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RESEARCH ARTICLE

Physical activity complexity, cognition, and risk of cognitive impairment and dementia in the Baltimore Longitudinal Study of Aging

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Abstract

INTRODUCTION: Studies on physical activity (PA) and dementia mainly focus on activity quantity or intensity. Yet PA requires neuro-coordination of movement, and it is unclear whether complexity of daily activity varies by cognitive status. Thus, we examined the association between PA complexity, using multiscale entropy, and cognitive function, mild cognitive impairment (MCI), and dementia in older adults in the Baltimore Longitudinal Study of Aging (BLSA).

METHODS: A total of 637 older adults (age 73.9 ± 11.3 years) in the BLSA completed a 7-day wrist-worn accelerometer assessment and neuropsychological tests from 2015 to 2020. Using logistic regression and structural equation modeling, we examined cross-sectional associations of PA complexity with MCI/dementia and cognition. Cross-lagged panel models (CLPMs) were used to assess bidirectional associations at baseline and 2-year follow-up. Multivariable models were adjusted for age, sex, race, education years, body mass index, and comorbidities.

RESULTS: Participants in the lowest tertile of PA complexity had over double the odds of MCI/dementia (odds ratio = 2.63, 95% confidence interval [CI]: 1.02 to 6.79, $p = 0.045$) compared to those in the highest tertile in the fully adjusted model. Structural equation modeling showed that PA complexity was associated with global cognitive function (standardized B [SB] = 0.102, 95% CI: 0.033 to 0.171, $p = 0.004$), executive function (SB = 0.119, 95% CI: 0.049 to 0.189, $p = 0.001$), and visuospatial ability (SB = 0.096, 95% CI: 0.026 to 0.167, $p = 0.008$). CLPMs showed bidirectional associations between lower PA complexity and poorer executive function.

DISCUSSION: Lower complexity of accelerometry-detected movement is associated with poorer cognition and higher risk of MCI/dementia. Future studies should explore whether low PA complexity is an early indicator of dementia.

KEYWORDS
cognitive function, cognitive impairment, dementia, physical activity, structural equation modeling

Highlights

- Prior studies mainly focused on quantity or intensity of physical activity.
- Poorer cognitive function was associated with lower complexity of daily activity.
- Lower complexity of physical activity may be an early indicator of dementia.

1 | BACKGROUND

Alzheimer's disease (AD) begins with a preclinical phase with normal cognitive ability up to 20 years prior to a dementia diagnosis.[1,2] Identifying subtle and early changes in daily life that occur prior to clinically recognizable symptoms of dementia is crucial for preventive interventions to slow pathological progression at early stages.

A growing body of evidence suggests that physical inactivity plays an important role in cognitive decline. Higher levels of daily physical activity (PA) have been associated with slower global cognitive (GC) decline and lower risk of incident AD and related dementias (ADRD) in several longitudinal studies.[3–5] Recent research highlights a bidirectional relationship between PA and cognition, as engagement in daily PA requires planning and neuro-coordination of movement, and low PA may occur early in the pathological pathway of dementia,[6] suggesting that detailed measures of changes in PA may act as an indicator of adverse cognitive change.

However, most research relied on self-reported PA, which is prone to recall bias and misclassification, especially in older adults with memory problems.[6–8] In addition, previous studies focused mainly on PA volume (e.g., steps per day) and/or intensity (e.g., moderate to vigorous PA [MVPA]),[5,6,8] which may underestimate the true association between PA and cognition in older adults with slower speeds of movement and lower aerobic capacity.[9] The use of continuous accelerometer signals to quantify PA patterns may provide more detailed information on physiological regulation and endurance, which may be more sensitive than the intensity/quantity of PA in identifying older adults in the early stages of the pathological progression to ADRD. It has been found that time-of-day activity and activity fragmentation, but not total daily activity, differ by mild cognitive impairment (MCI) and AD diagnosis,[10] which warrants further in-depth investigation into daily activity patterns in older adults with and without MCI and ADRD.

Multiscale entropy (MSE), a measure of physiological complexity, has been used to quantify the dynamics of multiple types of neurophysiological signals (e.g., postural sway,[11,12] continuous systolic blood pressure[13]). Lower complexity of these signals has been linked to aging and adverse health outcomes (e.g., falls, dementia).[11,13,14] This method has advantages of quantifying complexity of signals over multiple time scales, but to date it has not been used to quantify complexity of continuous accelerometer-measured activity/movement patterns. Unraveling the complexity of daily activity and its potential bidirectional association with cognition may help identify subtle alterations of physiological regulations preceding MCI or AD diagnosis and assist in earlier identification of those at risk. To this end, our study explored the association of accelerometer-derived activity complexity with MCI and dementia, as well as cognitive function in multiple domains. We hypothesized that a lower complexity of daily activity was associated with poorer cognitive function and higher risk of MCI/dementia.

