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Physical Activity and Executive Function in Aging: The MOBILIZE Boston Study

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Abstract

OBJECTIVES—To determine the relationship between physical activity and cognition, specifically executive function, and the possible mediating role of factors such as cardiovascular disease (CVD) and CVD risk factors, chronic pain, and depressive symptoms.

DESIGN—Cross-sectional study.

SETTING—Population-based study of individuals aged 70 and older in the Boston area.

PARTICIPANTS—Older community-dwelling adults (n = 544; mean age 78, 62% female).

MEASUREMENTS—Presence of heart disease (self-reported physician diagnosed), pain, and depressive symptomatology were assessed using interviewer-administered questions. Blood pressure was measured. Engagement in physical activity was determined using the Physical Activity Scale for the Elderly (PASE). Cognitive function was measured using a battery of neuropsychological tests.

RESULTS—The older adults who engaged in more physical activity had significantly better performance on all cognitive tests, except for Letter Fluency and the memory test of delayed recall, after adjusting for age, sex, education, and total number of medications. With further adjustment for CVD and CVD risk factors (heart disease, diabetes mellitus, stroke, and hypertension), pain, and depressive symptoms, PASE score remained significantly associated with executive function tests.

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CONCLUSION—Even after multivariate adjustment, neuropsychological tests that were executive in nature were positively associated with physical activity participation in this cohort of older community-dwelling adults. In contrast, delayed recall of episodic memory was not associated with physical activity, supporting the idea that the relationship with executive function represents a specific biologically determined relationship.

Keywords

aging; physical activity; cognition; cardiovascular disease; pain

With aging, many changes occur in the brain that may lead to neurocognitive decline. More specifically, the prefrontal regions of the brain, which mediate executive control processes such as inhibition, planning, and taking initiative, are most prone to age-related degeneration.¹ These executive functions play a pivotal role in a person's ability to function independently.² Therefore, preservation of these frontal brain areas and executive functions is a major concern in aging. One mechanism that is associated with a reduction of age-related frontal atrophy is engagement in physical activity.¹ Older adults with greater aerobic fitness have a higher density of frontal gray and white matter areas than older less-fit individuals.³ Consistent with these findings, a positive relationship between physical activity and executive function in aging has been found.¹ More specifically, randomized controlled trials show that older sedentary adults who engage in exercise programs have better executive function.⁴

Many factors may mediate the relationship between physical activity and executive function in aging, for example, cardiovascular risk factors that are associated with low physical activity levels⁵ and worse executive function.⁶ Risk factors for cardiovascular and cerebrovascular disease may reduce blood flow to frontal, subcortical regions of the brain that mediate executive and motor function⁷ and thus may attenuate the relationship between physical activity and executive functions. Another factor that may influence the relationship between physical activity and executive function is the presence of pain. Chronic pain is associated with less physical activity participation in older adults.⁸ Additionally, research suggests that pain intensity is inversely related to executive function in older adults.⁹ Finally, depression is known to be associated with less physical activity¹⁰ and is associated with poorer executive function.¹¹

The present study investigated the relationship between physical activity and cognitive function in a population-based cohort of older adults living in the Boston area. Potential mediators of this relationship, including the presence of cardiovascular disease (CVD) and CVD risk factors, chronic pain, and depressive symptoms, were also investigated.

METHODS

The Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly (MOBILIZE) Boston Study is a longitudinal study of mobility and falls in older individuals living in the community in and around Boston. The present study included data from the first 600 persons enrolled in the cohort. Eligibility criteria for study participation were aged 70 and older, understanding and communicating in English, and independence in walking across a small room (use of a walker or cane allowed). For these analyses, 15 spouses or companions younger than 70 who joined the study, because they were living with a study participant were excluded. People were excluded for presence of a terminal condition (e.g., receiving hospice services, metastatic cancer) or moderate or severe cognitive impairment, as determined by a score less than 18 on the Mini-Mental State Examination (MMSE).¹² Before the baseline health interview that included the MMSE, participants provided written

informed consent for the study that entailed describing the study requirements in their own words and stating that they were voluntarily enrolling in a longitudinal research study. As a final indication of their cognitive abilities at baseline, participants had to demonstrate that they comprehended the instructions for completing and returning monthly fall calendar postcards. Even with the lower race-and education-adjusted cutpoint of the MMSE for eligibility, 87.7% of enrollees had MMSE scores above 23 and only 2.6% had MMSE scores of 18 to 20. The two-visit baseline assessment consisted of a home interview by a trained research assistant and a nurse examination in the study clinic at the Hebrew Rehabilitation Center. During the home interview, participants were given a questionnaire to be self-administered and returned at the time of the study clinic appointment, which usually took place within 2 to 4 weeks of the home interview. Forty-one people did not complete the physical activity questionnaire and thus were not included in the present analyses. Participants signed informed consent for participation. The institutional review board of the Hebrew Rehabilitation Center approved all study procedures. Details of the study methods and recruitment have been published elsewhere.^{13,14}

Demographic and Health Characteristics

Demographic characteristics included age, sex, race, and education (in years). Body mass index (BMI) was calculated as measured weight in kilograms divided by height in squared meters.

