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Original Report

Cognitive Function as a Predictor of Major Mobility Disability in Older Adults: Results From the LIFE Study

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Abstract

Background and Objectives: Many cross-sectional studies have confirmed a link between gait speed and cognitive function. However, it is unknown whether cognitive function plays a role in the onset of major mobility disability (MMD) and if the effects are independent of physical function. This study examined cognitive and physical function as predictors of MMD across an average of 2.6 years of follow-up in community-dwelling older adults with compromised mobility.

Research Design and Method: Data were collected from 1,635 participants in the Lifestyle Interventions and Independence for Elders (LIFE) study ages 70–89 years free of MMD at baseline. MMD was assessed every 6 months and defined as the inability to walk 400 m in ≤15 min without assistance or sitting. Cognitive function was assessed at baseline, 18 months, and 24 months using a cognitive battery categorized into four domains: global cognitive function, processing speed, verbal memory, and executive function.

Results: Across the study duration of 2.6 years, 536 participants (32.8%) developed MMD. Cox Proportional Hazard models indicated a protective relationship for higher baseline processing speed (Hazard Ratio [HR] per standard deviation: 0.86, $p = .006$), executive function (HR: 0.86, $p = .002$), and global cognition (HR: 0.85, $p = .001$) on incidence of MMD adjusted for demographics, intervention, and comorbidities. Results were not significant after adjustment for gait speed. In adjusted longitudinal models, a positive change in processing speed was significantly associated with reduced risk of MMD (HR: 0.52, $p < .001$) while other domains were not.

Discussion and Implications: In the LIFE study, processing speed at baseline and follow-up was a significant predictor of subsequent MMD although the observed association may be explained by physical function as reflected in gait speed. More studies are needed to understand how cognitive function, alone and in combination with physical function, influences risk of MMD.

Translational Significance: Cognitive function and mobility are important for older adults to remain independent. We found that processing speed and lower-extremity physical function are predictors of major mobility disability and future strategies should target improving function of older adults in order to prevent major mobility disability.

Key words: Cognition, Disabilities, Function/mobility.

Nearly one in four U.S. older adults report having a disability, most commonly in the area of mobility (1). Major mobility disability (MMD) has been defined in some investigations as the inability to walk 400 m without assistance in under 15 min (2), which is similar to being unable to walk several street blocks. For the first time, recent evidence from the Lifestyle Interventions and Independence for Elders (LIFE) study showed that a structured physical activity program was able to reduce the incidence of MMD by 18% in older participants who had compromised mobility as baseline (2). However, it is not known if there is an association between cognitive function and MMD, or if cognition and physical function represent separate versus shared risks for MMD.

The relationship between gait speed and cognitive function has been well investigated and evidence from several meta-analyses (3–5) including over 26 cross-sectional studies has shown an association between gait speed and global cognition, executive function, memory, and processing speed. To note, majority of these studies included gait speed over a short distance (≤10 m) and it is unclear whether cognition is associated with walking a longer distance such as 400 m and/or the development of MMD. Additionally, there are few longitudinal studies (6–11) that have examined the relationship between cognitive function and changes in mobility that include multiple cognitive and physical function domains.

The primary aim of this study was to investigate whether baseline cognitive function was a predictor of the development of MMD in the LIFE study and whether baseline cognitive function was related to baseline physical function (400 m gait speed and Short Physical Performance Battery [SPPB]). The secondary aim was to examine whether longitudinal changes over 18–24 months in cognitive function were related to changes in physical function and risk of MMD. We hypothesized that baseline cognitive function would be related to the development of MMD, and there would be a direct relation between baseline cognitive function and baseline physical function, independent of baseline physical function status.

Method

Data Source

The current study analyzed data from the LIFE study (2). The LIFE study was a multisite, single-blind, randomized control trial of a structured physical activity intervention compared with a health education control conducted at eight U.S. field centers that targeted sedentary older adults with compromised mobility. Briefly, the study included 1,635 community-dwelling older adults between 70 and 89 years old who were sedentary (<20 min per week of regular physical activity and <125 min/week of moderate physical activity), had compromised mobility (SPPB of ≤9), but were able to walk 400 m in ≤15 min without assistance, sitting, or use of a walker. Eligible participants were free of MMD at baseline, had no diagnosis of dementia or significant cognitive impairment, and could safely participate in the intervention.