2 | METHODS

2.1 | Study design and participants

The Baltimore Longitudinal Study of Aging (BLSA) is a longitudinal cohort study established in 1958 and conducted by the National Institute on Aging (NIA) Intramural Research Program. The study explores the interdependence of aging and disease processes and their mutual impact on physical and cognitive performance. Detailed descriptions of the study design are published elsewhere.[15] Once enrolled, participants are followed for health characteristics, cognitive assessments, and physical function tests every 4 years if aged <60 years, every 2 years if aged 60 to 79 years, and annually if aged ≥80 years. The study protocol was approved by the National Institutes of Health Intramural Research Program Institutional Review Board. Informed consent was obtained from all participants at each study visit. In the current study, participants aged ≥50 years with complete health interview, cognitive assessments, and ActiGraph accelerometer data collected between 2015 and 2020 were included.

2.2 | Accelerometer assessment

Objective PA was assessed using the triaxial wrist-worn Actigraph GT9X Link (Actigraph, Pensalcola, FL, USA) accelerometer on the non-dominant wrist with a sampling frequency of 80 Hz starting in 2015. On the last day of each clinic visit, participants were fitted with the accelerometer and instructed to wear it for the next 7 days, 24 h/day,

in the free-living environment. After completing the 7-day data collection, participants returned the accelerometer to the clinical research center by prepaid mailer. Data were downloaded and preprocessed using the ActiLife software (version 6.13.4) to derive 1-min epoch activity counts. Participants with ≥3 valid days of accelerometer data were included in the analysis. A valid day was defined as ≤10% missing data; non-valid days were excluded. For valid days, missing values were imputed as the average activity counts per minute during the same minute across all other valid days for each participant.[16] We removed typical sleep time from 11 p.m. to 5 a.m. to calculate PA complexity and other PA metrics, including total activity counts (TAC), activity fragmentation, and time spent in active states. TAC was derived from the sum of activity counts for each minute during a valid day. Each minute was labeled as active if the activity counts for that minute were ≥1853 or sedentary if they were <1853.[17] Active bouts were calculated as the sum of consecutive active minutes. The activity fragmentation index was calculated as the reciprocal of the average activity bout duration for each participant.[18] Active minutes were summed to obtain the total time spent in an active state.

2.3 | Multiscale entropy as a measure of complexity

MSE is a technique to quantify fluctuations of physiologic systems.[19] The rationale behind the use of entropy techniques, which effectively quantify the probability that neighboring points in a time series will be within a predetermined range, is that healthy systems display dynamics indicative of a highly adaptable network of neuromuscular connections.[12,19,20] To calculate MSE, we first constructed consecutive coarse-grained time series, determined by scale factor. The length of each coarse-grained time series is equal to the length of original time series divided by the scale factor. Then we calculated SampEn for each coarse-grained time series plotted as a function of the scale factor (MSE curve).[11,13,19] The complexity is identified as the area under the MSE curve, and lower complexity indicates poor regulation of physiologic systems.[11,13,14,21,22] We used accelerometer-derived 1-min epoch data to calculate PA complexity during waking hours.

2.4 | Cognitive assessment and clinical adjudication diagnoses

At each study visit, BLSA participants underwent a comprehensive neuropsychological examination assessing global and domain-specific function (i.e., verbal learning and memory, executive function, processing speed and attention, visuospatial ability, and language). The Mini-Mental State Examination (MMSE) and Blessed Information-Memory-Concentration (BIMC) tests were used to assess global mental status. Neuropsychological tests include the California Verbal Learning Test (CVLT) immediate and long-delayed free recall, Trail-Making Test Parts A (TMT-A) and B (TMT-B), Wechsler Adult Intelligence Scale (WAIS) Revised Digit Span and Digit Symbol Substitution Test (DSST), letter and category fluency, Boston Naming Test (BNT), a modified version of the Educational Testing Service Card Rotations test, and the Clock Drawing test.

The Clinical Dementia Rating (CDR) scale was completed at each visit for BLSA participants with a BIMC score ≥4 and for participants in the BLSA autopsy program and positron emission tomography (PET) substudy at every visit. Participants with BIMC ≥ 4 or CDR ≥ 0.5 were reviewed at consensus diagnostic conferences to adjudicate cognitive status and research diagnoses of MCI per Petersen criteria[23] and dementia per Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised criteria.[24]

2.5 | Covariates assessments

Data on sociodemographic (e.g., age, sex, race, and education years) and health characteristics were collected from a health interview. Height and weight were assessed using a stadiometer and a calibrated scale, respectively. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Chronic conditions, including cardiovascular disease, diabetes, stroke, lung disease, hypertension, kidney disease, osteoarthritis, and cancer, were self-reported by participants. Other covariates included apolipoprotein E (APOE) ε4 status, 6-m usual gait speed (m/s),[25] and physical functioning measured by the Short Physical Performance Battery (SPPB).[26]

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional sources (e.g., PubMed) and meeting abstracts and presentations. Previous studies suggest that older adults with cognitive impairment had lower PA levels. However, it is unclear whether the complexity of daily activity, derived from continuous accelerometer data, varies by cognitive status.
2. **Interpretation**: Our study found that lower complexity in accelerometer-measured PA during daytime was associated with poorer cognitive function and greater risk of MCI/dementia. Lower complexity of daily PA may predict a decline in cognitive function and may act as a sign of ADRD at early stages when interventions are more likely to be effective.
3. **Future directions**: Validation of this novel metric in other cohorts of older adults are needed. Future studies with longer follow-up periods and more dementia cases are warranted to examine whether altered PA complexity is a preclinical marker of ADRD.

