paper and asked to "draw a clock that says 1:45" and "set the numbers and face of the clock so that a child can read them."²⁸ The score ranged from zero (poorest performance) to 15 (best performance). A high degree of reliability (*r*=0.94) was reported in elderly subjects.²⁸

RAVLT was evaluated by giving five trials to participants to learn a 15-word list and then asking them to recall the words after a brief interval (immediate recall) and a 20-minute delay (delayed recall).²⁹ The number of words correctly recalled at each time point was recorded. The score ranged from zero (poorest performance) to 90 (best performance). Cronbach's α of 0.85 was reported in elderly aged ≥ 60 years.³³ The digit symbol test, with an intraclass correlation coefficient of 0.846,³⁴ was used to assess psychomotor performance, attention, and ability to remember and operate on complex symbols.³⁰ Participants were given paper and a pencil and required to copy as many novel symbols corresponding to numbers as possible in 120 seconds. The score ranged from zero (poorest performance) to 133 (best performance).

In the digit span test, with an intraclass correlation coefficient of 0.78,³⁰ the participants were given a list of digits and asked to repeat it back. If the participants could repeat a two-digit list, a three-digit list, four-digit list, and so on was given until the participants failed to repeat two listed digits continuously.^{30,35} The score ranged from zero (poorest performance) to 30 (best performance). The matrix reasoning test (test-retest reliability of r=0.77) was carried out by giving participants an incomplete matrix and asking them to select the response option that completed the matrix.³⁶ The score ranged from zero (poorest performance) to 26 (best performance). In the block design test (test-retest reliability of r=0.82), participants were given a picture and asked to use red and white blocks to recreate the design.^{30,37} The score ranged from zero (poorest performance) to 68 (best performance).

Statistical analysis

All statistical analyses were performed using SPSS® version 20.0 (IBM Corporation, Armonk, NY, USA). Descriptive analyses of the demographic characteristics of the participants were expressed as mean ± standard deviation (SD) or percentage. The Kolmogorov-Smirnov test was performed to examine the normality of data (P > 0.05). Raw scores of the digit span test, digit symbol test, block design test, and matrix reasoning test were converted into scale scores to reconstruct the original distribution of raw scores for each age group. Pearson's correlation coefficients between physical and cognitive function tests were determined. Point-biserial correlation was used for medical conditions, which was dichotomized as 1= present and 0= not present. Variables found to be significant using univariate analysis at P < 0.05 were analyzed using multiple hierarchical regression while controlling for the influential demographics (age, sex, race, and education level) and medical conditions (associated with neurocognitive or physical function: hypertension, hyperlipidemia, diabetes, stroke, heart disease, asthma, osteoporosis, hip fracture, and arthritis diagnosed by a physician). An unstandardized coefficient was used in the regression - for every unit (score) change in the physical performance test, cognitive function changed by X units. Physical performance measures were defined as the independent variable, and cognitive performance tests were defined as the dependent variable. The number of cognitive performance test scores that were influenced by each of the four physical performance measure scores were determined.

Results

Table 1 shows the baseline characteristics of participants. A total of 164 participants participated in the study aged from 69–80 years, with a mean age of 66±4.6 years. The majority of the participants were women (65.6%) and the mean \pm SD number of education years was 11.9±0.3 years. Most participants were generally healthy with a very low mean Geriatric Depression Scale score (mean \pm SD, 2.6±2.1), indicating no depression among the participants.

Table I Baseline characteristics of participants (n=16	Table I	Baseline	characteristics	of partici	pants ((n= 16 4	ł)
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Characteristics	Mean ± SD or %
Demographic data	
Age, years	66.0±4.6
Female	66.5%
Education, years	11.9±0.3
Cognitive function	
MMSE, score ²⁷	25.9±3.4
CLOXI, score ²⁸	6.9±2.2
Total RAVLT, score ²⁹	41.6±13.9
Digit symbol, score ³⁰	5.5±2.7
Digit span, score ³⁰	8.4±2.4
Matrix reasoning, score ³⁰	8.0±3.3
Block design, score ³⁰	6.4±3.3
Psychological function	
GDS, score ³¹	2.6±2.1
Physical function	
TST, seconds ¹⁹	17.1±3.6
SPPB, score ²⁰	11.7±0.6
Pro.Balance board, seconds ²²	2.2±1.0
FRT, cm ²⁵	29.5±5.5
IADL, score ¹⁸	13.4+1.2
Medical conditions	
Hypertension	58.5%
Hyperlipidemia	53.7%
Diabetes	31.7%
Stroke	1.8%
Heart attack	4.9%
Heart failure	3.0%
Asthma	4.3%
Osteoporosis	1.8%
Hip fracture	0.6%
Arthritis	26.2%