Comorbid Conditions and Medication Use

Major chronic diseases were assessed during the home interview, in which participants were asked whether a doctor had ever told them they had heart disease (myocardial infarction, atrial fibrillation, pacemaker, angina pectoris, or congestive heart failure), diabetes mellitus, spinal stenosis or disc disease, lung disease, or stroke. Use of prescription and over-the-counter medications in the previous 2 weeks was assessed during the home interview, with information recorded from the medication bottles. Hypertension was determined according to use of a disease algorithm that included information from the blood pressure measurement, from self-report, and from the medication list. In the home interview, participants were asked whether a physician had ever told them that they had high blood pressure or hypertension. The study nurse measured blood pressure (BP) during the clinic visit, and high BP was defined as systolic BP (SBP) of 140 mmHg or greater or diastolic BP (DBP) of 90 mmHg or greater, as determined by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.¹⁵ Presence of hypertension was coded as 0 (normotensive: no history of reported hypertension, not taking any antihypertensive medication, and no high blood pressure measured by the study nurse), 1 (controlled hypertension: history of reported hypertension or taking antihypertensive medication but no high blood pressure upon measurement), or 2 (uncontrolled hypertension: measured high blood pressure). Presence of depressive symptomatology was determined based on the Hopkins Revision of the Center for Epidemiologic Studies Depression Scale.¹⁶

Pain Measurement and Categorization

Musculoskeletal pain was assessed using interviewer-administered questions ascertaining pain in musculoskeletal sites (hand or wrist, shoulder, back, hip, knee, or foot) lasting 3 or more months in the previous year and present in the previous month.¹⁷ Responses were categorized into four groups: no pain, single site pain, more than one pain site (multisite pain) that did not meet criteria for widespread pain, and widespread pain (the greatest pain category). Classification of widespread pain was based on a modification of the American College of Rheumatology criteria: pain above and below the waist, pain on the right and left sides of the body, and axial pain (back or nonanginal chest pain).¹⁸ Information on laterality

was not included in the definition, which classified widespread pain based on the presence of upper and lower body pain and axial pain.¹⁷

Physical Activity Assessment

Summary performance of physical activities across the spectrum of exertion levels was determined using the Physical Activity Scale for the Elderly (PASE).¹⁹ This self-administered questionnaire included 10 items on the performance of activities commonly engaged in by older persons (walking, sports and recreational activities, exercises, housework, yard work). The reference period comprises the previous 7 days; performance of activities (assigned weights according to level of exertion: light, moderate, and strenuous) are recorded as never, seldom (1–2 d/wk), often (3–4 d/wk), and most of the time (5–7 d/wk). The amount of time spent in each activity (h/wk) is multiplied by the item weight for each activity, based on metabolic equivalents. The few missing responses in the PASE items were imputed using a single stochastic imputation procedure.²⁰ Total PASE score is the weighted sum of all reported activities.

Cognitive Function Measures

All cognitive measures were assessed during the home interview. The study neuropsychologist (WM) trained interviewers in performance of the tests, and strict protocols were followed for test administration to minimize distractions and provide a quiet comfortable atmosphere for testing. In the Letter Fluency²¹ test, the participant was asked to name as many words as possible beginning with a given letter (F, A, and S) for 60 seconds each. An additional 60-second trial was given to assess Category Fluency; the category was animals (Animal Naming). Performance was based on the number of items generated for each trial.