2.6 | Statistical analysis

Data distributions were checked for normality. We selected the most recent visit (the last visit in the currently available dataset) for cross-sectional analyses. The earliest visit for accelerometer assessment was defined as the baseline visit. The differences in sociodemographic characteristics, health conditions, and PA complexity by MCI or dementia diagnosis were compared using independent *t*-tests for continuous variables or chi-squared tests for categorical variables. PA complexity was treated as both a continuous measure and tertiles in regression models. Logistic regression models were used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) of MCI and dementia diagnosis by PA complexity at the most recent visit.

To examine the association of PA complexity with GC function and different cognitive domains, we used structural equation modeling (SEM) with maximum likelihood estimation; participants who developed MCI or dementia were excluded from this analysis. Before estimating the full SEM, we tested a correlated-factors measurement model with four latent factors (memory, executive function/attention, language/fluency, and visuospatial ability) and a model with one latent factor – GC function using confirmatory factor analysis (CFA) to ensure proper fit. The composite factor scores for GC function and the specific cognitive domains were derived from CFA. After the estimation of measurement models, we ran two full structural equation models with PA complexity predicting cognitive outcomes as linear paths for GC function and specific cognitive domains separately. The goodness-of-fit statistics used to assess model fit included the chi-squared statistic, root mean square error of approximation (RMSEA), the standardized root mean square residual (SRMR), comparative fit index (CFI), and Tucker–Lewis index (TLI). A p value >. 05 for the chi-squared statistic, RMSEA, and SRMR $\leq$ 0.08, CFI, and TLI $\geq$ 0.95 signified good model fit.[27]

Finally, we ran longitudinal analyses to examine the bidirectional associations between PA complexity and cognitive function over time. Due to systematic age differences in follow-ups between baseline and 2 years, we restricted the sample to those with baseline and 2-year follow-up data. Participants who had MCI or dementia at baseline or at the 2-year follow-up were excluded from this analysis. Cross-lagged panel models (CLPM) were fit to examine the associations between PA complexity cognitive factors over the 2-year period using maximum likelihood estimation. To assess moderation by sex and APOE ε4 status, multigroup analysis of the CLPM was implemented with Wald's test for the equality of parameter estimates between groups signaling where autoregressive and cross-lag paths significantly differed between groups.

All models were further stratified by sex, TAC, age groups (50 to 64, 65 to 79, $\geq$80 years), and APOE ε4 status to examine the potential modifying effects on the association of PA complexity with MCI/dementia diagnosis and cognitive function.

The significance level α was set at 0.05. Descriptive statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA). The SEM analysis was performed using Mplus 8.4 (Muthén & Muthén, Los Angeles, CA, USA).

3 | RESULTS

3.1 | Cross-sectional association between PA complexity and MCI/dementia diagnosis

A total of 637 participants had valid accelerometer assessments and cognitive measures at their most recent visit. The number of valid days were 3 (n = 2, 0.3%), 4 (n = 16, 2.5%), 5 (n = 34, 5.3%), 6 (n = 543, 85.2%), and 7 (n = 42, 6.6%). Participants excluded due to insufficient accelerometer wear time (<3 valid days; n = 38) were older (79.2 years vs 73.9 years, p = 0.006) and had slower gait speed (1.0m/s vs 1.1m/s, p = 0.022) compared to those included in the analyses (Figure S1). There were no differences in education years, BMI, SPPB score, or distribution of sex, race, or comorbidities. The mean age of the analytic sample was 73.9 (SD = 11.3) years, and half (54.5%; n = 347) were females. Most participants were White and had an average educational attainment of 17.8 years. Participants with MCI/dementia (n = 44) had lower PA complexity (0.52 vs 0.67, p <.001; Figure 1), lower TAC/day, higher activity fragmentation, fewer active minutes/day, slower gait speed, and lower SPPB and MMSE scores than those without MCI/dementia (Table 1).

In unadjusted logistic regression models, every 0.1-unit lower in PA complexity was associated with 50% greater odds of MCI/dementia (OR = 1.50, 95% CI: 1.22 to 1.85, $p < 0.001$) (Table 2; Model 1). Participants in the lowest tertile of PA complexity had over four times the odds of having MCI/dementia (OR = 4.46, 95% CI: 1.90 to 10.45, $p < 0.001$) compared to the highest tertile. After adjusting for covariates, the association remained significant (Table 2; Models 2 and 3). Although we did not find a significant interaction between PA complexity and sex, after stratifying by sex, these associations were apparent in males but not females (Table 2). There was no significant interaction between PA complexity and TAC, and these associations were diminished after stratifying participants into low- and high-TAC groups (Table S1). Similarly, there was no significant interaction between PA complexity and age groups. However, in the analysis stratified by age group, we found the association between PA complexity and MCI/dementia diagnosis only remained significant among participants aged 80 and older (Table S2). These associations did not differ by APOE ε4 status (Table S3).