Abbreviations: CLOX1, clock drawing test; FRT, functional reach test; GDS, Geriatric Depression Scale; IADL, instrumental activities of daily living; MMSE, Mini Mental State Examination; RAVLT, Rey auditory verbal learning test; SD, standard deviation; SPPB, short physical performance battery; TST, ten step test. There was a negative and significant (P<0.01) correlation between TST and the digit span test, digit symbol test, clock drawing test, matrix reasoning, RAVLT, and MMSE based on univariate Pearson's correlation test, with a correlation coefficient ranging from -0.315 to -0.441 (Table 2). A positive and significant correlation was found between dynamic balance and the digit symbol test (r=0.301, P<0.01), clock drawing test (r=0.201, P<0.05), and matrix reasoning test (r=0.251, P<0.05). A similar trend was noted for the SPPB and digit span test (r=0.265, P<0.01), digit symbol test (r=0.246, P<0.05), and clock drawing test (r=289, P<0.01), which were also strongly positive and significant. However, the relationship between static balance and all cognitive measures was not significant.

Further analysis using the multiple hierarchical regression model was performed to examine the physical performance measures that seemed to be predictors for cognitive performance (Table 3). Agility as assessed using TST was detected as a significant predictor of the digit span test (R^2 =0.183, P<0.05), clock drawing test (R^2 =0.299, P<0.01), and MMSE (R^2 =0.407, P<0.05) after adjusting for age, sex, education, and medical condition. No significant association with the block design test, digit symbol test, matrix reasoning test, and RAVLT was detected with all physical measures (agility, physical performance, dynamic balance, and static balance).

Discussion

The main objective of this study was to determine the association between cognitive and physical performance measures among community-dwelling older adults. To the best of the authors' knowledge, this is the first study to report TST - anagility test – as the strongest predictor for cognitive performance that is related to global cognitive function, executive control function, verbal memory, processing speed, working memory, and perceptual organization.

TST has been used to measure agility among older adults.³⁸ Agility represents the capability to accurately alter position and direction as fast as possible without losing balance.³⁹ It can be argued that TST is a complex movement whereby one will need quick visual neuromotor actions to place each foot repetitively, alternately, and precisely ten times on a stool while maintaining equilibrium. It is presumed that to perform TST one must have adequate mobility, strength, endurance, speed, precision, proprioception, balance, and executive ability. Executive ability can be defined as the execution of a specific goal-orientated composite task that requires planning, monitoring, and execution.⁴⁰ Thus, TST

Factors	Cognitive functions						
	Digit span	Digit symbol	BD	MR	CLOXI	MMSE	RAVLT total
Sociodemographic							
Age	0.085	0.021	0.438**	0.084	-0.257**	-0.156	-0.287**
Sex	-0.195**	-0.285**	-0.336**	-0.301**	-0.150	-0.114	0.048
Education years	0.232*	0.370**	0.189	0.296**	0.270**	0.560**	0.241*
Medical conditions							
Hypertension	-0.114	-0.115	-0.076	-0.054	-0.189*	-0.073	-0.195**
Hyperlipidemia	0.033	0.002	-0.037	-0.008	0.095	0.119	-0.017
Diabetes	-0.177*	-0.175*	-0.142	-0.058	-0.172*	-0.070	-0.183*
Stroke	-0.077	-0.100	-0.076	-0.173*	-0.121	-0.05 I	-0.030
Heart attack	-0.038	0.131	0.020	0.008	0.055	-0.016	0.017
Heart failure	0.028	0.139	0.119	0.163*	0.078	0.110	0.151*
Asthma	-0.029	-0.022	0.013	0.020	-0.083	-0.071	-0.125
Osteoporosis	0.038	-0.016	-0.005	-0.099	0.075	-0.07 I	0.107
Hip fracture	0.079	0.046	-0.140	-0.081	-0.084	-0.091	-0.028
Arthritis	0.018	-0.036	0.004	-0.023	-0.09 I	-0.071	-0.005
Physical functioning							
TST ¹⁹	-0.355**	-0.355**	-0.045	-0.315**	-0.441**	-0.374**	-0.352**
FRT ²⁵	0.118	0.301**	0.107	0.251*	0.201*	0.168	0.142
Pro.Balance ²²	-0.052	-0.023	0.081	0.072	-0.077	-0.022	-0.070
SPPB ²⁰	0.265**	0.246*	0.059	0.123	0.289**	0.134	0.155
IADL ¹⁸	0.022	0.122	0.128	0.062	0.130	0.241**	0.111