The Trailmaking Test (TMT) (parts A and B), required the individual to connect encircled items in sequential order.²¹ Part A comprised number targets to be connected in order (e.g., 1-2-3-4), and provided an estimate of attention and psychomotor speed. Part B included number and letter targets that were to be connected in alternating sequence (e.g., 1-A-2-B-3-C), providing an estimate of set-shifting. Performance was based on the length of time (in seconds) required to complete each task. To control for the effect of motor function and information processing speed, the TMT Delta was calculated by subtracting time to perform part A from time to perform part B, a variable that has been used in previous studies.^{22,23} The TMT is frequently applied in the clinical setting and is sensitive to the presence of frontal lobe pathology and cerebrovascular risk.⁶

The Clock-in-a-Box Test (CIB) was designed as a cognitive screening measure for use in the medical setting.²⁴ The CIB requires the participant to read and follow written directions by drawing a clock in a specific location on the response form and setting the clock to the correct time. Performance on the CIB was based on eight features: four associated with working memory for the written instructions and four associated with the organization and planning of the drawing. Performance on the CIB has been shown to be predictive of performance on standardized measures of memory and executive function.²⁴

The Hopkins Verbal Learning Test—Revised (HVLT-R) is a 12-item word list learning test that has been identified as a reliable verbal episodic memory measure for older patients and those suspected of having dementia.²⁵ The score is a sum of correct responses in each of three learning trials (encoding) and a delayed recall trial. In older adults, the encoding procedure requires executive and working memory processes.²⁶

Statistics

Physical activity, as measured according to PASE score (range 0–559), was categorized into quartiles; quartile cut-points were as follows: 52 or less (lowest quartile), 53 to 89 (second quartile), 90 to 136 (third quartile), 137 or higher (highest quartile). Participant characteristics and health indicators were examined according to physical activity levels in percentages and compared using chi-square tests. General linear models were constructed to estimate marginal means for the cognitive function measures according to the different levels of physical activity (PASE quartiles), adjusted for age, sex, and education. Linear trends were determined using chi-square tests (1 degree of freedom (*df*)). Multivariate linear regression models were performed to examine the relationship between PASE quartile and cognitive function measure: unadjusted (Model 1), adjusted for sociodemographics (age, sex, race, education) and total number of medications (Model 2), and further adjusted for CVD and CVD risk factors (heart disease, diabetes mellitus, stroke, and hypertension), pain categories, and depressive symptoms (Model 3). For all models, linear trends were determined using an additional set of models in which the PASE categorical term was entered as an ordinal variable (1 *df*). An additional set of models was performed using the PASE as a continuous measure. No major outliers were detected in any of the models. Data were analyzed using SPSS version 15 (SPSS, Inc., Chicago, IL).

RESULTS

The average age $\pm$ standard deviation of the 544 participants who completed the PASE questionnaire was 78.2 ± 5.3 , range 70–97). The 41 persons who did not complete the PASE questionnaire were less educated ($P < .01$) and were more likely to be female ($P < .05$) than the 544 persons without missing information. Characteristics associated with physical activity included age, education, CVD, stroke, diabetes mellitus, depressive symptoms, number of medications, and musculoskeletal pain (Table 1). For all cognitive tests, except for Letter Fluency and HVLT-R delayed recall, a dose-response relationship with physical activity was observed. Older adults who engaged in more physical activity had significantly better performance after adjusting for sociodemographics such as age, sex, and education (Table 2). Although the linear trend for Letter Fluency did not reach significance, the adjusted means were in the expected direction.

According to the unadjusted models, persons who reported higher levels of physical activity scored better on all cognitive tests than their less-active counterparts (trend, $P < .01$) (Table 3). After adjustment for sociodemographics (age, sex, race, education) and total number of medications, greater physical activity remained significantly associated with better performance on most tests of executive functioning (Clock Test, Animal Naming, TMT measures). In addition, an association was observed between physical activity and HVLT-R encoding, a test that requires memory and executive function, although the test of delayed recall was not associated with physical activity in the adjusted models. With further adjustment for CVD and CVD risk factors (heart disease, diabetes mellitus, stroke, and hypertension), pain, and depressive symptoms, physical activity remained associated with most measures of executive function, although the association with the TMT Delta was of borderline significance ($P = .06$). Using a similar modeling strategy, the continuous form of the PASE was examined in relation to cognitive measures, and the results were generally similar, although in the fully adjusted models, PASE scores were only statistically significantly associated with scores on the Animal Naming and TMT Part A tests.

DISCUSSION

The present study examined the relationship between physical activity participation and cognitive function in a large group of community-dwelling older men and women. As

expected from previous studies,^{4,22} the relationship between physical activity participation was strongest for tests that were executive in nature. For example, Clock Drawing, Category Fluency (Animal Naming), and TMT measures are all generally considered to be measures of executive functioning.²¹ No relationship was found between physical activity and the memory test of delayed recall.