The primary outcome was MMD defined as the loss of the ability to walk 400 m in ≤15 min. Recruitment occurred from February 2010 through December 2011; the trial ended in December 2013. The mean follow-up time was 2.6 years (interquartile range: 2.3–3.1 years). The LIFE study was approved by the institutional review board at all eight study sites and all participants provided informed consent [clinicaltrials.gov identifier: NCT01072500]. LIFE study's design, recruitment, and primary results are published elsewhere (2,12,13).

Outcome Measure

The LIFE study defined MMD as the inability to complete the 400 m walk within 15 min without sitting and without the help of another person or walker. The 400 m walk was timed and participants were asked to walk 10 laps of a 20 m course at their usual walking speed (2). A 1 min break and use of a straight cane were allowed. MMD was ascertained every 6 months during the study. Our outcome is defined as time (days) to first occurrence of MMD.

Demographic Measures

At baseline, participants' demographic characteristics (age, sex, ethnicity, and education) and medical history (smoking status, history of hypertension, diabetes, cardiovascular disease, and stroke) were collected through a structured self-report interview. Depressive symptoms are assessed with the 11-item version of the Center for Epidemiologic Studies Depression Scale (CES-D) (14). Participants also completed a physical examination which included body weight measured in kilograms, and height measured in centimeters. Body mass index (BMI) was calculated as body

weight (kilograms) divided by height squared (meters). A blood sample was collected for APOE-4 genotyping.

Cognitive Function

Cognitive function was assessed using a battery of neuropsychological tests (15). Speed of processing/attention was assessed using the WAIS-III Digit Symbol Copy Score (16) (range: 0–133). Verbal memory was assessed using a 12-item word list from the revised Hopkins Verbal Learning Test (HVLT-R) (17) including immediate recall on three trials (range: 0–36) and a delayed recall (range: 0–12). These two measures were administered at baseline for all participants and at 24 month follow-up (n = 1,416).

Executive function was measured utilizing the following three computerized tasks: the n-back test, 1-back, and 2-back (% correct, range: 0–100) (18), the Eriksen Flanker test, with congruent and incongruent conditions (reaction time in seconds) (19), and a task-switching exercise, with no-switch and switch conditions (reaction time in seconds) (20). Higher values on the Flanker test and task-switching tests indicate a slower (worse) performance. For all other cognitive tests, higher scores represent better performance. Executive function tasks were administered at baseline for all participants and at one follow-up visit, either 18 month (n = 1,002) or 30 month (n = 394), for different participants. This analysis included only 18 m follow-up on executive function tasks.

Physical Function

Physical function at baseline and follow-up was measured objectively by conducting a usual pace 400 m walk test (21), from which continuous variables reflecting physical function levels were derived. For those that completed the 400 m walk, gait speed was calculated as distance (meters) divided by time (seconds).

The SPPB (22,23) is a summary performance measure comprised of three lower extremity performance tasks: a 4 m usual paced walk done twice, timed rising from a chair 5 times as fast as possible without using arms, and the ability to maintain standing balance for at least 10 s with progressively more challenging stances (side by side, semi-tandem, and full tandem). The faster of the two walks and times on the other tests are used to calculate a total score with participants earning up to 4 points for each task (range: 0–12). This analysis included baseline and 24 month follow-up data for the 400 m walk gait speed and total SPPB scores.

Statistical Analyses

Group differences were analyzed comparing those who developed MMD and those who did not develop MMD using chi-square test for categorical variables and two-sample t-tests for continuous variables. For ease of interpretation, we created four standardized composite cognitive function scores corresponding to four different cognitive domains; processing speed, verbal memory, executive function, and global cognition. Rationale for combining the cognitive measures was based on a previously published paper by Sink et al. (2015) which also examined cognitive function in LIFE (24). First, z-scores were formed for each cognitive test. Composite scores were formed by averaging the task components as follows: processing speed (Digit Symbol Coding), verbal memory (HVLT-R immediate and delayed recall), executive function (n-back [1- and 2-back scores], task switching (no switch and switch reaction times), and Flanker tasks [congruent and incongruent reaction times]). The global cognitive function score was the average of scores from these composites renormalized to have a mean of 0 and a *SD* of 1. In creating these composite scores, averages were taken of all available data (i.e., missing data if participants did not complete the full battery were ignored). Change scores were calculated by subtracting the baseline value from the follow-up value.