Table 2 Correlation coefficients of cognitive and physical function tests

Notes: *P<0.05; **P<0.01.

Abbreviations: BD, block design; CLOXI, clock drawing test; FRT, functional reach test; IADL, instrumental activities of daily living; MMSE, Mini Mental State Examination; MR, matrix reasoning; RAVLT, Rey auditory verbal learning test; SPPB, short physical performance battery; TST, ten step test.

may have appeared as a predictor for cognitive performance, as shown in this study.

that MMSE scores of the participants increased by 3.1 after 1 year of exercise.

Significant correlation was found between dynamic balance – measured using FRT – and cognitive measures, including the digit symbol test, matrix reasoning test, and clock drawing test, among community-dwelling older adults in this study. Similarly, in a previous study among 50 healthy participants using FRT to measure physical performance, a decline in both physical and cognitive performance was reported.⁴¹ Dynamic balance ability is one of the key prerequisites in performing activities of daily living. A Canadian study of health and aging reported that FRT score was higher in participants with higher activities of daily living score.²⁶

Among all cognitive performance being investigated, a global cognitive performance measured using MMSE was most influenced by physical function (β =-0.065, R^2 =0.338). This is in agreement with a cross-sectional study among 207 participants. MMSE is a complex tool that can be used to systematically and comprehensively assess mental health.²⁷ A study on an elderly population aged 85 years old reported that MMSE was significantly associated with physical fitness measurements.⁴² A study on participants aged 75–99 years with seated range-of-motion exercises and strength training using elastic resistance bands and soft weights reported Multiple hierarchical regression – a type of multiple comparison model – was performed to find the best predictors of cognitive function in the present study. This model controls the potential effects of other variables such as age, sex, education, and medical condition. Multiple comparisons increased the potential for type I errors, which occur when statistical tests are performed repeatedly. When many comparisons were made among the variables, there was a chance for the *P*-value, which is related with each individual comparison, to be underestimated. This multiple comparisons problem was solved using the multiple hierarchical model to carry out partial pooling, eg, shifting estimates toward each other.

There are several strengths in this study. Firstly, performance-based measures for agility, overall physical performance, and balance were used. These minimized potential bias – either referral bias or bias regarding emerging cognitive impairment, as the study involved older adults. Secondly, the degree and significance of association between each of the physical performance measures and cognitive performance were examined. The limitation in this study was that the study population consisted of community-dwelling older adults with a lower level of financial status. Hence, it is not clear