The relationship between physical activity and executive function was maintained in the present study even after controlling for the presence of CVD and CVD risk factors such as heart disease and hypertension. This is particularly interesting from a clinical point of view. Although it is argued that CVD and CVD risk factors may attenuate the effect of physical activity on executive function, because persons with CVD disease show cerebral hypoperfusion during exercise,²⁷ persons with CVD and CVD risk factors in particular may be encouraged to engage in physical activity to benefit the cardiovascular condition²⁸ and thus to improve executive function.

Similar to CVD and CVD risk factors, the relationship between physical activity and executive function was still found after adjustment for chronic pain. This is interesting, because it suggests that persons with pain should not avoid participation in physical activity programs²⁹ in part because of the potential benefit for cognitive function. Exercise programs such as walking and resistance training have led to less pain and better function in persons with osteoarthritis.^{30,31} For some older persons, exercises such as swimming and water aerobics³² may be more tolerable depending on their pain symptoms. Finally, adjustment for depressive symptoms did not influence the positive relationship between physical activity and executive function. This cross-sectional finding does not support previous reports that an improvement in mood might mediate the positive effects of physical activity on cognition.³³

There are some limitations of this study that should be mentioned. First, the cross-sectional design of the present study precludes inferences about causality in the relationship between physical activity participation and executive function, although previous studies have shown that physical activity has a beneficial effect on executive functioning.⁴ Second, cognitive testing was performed at home; thus testing conditions may have differed from one individual to another. The investigators attempted to limit this variability through interviewer training and use of detailed testing protocols. Third, it has been suggested that the intensity of the physical activity that people engage in may play a role in its effects on cognitive function in older adults.³⁴ The present study did not use an objective measure of the level of physical activity such as accelerometry. Nonetheless, the PASE questionnaire assigned weights according to level of exertion of the activities. In other words, although energy expenditure was not objectively measured, the intensity of the physical activities based upon self-report was included in the estimate of total physical activity in the PASE score. Finally, it cannot be excluded that the association between physical activity and TMT scores were not related to psychomotor speed, although the consistency of the results across neuropsychological tests support the conclusions about the association between physical activity and executive function.

In conclusion, the present findings confirm former reports about a positive relationship between physical activity participation and executive function. In contrast to the relationship between physical activity and executive function tests, the measure of episodic memory used, the delayed recall test, was not associated with physical activity, which supports the notion that the relationship with executive function represents a specific biologically determined relationship. It was found that the observed relationships were independent of CVD and CVD risk factors, chronic pain, and depressive symptoms. In older community-

dwelling men and women, a physically active lifestyle may contribute to the maintenance of executive function and thus independent functioning.

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Table 1
Participant Characteristics and Health Indicators According to Physical Activity Levels: The MOBILIZE Boston Study

Characteristic	n (%)				p [‡]
	Physical Activity Scale for the Elderly Quartile [*]				
	1st (Least Active)	2nd	3rd	4th (Most Active)	
Age					
70–74	30 (22.6)	45 (32.1)	44 (32.6)	54 (49.7)	
75–84	75 (56.4)	75 (53.6)	71 (52.6)	75 (55.1)	
≥85	28 (21.1)	20 (14.3)	20 (14.8)	7 (5.1)	<.001
Sex					
Male	53 (49.8)	48 (34.3)	46 (34.1)	58 (42.6)	
Female	80 (60.2)	92 (65.7)	89 (65.9)	78 (57.4)	.65
Race					
White	100 (75.2)	111 (79.3)	107 (79.3)	108 (80.0)	
Black	26 (19.5)	18 (12.9)	24 (17.8)	21 (15.6)	
Other	7 (5.3)	11 (7.9)	4 (3.0)	6 (4.4)	.30
Body mass index					
<25.0	43 (33.9)	48 (35.0)	42 (31.1)	49 (37.1)	
25.0–29.9	48 (37.8)	54 (39.4)	54 (40.0)	60 (45.5)	
≥30.0	36 (28.3)	35 (25.5)	39 (28.9)	23 (17.4)	.24
Education, years					
<12	21 (15.8)	11 (7.9)	15 (11.1)	8 (5.9)	
12–15	54 (40.6)	65 (46.4)	61 (45.2)	57 (41.9)	
≥16	58 (43.6)	64 (45.7)	59 (43.7)	71 (52.2)	.048
Heart disease	72 (54.1)	54 (38.6)	54 (40.0)	46 (33.8)	.002
Diabetes mellitus	33 (24.8)	24 (17.1)	23 (17.0)	19 (14.0)	.03
Stroke	23 (17.3)	13 (9.3)	9 (6.7)	11 (8.1)	.01
Hypertension	35 (26.9)	47 (33.6)	27 (20.0)	29 (21.5)	.07
Spinal stenosis or disc disease	32 (24.1)	30 (21.4)	23 (17.0)	24 (17.6)	.13
Lung disease	26 (19.5)	16 (11.4)	21 (15.6)	24 (17.6)	.93
Depressive symptoms	15 (11.3)	11 (7.9)	8 (5.9)	4 (2.9)	.002