3.2 | Cross-sectional association between PA complexity and cognitive domains

The associations of PA complexity with GC function and each cognitive domain are presented in Figure 1. The unadjusted model showed that PA complexity was significantly associated with GC function (standardized B [SB] = 0.173, 95% CI: 0.094 to 0.253, $p < 0.001$), executive function (SB = 0.190, 95% CI: 0.111 to 0.269, $p < 0.001$), and visuospatial ability (SB = 0.175, 95% CI: 0.096 to 0.255, $p < 0.001$). These results remained significant after adjusting for covariates (Table 3; Models 2 and 3). Sex significantly modified the associations of PA complexity with GC function, executive function, and visuospatial ability (p values

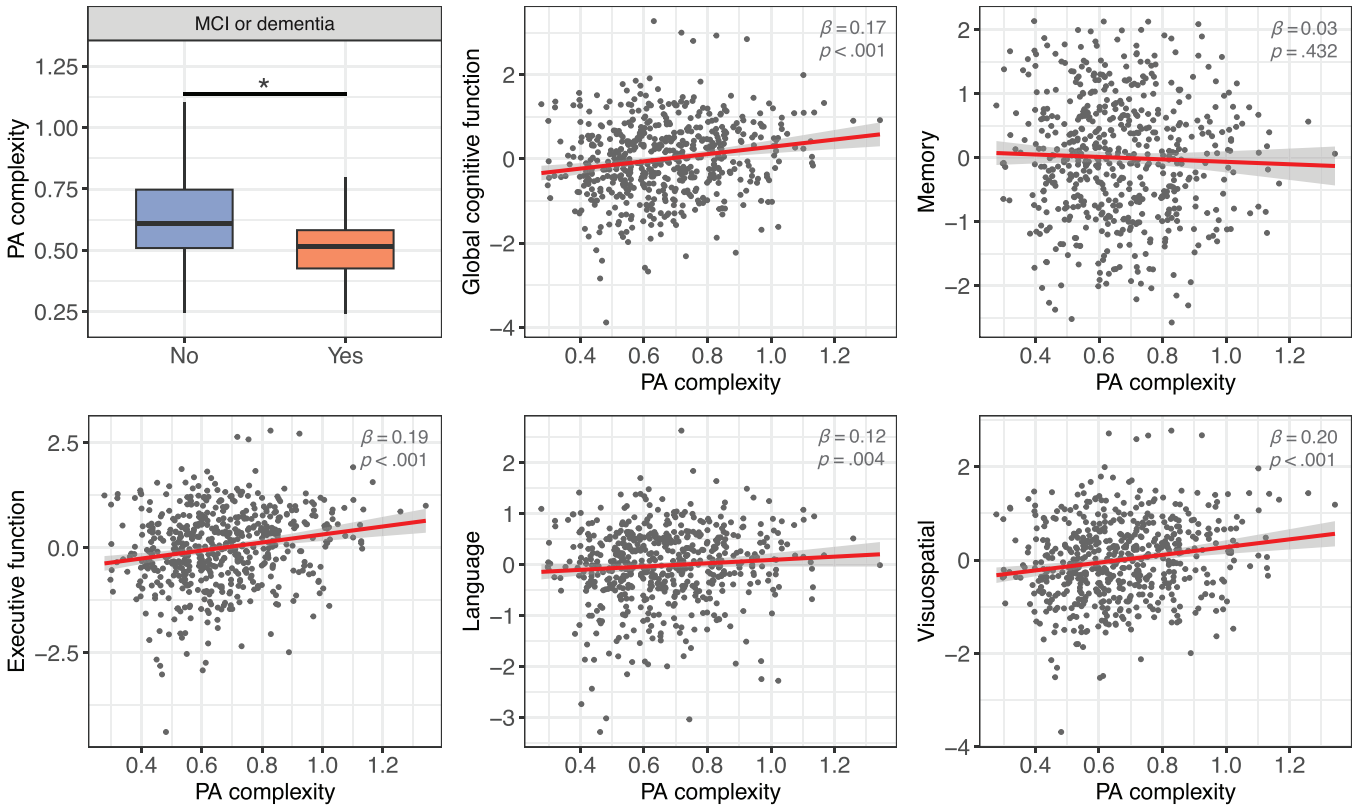

FIGURE 1 Linear regression lines and scatterplots of PA complexity with global cognitive function, memory, executive function, language, and visuospatial ability. Box plot for PA complexity by MCI or dementia diagnosis. The outcomes for linear regression plots were factor scores for global cognitive function, memory, executive function, language, and visuospatial ability, which were derived from CFA. *Independent *t*-test $p < 0.001$. CFA, confirmatory factor analysis; MCI, mild cognitive impairment; PA, physical activity.

for Wald chi-squared < 0.015). After stratifying by sex, these associations remained significant in males but not females (Table 3). There was no significant moderation by TAC, and the results were similar in the low- and high-TAC groups. Although there was no significant moderation by age group, we found these associations remained significant in older adults aged 65 to 79 years and ≥80 years but not in those aged 50 to 64 years in the stratified analyses (Table S4). APOE ε4 status significantly modified these associations (*p* values for Wald chi-squared < 0.014), with significant associations observed only in APOE ε4 carriers (Table S5).