Cognitive outcome	Variable	β (95% CI)	R ²	$\Delta \mathbf{R}^2$
Digit span ³⁰	Step I		0.125**	0.125**
-	Sex	-0.591 (-1.60, 0.41)		
	Education	0.707* (0.18, 1.23)		
	Diabetes	-0.654 (-1.58, 0.27)		
	Step 2		0.183**	0.058*
	Sex	-0.447 (-1.44, 0.54)		
	Education	0.447 (-0.11, 1.00)		
	Diabetes	-0.420 (-1.35, 0.51)		
	TST ¹⁹	-0.148* (-0.28, -0.02)		
	SPPB ²⁰	0.271 (-0.48, 1.02)		
Digit	Step I		0.323***	0.323***
symbol ³⁰	Sex	-2.062* (-3.22, -0.90)		
	Education	1.124* (0.53, 1.72)		
	Diabetes	-0.818 (-1.87, 0.23)		
	Step 2		0.346***	0.023
	Sex	-I.873* (-3.08, -0.66)		
	Education	0.934* (0.29, 1.58)		
	Diabetes	-0.612 (-1.70, 0.47)		
	TST ¹⁹	-0.088 (-0.25, 0.08)		
	SPPB ²⁰	0.228 (-0.89, 1.34)		
	FRT ²⁵	0.30 (-0.08, 0.14)		
Block	Step I		0.270***	0.270**
design ³⁰	Age	0.250* (0.13, 0.37)		
	Sex	-2.108* (-3.28, -0.93)		
Matrix	Step I		0.190**	0.190**
reasoning ³⁰	Sex	-1.095 (-2.42, 0.23)		
	Education	1.086* (0.40, 1.77)		
	Stroke	-2.084 (-5.92, 1.74)		
	Heart failure	0.554 (-2.23, 3.34)		
	Step 2		0.229**	0.052
	Sex	-0.850 (-2.22, 0.52)		
	Education	0.778* (0.03, 1.53)		
	Stroke	-2.027 (-5.81, 1.75)		
	Heart failure	0.919 (-1.94, 3.78)		
	TST ¹⁹	-0.152 (-0.34, 0.04)		
	FRT ²⁵	0.042 (-0.07, 0.16)		
CLOX I ²⁸	Step I	-	0.221***	0.221**
	Age	-0.119* (-0.20, -0.04)		
	Education	0.695* (0.25, 1.14)		
	Hypertension	-0.597 (-1.45, 0.26)		
	Diabetes	-0.392 (-1.28, 0.50)		
	Step 2	·	0.299***	0.078*
	Age	-0.083* (-0.16, 0.00)		
	Education	0.419 (-0.08, 0.87)		
	Hypertension	-0.348 (-1.21, 0.48)		
	Diabetes	-0.275 (-1.13, 0.60)		
	TST ¹⁹	-0.169* (-0.28, -0.04)		
	SPPB ²⁰	0.140 (-0.66, 0.74)		
	FRT ²⁵	0.030 (-0.05, 0.11)		
			0 283***	0.283**
RAVLT	Step I		0.205	

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Cognitive outcome	Variable	β (95% CI)	R ²	ΔR^2
	Education	3.878* (0.89, 6.87)		
	Hypertension	-3.573 (-9.15, 2.01)		
	Diabetes	-3.722 (-9.48, 2.04)		
	Heart failure	10.938 (-1.69, 23.56)		
	Step 2		0.310***	0.028
	Age	-0.949* (-1.49, -0.41)		
	Education	2.638 (-0.59, 5.86)		
	Hypertension	-2.640 (-8.23, 2.95)		
	Diabetes	-3.358 (-9.05, 2.33)		
	Heart failure	12.377 (0.16, 24.92)		
	TST ¹⁹	-0.742 (-1.52, 0.04)		
MMSE ²⁷	Step I		0.323**	0.323**
	Education	4.366* (1.31, 7.42)		
	Step 2		0.407***	0.084**
	Education	2.067* (-1.18, 5.31)		
	TST ¹⁹	-1.021* (-1.80, -0.25)		
	IADL ¹⁸	2.192* (-0.21, 4.59)		

Table 2 (Continued)

Notes: *P < 0.05; **P < 0.01; ***P < 0.001 using multiple hierarchical regression. The control variables were: age, sex, race, education level, hypertension, hyperlipidemia, diabetes, stroke, heart disease, asthma, osteoporosis, hip fracture, and arthritis.

Abbreviations: β , standardized regression coefficient; CLOXI, clock drawing test; CI, confidence interval; ΔR^2 , change in R^2 ; FRT, functional reach test; IADL, instrumental activities of daily living; MMSE, Mini Mental State Examination; RAVLT, Rey auditory verbal learning test; SPPB, short physical performance battery; TST, ten step test.

that comparable results could be obtained among older adults from a different socioeconomic background. Also, the high mean scores on cognitive performance reflect a ceiling effect, which might be caused by the small number of participants. Older participants might have felt too fatigued to complete all of the physical tests. However, rest was provided in between all of the physical tests. The analysis did not include smoking as a confounding factor, which might have affected the physical and cognitive performance.

Conclusion

This study provides evidence that a more demanding physical performance measure such as the TST is a predictor for cognitive performance measure among community-dwelling older adults. The results of this study suggest that it is imperative to use a more complex and cognitively demanding physical performance measure to identify the presence of an overall cognitive impairment among community-dwelling older adults. It may also be beneficial to promote more complex and cognitively challenging exercises and activities among older adults for optimal physical and cognitive function. Further research, such as a longitudinal study, is needed for inferences of causation.

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Disclosure

The authors report no conflicts of interest in this work.

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