Next, multiple linear regression models were fit to examine the relationship between each cognitive function domain and physical function measure at baseline and changes over follow-up including adjustment for age, sex, site, education, BMI, intervention arm, hypertension, diabetes, CVD, stroke, and ApoE4. Lastly, separate Cox Proportional Hazard models were fit to assess (a) each baseline cognitive domain as a predictor of time to onset of MMD with and without adjustment for baseline physical function, and (b) changes in cognition and physical function as a predictor of MMD. For analysis of change in processing speed, HVLT, and physical function with MMD, participants who were censored or developed MMD prior to 24 month visit were excluded, leading to a sample size of 1,099. Similarly, for analysis of change in executive function and global function with MMD, participants who were censored or developed MMD prior to 18 month visit were excluded, leading to a sample size of 833. Models were adjusted for age, education, BMI, intervention arm, hypertension, diabetes, CVD, stroke, and ApoE4. Sex and site were used as stratification factors, per the parent study results (2). All analyses were conducted using SAS 9.4 (Cary, NC).

Results

Of the 1,635 participants free of MMD at baseline, 536 (32.8%) participants developed MMD during the study period, which averaged 2.6 years in duration. There were significant baseline differences in those who developed MMD compared with those who did not (Table 1). Those who developed MMD were older, had a higher BMI, more symptoms of depression, and were more likely to have hypertension, diabetes, and cardiovascular disease. Baseline cognitive function also differed between these two groups. Those who developed MMD had, at baseline, slower processing speed (lower score on digit symbol copy), lower

Table 1. Baseline Characteristics by Development of Major Mobility Disability During the LIFE Trial, Mean (*SD*) or *n* (%)

Participant Characteristics	Total (*n* = 1,635)	No MMD (*n* = 1,099)	MMD (*n* = 536)	*p* Value
Age	78.9 (5.3)	78.4 (5.1)	79.9 (5.4)	<.001
Female	1,098 (67.2)	723 (65.8)	375 (70.0)	.090
Ethnicity				
White	1,239 (76.0)	823 (75.2)	416 (77.6)	.290
Nonwhite	391 (24.0)	271 (24.8)	120 (22.4)	
Education				
High School or less	536 (32.9)	348 (31.7)	188 (35.3)	.150
College/Post Graduate	1,094 (67.1)	749 (68.3)	345 (64.7)	
Body mass index (kg/m^2)	30.2 (6.0)	29.7 (5.5)	31.2 (6.7)	<.001
Current smoker	50 (3.1)	32 (3.0)	18 (3.5)	.590
CES-D score (range:0–60)	8.6 (7.8)	8.0 (7.6)	9.9 (8.1)	<.001
History of hypertension	1,151 (71.0)	753 (69.2)	398 (74.8)	.018
History of diabetes	415 (25.5)	260 (23.7)	155 (29.1)	.020
History of cardiovascular disease	490 (30.0)	296 (26.9)	194 (36.2)	<.001
History of stroke	109 (6.7)	70 (6.4)	39 (7.3)	.490
Apolipoprotein E-4 allele				
0 alleles	1,054 (76.8)	739 (77.7)	315 (74.8)	.240
1–2 alleles	318 (23.2)	212 (22.3)	106 (25.2)	
Intervention adherence, %	68.0 (26.3)	70.2 (26.1)	63.5 (26.2)	<.001
Cognitive function				
Processing Speed				
Digit Symbol Copy Score	46.30 (12.72)	47.07 (12.53)	44.72 (12.97)	<.001
Verbal memory				
Hopkins Verbal Learning Test (HVLT)				
Immediate word recall	23.21 (5.27)	23.51 (5.21)	22.60 (5.36)	.001
Delayed word recall	7.70 (2.84)	7.78 (2.83)	7.52 (2.85)	.080
Executive function				
n-back test, % correct				
1-back	81.50 (17.6)	82.52 (16.8)	79.35 (19.0)	.001
2-back	50.68 (20.9)	50.57 (20.9)	50.9 (20.7)	.770
Flanker test				
Congruent, median rt	0.66 (0.21)	0.64 (0.20)	0.68 (0.25)	.003
Incongruent, median rt	0.73 (0.30)	0.72 (0.28)	0.76 (0.35)	.011
Task-switching test				
No switch, median rt	1.47 (0.93)	1.44 (0.85)	1.55 (1.09)	.040
Switch, median rt	2.43 (1.21)	2.38 (1.15)	2.55 (1.31)	.013
Physical function				
400 m gait speed (m/s)	0.82 (0.17)	0.87 (0.15)	0.73 (0.15)	<.001
SPPB (range: 0–12)	7.37 (1.61)	7.62 (1.50)	6.85 (1.70)	<.001