3.3 | Longitudinal association between PA complexity and cognitive function

A total of 218 participants had non-missing cognitive data and valid accelerometer assessment at both baseline and the 2-year follow-up visit. Nine participants with MCI/dementia diagnosis were removed from the analysis. The unadjusted CLPM showed that over a 2-year period, each one-unit increase in PA complexity was associated with 0.13 SD higher in GC function (SB = 0.13, 95% CI: 0.05, 0.22, $p = 0.003$) at the 2-year visit. Executive function at baseline was associated with PA complexity (SB = 0.15, 95% CI: 0.06, 0.23, $p = 0.001$) at the 2-year visit (Figure S2). After adjusting for sociodemographics, BMI, and comorbidities, each one-unit increase in PA complexity at baseline was associated with a 0.16-SD increase in GC function (SB = 0.16, 95% CI: 0.07 to 0.25, $p = 0.001$) and 0.11-SD increase in executive function (SB = 0.11, 95% CI: 0.01 to 0.20, $p = 0.031$) at the 2-year visit (Figure 2). Additionally, each one-unit increase in executive function at baseline was significantly associated with a 0.16-SD increase in PA approximately 2 years later (SB = 0.16, 95% CI: 0.06 to 0.26, $p = 0.002$). We found that sex modified the model where the cross-lagged path from GC function at baseline to PA complexity at the 2-year visit differed between females and males (Wald chi-squared = 4.77, $p = 0.029$). Age groups significantly modified the model where the cross-lagged path from GC function at baseline to PA complexity at the 2-year visit were only significant in participants aged <65 years (Wald chi-squared = 7.50, $p = 0.024$). The cross-lagged path from language at baseline to PA complexity at the 2-year visit were only significant in participants aged <65 years (Wald chi-squared = 14.30, $p < 0.001$). APOE ε4 status significantly modified the model where the autoregressive paths for PA complexity, GC function, executive function, and language were stronger in APOE ε4 carriers compared to non-APOE ε4 carriers ($p < 0.05$ for all).

TABLE 1 Sample characteristics at most recent visit ($N = 637$).

Characteristics	All ($N = 637$)	MCI/dementia		p value[a]
		No ($n = 593$)	Yes ($n = 44$)	
Age (years)	73.9 ± 11.3	73.0 ± 11.1	86.4 ± 5.0	**<0.001**
Female	347 (54.5)	326 (55.0)	21 (47.7)	0.352
White ($n = 636$)	439 (69.0)	406 (68.6)	33 (75.0)	0.374
Education (years) ($n = 633$)	17.8 ± 2.6	17.8 ± 2.6	17.6 ± 3.6	0.748
BMI (kg/m^2) ($n = 632$)	27.4 ± 5.3	27.5 ± 5.3	26.7 ± 4.7	0.375
Comorbidity				0.873
0	80 (12.6)	73 (12.3)	7 (15.9)	
1	154 (24.2)	145 (24.5)	9 (20.5)	
2	170 (26.7)	158 (26.6)	12 (27.3)	
≥3	233 (36.6)	217 (36.6)	16 (36.4)	
APOE ε4 carrier ($n = 581$)	155 (26.7)	142 (26.4)	13 (30.2)	0.584
Valid ActiGraph wear days	6.0 ± 0.5	6.0 ± 0.5	5.9 ± 0.6	0.770
PA complexity	0.63 ± 0.18	0.67 ± 0.19	0.52 ± 0.16	**<0.001**
TAC/day (×1000)	1995.2 ± 588.1	2030.6 ± 578.1	1516.8 ± 512.4	**<0.001**
Activity fragmentation (%)	24.2 ± 6.0	23.8 ± 5.7	28.6 ± 7.8	**<0.001**
Active minutes/day	395.9 ± 105.0	400.8 ± 102.5	330.1 ± 116.7	**<0.001**
Gait speed (m/s) ($n = 635$)	1.12 ± 0.26	1.14 ± 0.24	0.84 ± 0.32	**<0.001**
SPPB total score ($n = 613$)	11.3 ± 1.8	11.4 ± 1.6	8.9 ± 3.3	**<0.001**
MMSE score ($n = 549$)	28.5 ± 1.5	28.6 ± 1.4	26.2 ± 2.3	**<0.001**

Abbreviations: APOE, apolipoprotein E; BMI, body mass index; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; PA, physical activity; SPPB, short physical performance battery; TAC, total activity counts.
The bold values indicate statistically significant results ($p < 0.05$).
[a]Independent t-tests were used for continuous variables and chi-squared tests for categorical variables.

4 | DISCUSSION

Older adults who exhibited lower complexity in objectively assessed daily activity were more likely to have concurrent MCI or dementia and demonstrated poorer performance in GC function, particularly executive function and visuospatial ability. Baseline activity complexity was associated with GC function and executive function at the 2-year visit. This relationship appeared to be bidirectional as baseline executive function was associated with PA complexity 2 years later. These findings indicate that low or diminished activity complexity may serve as an early marker of adverse cognitive change and therefore may facilitate more timely and effective intervention.

This study introduced a novel metric to analyze continuous data signals derived from accelerometers. According to the so-called complexity theory of aging, age-related alterations in the quantity and quality of inputs and regulatory elements in neurophysiological signals are associated with reduced system functionality and consequent reduced ability of the organism to adapt to stress.[22] Lower complexity of these signals analyzed using the MSE method are indicators of aging and age-related diseases.[13,22,28] For instance, lower complexity of standing postural sway is predictive of future falls.[11,13] Low complexity in accelerometer-derived movement likely reflects lower physical endurance and conservation of movement. Conversely, a higher complexity of signals may indicate a more stable physiological system with the ability to regulate daily activity to adapt to external stressors. Healthy older adults tend to perform multiple types of activities with variable intensities, whereas individuals with declining cognition or MCI may have a routine or single intensity of daily activity.

Lower PA complexity was linked to greater odds of MCI and dementia cross-sectionally and cognitive decline longitudinally. Similarly, previous studies demonstrated associations between higher levels of PA and lower risk of ADRD and lower rates of cognitive decline.[4,5,29] Yet most studies used limited PA variables, which only measure a single dimension of daily activity. For instance, MVPA has been associated with improved performance in processing speed, memory, and executive function.[30,31] With the advantages of more accurately capturing light-intensity activity and sedentary behavior patterns using accelerometers, an emerging body of evidence points to associations of more light-intensity PA with better cognitive function and higher brain volumes.[32,33] Studies examining patterns of daily activity found that higher activity fragmentation and lower PA complexity, defined as the standard deviation of all minute-to-minute PA intervals, were associated with lower white matter volumes and mild AD, respectively.[34,35] Further exploration of continuous accelerometer signals, using the MSE method to estimate signal complexity, may allow for the detection

TABLE 2 Cross-sectional association between physical activity complexity and MCI/dementia diagnosis at most recent visit ($N = 637$).

	Model 1			Model 2			Model 3		
Physical activity complexity	**OR**	**95% CI**	***p* value**	**OR**	**95% CI**	***p* value**	**OR**	**95% CI**	***p* value**
All participants	**Model 1 ($n = 637$)**			**Model 2 ($n = 633$)**			**Model 3 ($n = 629$)**		
Continuous (every 0.1 unit lower)	**1.50**	**1.22 to 1.85**	**<0.001**	**1.30**	**1.04 to 1.63**	**0.021**	**1.30**	**1.04 to 1.63**	**0.024**
Categorical									
1st tertile	**4.46**	**1.90 to 10.45**	**<0.001**	**2.68**	**1.05 to 6.81**	**0.039**	**2.63**	**1.02 to 6.79**	**0.045**
2nd tertile	1.29	0.47 to 3.53	0.618	1.07	0.37 to 3.14	0.898	1.09	0.37 to 3.25	0.876
3rd tertile	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Females	**Model 1 ($n = 347$)**			**Model 2 ($n = 345$)**			**Model 2 ($n = 344$)**		
Continuous (every 0.1 unit lower)	**1.35**	**1.02 to 1.80**	**0.038**	1.18	0.85 to 1.63	0.329	1.23	0.88 to 1.71	0.232
Categorical									
1st tertile	3.01	0.95 to 9.53	0.061	1.55	0.42 to 5.72	0.510	1.72	0.45 to 6.58	0.429
2nd tertile	0.85	0.21 to 3.48	0.818	0.64	0.14 to 2.97	0.573	0.65	0.13 to 3.17	0.589
3rd tertile	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Males	**Model 1 ($n = 290$)**			**Model 2 ($n = 288$)**			**Model 2 ($n = 285$)**		
Continuous (every 0.1 unit lower)	**1.69**	**1.25 to 2.29**	**<0.001**	**1.44**	**1.05 to 1.98**	**0.025**	**1.51**	**1.07 to 2.13**	**0.020**
Categorical									
1st tertile	**6.91**	**1.93 to 24.70**	**0.003**	**4.34**	**1.13 to 16.74**	**0.033**	**4.70**	**1.16 to 19.03**	**0.030**
2nd tertile	2.04	0.47 to 8.76	0.340	1.65	0.36 to 7.57	0.523	1.90	0.40 to 9.02	0.422
3rd tertile	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref

Note: Logistic regression Model 1 is the unadjusted model. Model 2 is adjusted for age, sex, race, and education years. Model 3 is additionally adjusted for body mass index and comorbidities.
Abbreviations: CI, confidence interval; MCI, mild cognitive impairment; OR, odds ratio.
The bold values indicate statistically significant results ($p < 0.05$).

of subtle changes in activity patterns, which may serve as a preclinical indicator of ADRD. Future studies are warranted to validate this novel metric and its potential to predict the onset of MCI and dementia in other cohorts of older populations.