Note: CES-D = Center for Epidemiologic Studies – Depression scale; Rt = reaction time in seconds; SPPB = Short Physical Performance Battery.

verbal memory (lower score on HVLT immediate and delayed), and lower executive function (lower score on 1-back test, slower Flanker reaction time, and slower task switching time). The MMD group also had lower baseline SPPB and gait speed.

In multiple linear regression models (Table 2), all baseline cognitive function domains were significantly related to baseline SPPB (standardized [std] β = 0.15–0.08, *p*'s < 0.05) and 400m gait speed (std β= 0.16-0.09, *p's* < 0.05). Similar results were seen when examining changes in cognitive and physical function (Table 3) (SPPB: std β= 0.11-0.05, *p's* < 0.05, 400m gait speed: std β= 0.10-0.03, *p's* < 0 .05), except executive function was not statistically significant. In analyses with baseline cognitive function predicting time to first MMD (Table 4), all cognitive domains were statistically significant in unadjusted models (model 1), Hazard Ratios (HR's) = 0.82–0.87, *p's* <.05. Physical function was also a significant predictor of MMD (HR'*s* = 0.44–0.69, *p's* < 0.05). When adjustment was made for the intervention arm, demographics, and comorbidities (model 2), all cognitive and physical function domains remained significant, except verbal memory. Individual cognitive tasks are shown in Supplementary Material. Results were attenuated when accounting for baseline physical function measures (models

Table 2. Standardized Regression Coefficients Demonstrating a Positive Relationship Between Baseline Cognition and Baseline Physical Function in the LIFE Trial

	SPPB			400 m gait speed		
Cognitive function	Estimate	*SE*	*p* Value	Estimate	*SE*	*p* Value
Global cognition	0.15	0.05	.001	0.16	<0.01	<.001
Processing speed	0.13	0.04	<.001	0.16	<0.01	<.001
Verbal memory	0.08	0.05	.007	0.09	<0.01	<.001
Executive function	0.13	0.05	<.001	0.11	<0.01	<.001

Notes: Models adjusted for age, sex, site, intervention arm, education, BMI, hypertension, diabetes, CVD, stroke, and ApoE4.
Units = Standard Deviation; SPPB = Short Physical Performance Battery; 400 m gait speed = meters per second.

Table 3. Standardized Regression Coefficients Demonstrating a Positive Relationship Between Changes in Cognition and Changes in Physical Function From Baseline to 18–24 Month Follow-Up: The Life Trial

	Δ SPPB			Δ 400 m gait speed		
Cognitive function	Estimate	*SE*	*p* Value	Estimate	*SE*	*p* Value
Δ Global cognition	0.10	0.13	.004	0.08	0.01	.023
Δ Processing speed	0.09	0.10	.001	0.10	0.01	<.001
Δ Verbal memory	0.11	0.08	<.001	0.10	0.01	<.001
Δ Executive function	0.05	0.10	.113	0.03	0.01	.330

Notes: Models adjusted for age, sex, site, intervention arm, education, BMI, hypertension, diabetes, CVD, stroke, and ApoE4.
Units = Standard Deviation; SPPB = Short Physical Performance Battery; 400 m gait speed = meters per second.