Several mechanisms and pathophysiologic pathways could explain the association between PA and cognitive decline and dementia risk. Previous studies suggested that higher levels of PA could improve cardiorespiratory fitness, which in turn is associated with lower white matter lesion volume and larger brain volume.[36] Risk factors for cardiovascular disease also contribute to cognitive decline and increased dementia risk.[37] In addition, daily activity may directly contribute to neuroplasticity and neurogenesis by increasing the concentration of brain-derived neurotrophic factor.[38] However, de Bruijn and colleagues found that the beneficial association between PA and dementia was limited to 4 years.[39] The Whitehall II cohort study reported similar results – that leisure-time PA levels began to decline in adults with dementia, starting 9 years before diagnosis, which suggests the potential for reverse causality.[6] The reverse causation bias between MVPA and dementia was also found in a study by Ihira and colleagues,[31] where older adults in the early stage of AD showed different daily average and diurnal PA patterns compared to cognitively normal controls independent of mobility and physical function.[35] Collectively, this evidence suggests reduced PA levels and changes in PA patterns may be early indicators of cognitive change. It is also possible that higher levels of PA may delay clinical onset for older adults already on the verge of developing dementia. Future studies with longer follow-up periods are needed to better understand how AD neuropathology may lead to changes in daily activity amount and patterns.

The potential moderating effect of sex on the association between PA and dementia risk is not well understood. A systematic review of studies in older rodents reported that forced aerobic training enhanced hippocampus-dependent learning and memory more in females than males, while voluntary aerobic training enhanced non-spatial memory to a greater extent in males than females.[40] Other studies in humans found that daily walking activities and aerobic training tend to be more beneficial to older females relative to older males with regard to cognitive performance, brain-derived neurotrophic factor (BDNF) levels, and hippocampal volume.[41,42] Sex difference in dementia development related to hormone and APOE ε4 carrier status may also play a role.[43–45] In addition, how modification of the association between PA complexity and dementia by sex may be related to different types of activities in which females and males engage. A previous prospective cohort study found the association between a higher level of leisure-time MVPA and reduced risk of disabling dementia remained significant even after excluding participants diagnosed within the first 10 years in men but not in women.[31] In the current study, the types of daily activities, and whether they involved cognitive or social components, is unknown. Lower complexity of daily activities with aging may

TABLE 3 Cross-sectional structural equation modeling (SEM) of physical activity complexity and cognitive domains ($N = 568$).

	Model 1			Model 2			Model 3		
Paths	**Standardized B**	**95% CI**	***p* value**	**Standardized B**	**95% CI**	***p* value**	**Standardized B**	**95% CI**	***p* value**
All participants	**Model 1 ($n = 568$)**			**Model 2 ($n = 567$)**			**Model 3 ($n = 566$)**		
PA complexity → global cognitive function	**0.173**	**0.094, 0.253**	**<0.001**	**0.100**	**0.032, 0.169**	**0.004**	**0.102**	**0.033, 0.171**	**0.004**
PA complexity → memory	−0.036	−0.118, 0.046	0.389	−0.071	−0.149, 0.008	0.078	−0.067	−0.145, 0.012	0.096
PA complexity → executive function	**0.190**	**0.111, 0.269**	**<0.001**	**0.118**	**0.049, 0.188**	**0.001**	**0.119**	**0.049, 0.189**	**0.001**
PA complexity → language	0.066	−0.016, 0.148	0.115	0.020	−0.054, 0.094	0.593	0.024	−0.050, 0.098	0.529
PA complexity → visuospatial	**0.175**	**0.096, 0.255**	**<0.001**	**0.095**	**0.025, 0.166**	**0.008**	**0.096**	**0.026, 0.167**	**0.008**
Females	**Model 1 ($n = 311$)**			**Model 2 ($n = 311$)**			**Model 3 ($n = 311$)**		
PA complexity → global cognitive function	**0.111**	**0.001, 0.221**	**0.048**	0.016	−0.075, 0.108	0.726	0.017	−0.075, 0.108	0.722
PA complexity → memory	0.025	−0.086, 0.136	0.664	−0.056	−0.161, 0.048	0.289	−0.058	−0.162, 0.046	0.276
PA complexity → executive function	**0.109**	0.000, 0.219	**0.051**	0.019	−0.074, 0.111	0.696	0.019	−0.074, 0.112	0.691
PA complexity → language	0.074	−0.037, 0.184	0.191	0.017	−0.084, 0.117	0.744	0.018	−0.083, 0.118	0.727
PA complexity → visuospatial	0.087	−0.023, 0.198	0.121	−0.002	−0.096, 0.091	0.962	−0.003	−0.096, 0.091	0.955
Males	**Model 1 ($n = 257$)**			**Model 2 ($n = 256$)**			**Model 3 ($n = 255$)**		
PA complexity → global cognitive function	**0.275**	**0.162, 0.388**	**<0.001**	**0.178**	**0.077, 0.279**	**0.001**	**0.184**	**0.083, 0.286**	**<0.001**
PA complexity → memory	−0.044	−0.166, 0.078	0.480	−0.090	−0.211, 0.031	0.146	−0.071	−0.193, 0.052	0.257
PA complexity → executive function	**0.300**	**0.189, 0.411**	**<0.001**	**0.206**	**0.105, 0.307**	**<0.001**	**0.209**	**0.107, 0.310**	**<0.001**
PA complexity → language	0.093	−0.029, 0.214	0.134	0.024	−0.083, 0.132	0.656	0.043	−0.065, 0.152	0.432
PA complexity → visuospatial	**0.273**	**0.160, 0.386**	**<0.001**	**0.178**	**0.076, 0.279**	**0.001**	**0.188**	**0.086, 0.290**	**<0.001**

Note: Model 1 is the unadjusted model. Model 2 is adjusted for age, sex, race, and education years. Model 3 is additionally adjusted for body mass index and comorbidities.
Abbreviations: CI, confidence interval; PA, physical activity.
The bold values indicate statistically significant results ($p < 0.05$).

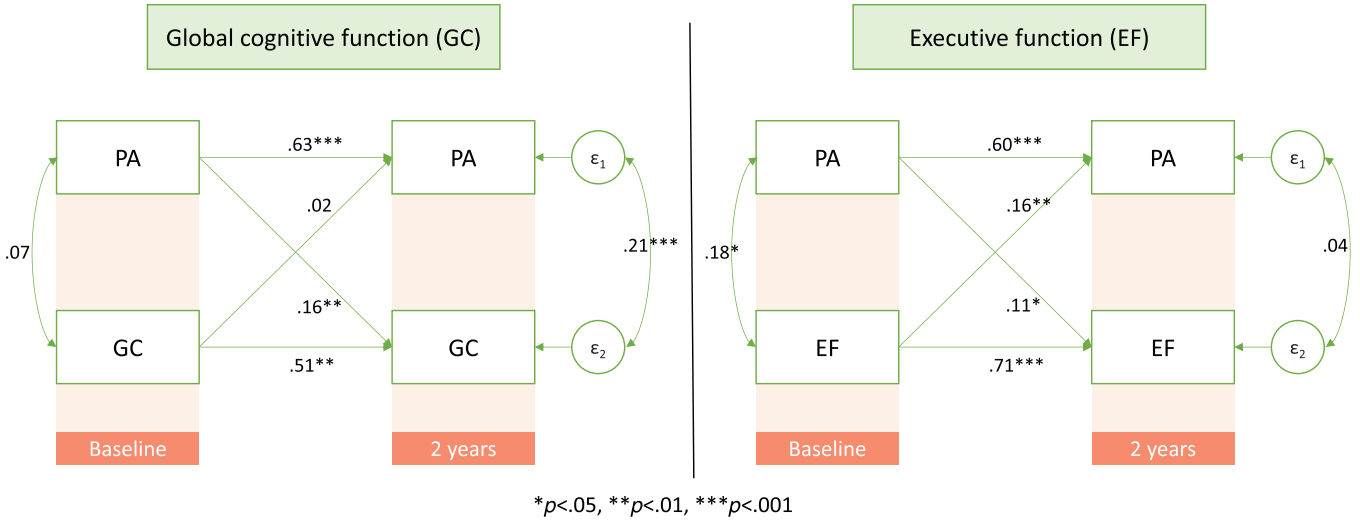

FIGURE 2 CLPM for bidirectional associations between PA complexity and cognitive domains at baseline and 2-year follow-up visit, adjusting for sociodemographics, body mass index, and comorbidities. The results for other cognitive domains including language, memory, and visuospatial ability are not statistically significant and so are not shown. CLPM, cross-lagged panel model; PA, physical activity.

differ between males and females, and type of activities compromised by aging and health conditions may also differ across individuals. It is possible that older men in the preclinical stage of dementia tend to disengage from daily activities involving cognitive and social components more than older women. Thus, multiple factors, including biological, behavioral, psychosocial, and environmental, can impact both daily physical activities and development of dementia, and whether sex modifies the impact of lower PA complexity on dementia risk warrants future research.

This study has several limitations. First, the BLSA is a relatively healthy cohort with only a few incident cases of MCI or dementia over the follow-up timeframe of the current study, which may understate the magnitude of the association. Future studies with larger numbers of dementia cases and participants in different stages of cognitive impairment would allow exploration of whether PA complexity may predict MCI and different types of dementia. Second, implementation of wrist-worn ActiGraph accelerometry began in 2015 with an annual accrual rate of less than 250 individuals. This relatively short follow-up period limited our ability to fully interrogate a potential causal relationship between PA complexity and cognitive function. Future studies with longer follow-up periods are needed to delineate the trajectory of change in PA complexity over time and to examine whether altered PA complexity could identify older adults in a preclinical stage of ADRD. Third, the PA complexity measure did not account for other factors such as sleep quality, sedentary behaviors, or seasonality. Further validation of the clinical significance of this novel measure is needed.

In conclusion, our study developed a novel metric – PA complexity – to analyze accelerometer-derived signals and found that lower PA complexity was associated with poorer cognitive performance and greater odds of MCI and dementia. Future studies with a longer follow-up period and more dementia cases are warranted to determine whether altered PA complexity is a preclinical marker of ADRD.

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CONFLICT OF INTEREST STATEMENT

J.A.S. is a consultant for Edwards Lifesciences and serves on the scientific advisory board of BellSant, Inc. E.M.S. serves on the scientific advisory board of BellSant, Inc. Other authors have no conflicts of interest to declare. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

Informed consent was obtained from all participants of the BLSA at each study visit.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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