Table 4. Cox Proportional Hazard Models (HR [95% CI]) for Baseline Cognitive and Physical Function Measures Until First MMD: The LIFE Trial

	Model 1: Unadjusted	Model 2: Adjusted for Demographics and Comorbidities	Model 3: Adjusted for Model 2 + SPPB	Model 4: Adjusted for Model 2 + 400 m gait speed
Global cognition	0.83 [0.76–0.90]	0.85 [0.77–0.94]	0.89 [0.81–0.99]	0.92 [0.83–1.03]
Processing speed	0.82 [0.75–0.89]	0.86 [0.77–0.96]	0.90 [0.81–1.01]	0.96 [0.86–1.07]
Verbal memory	0.87 [0.80–0.95]	0.91 [0.82–1.01]	0.95 [0.86–1.05]	0.96 [0.86–1.07]
Executive function	0.86 [0.79–0.93]	0.86 [0.78–0.95]	0.90 [0.82–0.99]	0.92 [0.83–1.02]
SPPB	0.69 [0.64–0.74]	0.67 [0.61–0.73]		
400 m gait speed	0.44 [0.40–0.48]	0.46 [0.41–0.52]		

Notes: Demographics and Comorbidity = age, education, BMI, intervention arm, hypertension, diabetes, CVD, stroke, and ApoE4. Sex and site were used as stratification factors.
Units = Standard Deviation; SPPB = Short Physical Performance Battery; 400 m gait speed = meters per second.

3–4). Only global cognition and executive function remained statistically significant after adjusting for SPPB (HR's = 0.89, $p = .03$ and .90, $p = .04$, respectively). Results were not statistically significant after adjusting for 400 m gait speed.

Figure 1 depicts adjusted HR values for baseline and change in cognitive function and physical function with time to onset of MMD. Higher baseline scores in global cognition, processing speed, executive function, SPPB, and 400 m gait speed indicated a lower risk of developing MMD. A positive change in processing speed was related to a reduced risk of MMD (HR per standard deviation = 0.52, $p < .001$). Positive changes in SPPB and 400 m gait speed were also related to lower risk (HR per standard deviation = 0.75, $p < .001$ and .58, $p = .001$). Other cognitive domains were not significantly related.

Discussion and Implications

Based on previous studies (3–6,9,25), we hypothesized that cognitive function would be related to physical functioning and MMD, and to the best of our knowledge, we are the first group to investigate cognitive function as a risk factor for MMD. We also examined the potential role of gait speed and SPPB as a mediator. Our results showed that in a sample of community-dwelling older adults with compromised physical function, baseline cognitive and

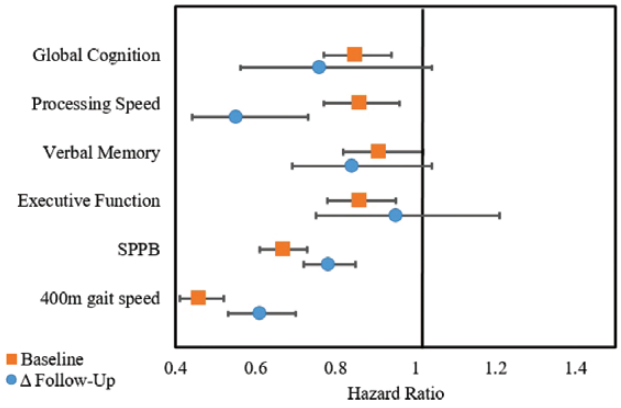

Figure 1. Baseline and 18–24 month follow-up measures of cognition and physical function with risk for MMD in the LIFE Trial, Hazard Ratios with 95% Confidence Intervals. Adjusted for age, education, BMI, intervention arm, hypertension, diabetes, CVD, stroke, and ApoE4. Sex and site were used as stratification factors. Units = Standard Deviation; SPPB = Short Physical Performance Battery; 400 m gait speed = meters per second.

physical function were significant predictors of MMD, although not independent of each other (Table 4).

In analyses examining changes in cognition and changes in physical function (Table 3), we found a significant relationship which may indicate that cognitive and physical functions are bi-directional. Evidence from other studies has shown that declines in gait speed often precede changes in cognitive function (26–28), whereas others have shown that cognition may predict changes in gait speed (29,30). Although our study cannot determine the temporal association, we are able to make inferences about specific cognitive domains and the relationship to physical function and MMD.

Our results are consistent with other studies that have found a significant relationship with gait speed and processing speed measured by the Digit Symbol Substitution Task (6,8,31,32). Interestingly, in our analyses, it was also a significant predictor of MMD. A one standard deviation increase in processing speed from baseline to 24 month follow-up was associated with a 48% lower risk of incidence of MMD (Figure 1). Similarly, a 1 standard deviation increase in 400 m gait speed... and a 1 standard deviation increase in SPPB from baseline to follow-up was related to 25% lower risk. Although we found evidence that better processing speed reduces risk for MMD, the contribution of physical function appears to be the driving force and one of the strongest risk factors for MMD independent of cognitive function. Identifying risk factors for MMD is clinically important because MMD is often related to loss of independence, increase in healthcare costs, hospitalizations, and mortality. Future strategies should target improving function of older adults in order to prevent MMD.

Mechanisms underlying the shared relationship between cognition and physical functions are not entirely understood and may represent a third process that is not captured in our study. For example, disruption in the central nervous system (CNS) involving white matter disease, cerebral small-vessel injury, and beta-amyloid has been postulated to influence cognition and physical performance in older adults (33–35). CNS abnormalities may adversely affect motor function, gait, and cognitive function; however, the current study did not collect neuroimaging data to investigate this mechanism. Overall, physical function and cognitive function may share a similar set of neural networks, but more research is needed to understand the complex interplay.

This study has many strengths. The LIFE study is the largest and longest physical activity intervention for older adults to date. LIFE was a multicenter, randomized intervention that included 1,635 older adults (70–89 years of age) targeting those with compromised mobility. A major strength of the LIFE study is the use of an objective test to assess MMD, which was ascertained every 6 months. The SPPB was used to measure objective functioning and screen individuals who had compromised mobility (SPPB ≤ 9). Additionally, other studies may use self-reported measures of mobility which may or may not be objectively accurate. The participants also received an intensive cognitive battery spanning multiple cognitive domains, which are lacking in many other large trials.

This study contributes to a gap in knowledge by showing a modest but significant connection between cognitive function, physical function, and the development of MMD. Additionally, no other studies, to the best of our knowledge, have examined cognitive function and MMD. We were able to examine the role of cognition and physical function in a novel way by including multiple domains of cognition and gait speed over a long distance. Furthermore, MMD is a construct that involves aspects of sensory input, motivation, perception, and pain not captured in a single measurement of gait speed (m/s) and may have underpinnings to cognitive performance.

Limitations should also be noted. First, the study population only included older adults with compromised mobility (required to have SPPB ≤9 at start of study), whereas cognitive function was screened to be normal at baseline. Thus, our results are applicable to older adults with initial difficulties in mobility performance. We hypothesize that older adults with normal functioning at baseline would show a weaker cognitive-mobility association. Future studies should examine individuals with normal physical function to confirm results. Similarly, our study did not include cognitively impaired older adults, and so our results do not apply to this population subset. Second, our outcome of interest was new onset of MMD, but does not speak to recovery from MMD. This could be examined in a follow-up study. Third, we acknowledge that all individuals in this study were participating in a clinical trial involving a physical activity intervention. The intervention arm included a moderate intensity physical activity program which may have an influence on brain chemistry and subsequent cognitive function. We adjusted for intervention arm in all of our longitudinal analyses; however, physiological changes due to the intervention cannot be ruled out. Additionally, Sink et al.

(2015) reported no significant relationship between the physical activity intervention and cognitive functioning in the LIFE study (24). Lastly, we are unable to describe physiological mechanisms (i.e., CNS, white matter integrity, and neuropathology) that may be contributing to the cognition-mobility connection.

Conclusion

In this study, we found that cognitive function, particularly processing speed, showed a significant albeit modest association with MMD. Baseline cognitive and physical function were both significant predictors of MMD, although the contribution of cognitive function was not independent of physical function. More research is needed to understand the complex interplay between cognitive and physical functions and its contribution to MMD.

Supplementary Material

Supplementary data are available at *Innovation in Aging* online.

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Conflicts of Interest

None declared.

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