Characteristic	n (%)				<i>P</i> [†]
	Physical Activity Scale for the Elderly Quartile *				
	1st (Least Active)	2nd	3rd	4th (Most Active)	
Hand osteoarthritis	18 (13.5)	26 (18.6)	26 (19.3)	20 (14.7)	.78
Knee osteoarthritis	33 (24.8)	35 (25.0)	33 (24.4)	33 (24.3)	.89
Number of medications					
<7	36 (27.1)	50 (35.7)	45 (33.3)	71 (52)	
≥7	97 (72.9)	90 (64.3)	90 (66.7)	65 (47.8)	<.001
Pain categories					
No pain	37 (27.8)	59 (42.1)	49 (36.3)	60 (44.1)	
Single-site pain	32 (24.1)	31 (22.1)	33 (24.4)	28 (20.6)	
Multisite pain	38 (28.6)	27 (19.3)	38 (28.1)	30 (22.1)	
Widespread pain	26 (19.5)	23 (16.4)	15 (11.1)	18 (13.2)	.02

* Range 0 to 559; quartile cut points 52, 89, 136.

[†]Test for linear trend. MOBILIZE = Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly.

Table 2
Cognitive Functioning According to Physical Activity Categories: The MOBILIZE Boston Study

Cognitive Test	Mean ± Standard Error				Trend <i>P</i> -Value [‡]
	Physical Activity Scale for the Elderly Quartile [*]				
	1st	2nd	3rd	4th	
Clock-in-a-Box drawing test (range 0–8)	6.1 ± 0.1	6.1 ± 0.12	6.5 ± 0.1	6.5 ± 0.1	.004
Animal Naming	14.7 ± 0.4	15.0 ± 0.4	16.8 ± 0.4	17.2 ± 0.4	<.001
Letter Fluency [‡]	35.6 ± 1.2	36.7 ± 1.1	37.9 ± 1.2	38.2 ± 1.2	.09
Trailmaking Test, seconds					
Part A	62.9 ± 2.5	56.4 ± 2.4	53.9 ± 2.4	50.4 ± 2.5	<.001
Part B	152.0 ± 6.3	146.3 ± 5.8	126.8 ± 6.0	131.0 ± 6.0	.003
Delta	93.2 ± 5.4	92.6 ± 4.9	74.9 ± 5.1	82.0 ± 5.2	.03
Hopkins Verbal Learning Test					
Encoding	8.0 ± 0.2	7.7 ± 0.2	8.2 ± 0.2	8.3 ± 0.2	.03
Delayed recall	5.8 ± 0.3	5.4 ± 0.3	6.0 ± 0.3	6.3 ± 0.3	.08

MOBILIZE = Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly.

^{*} Range 0 to 559; quartile cut points 52, 89, 136.

[‡] Estimated marginal means adjusted for age, sex, education; test for linear trend (1 degree of freedom).

[‡] Composite score of three tests of verbal fluency for words beginning with F, A, and S.

Table 3

Unadjusted and Adjusted Association Between Physical Activity Scale for the Elderly (PASE)[†] and Cognitive Function: The MOBILIZE Boston Study

Test and PASE Quartile	Beta (Standard Error)			Trend Model 3 <i>P</i> -value [‡]
	Model 1	Model 2	Model 3	
Clock Test				
1 (least active)	(Reference)	(Reference)	(Reference)	
2	0.09 (0.17)	−0.11 (0.17)	−0.08 (0.18)	
3	0.51 (0.17) **	0.40 (0.17) *	0.40 (0.18) *	
4 (most active)	0.60 (0.17) **	0.31 (0.18)	0.29 (0.18)	.01
Animal Naming				
1 (least active)	(Reference)	(Reference)	(Reference)	
2	1.40 (0.57) *	0.39 (0.59)	0.51 (0.59)	
3	2.80 (0.58) ***	2.15 (0.59) ***	2.05 (0.59) **	
4 (most active)	3.82 (0.57) ***	2.54 (0.61) ***	2.48 (0.62) ***	<.001
Letter Fluency				
1 (least active)	(Reference)	(Reference)	(Reference)	
2	3.42 (1.66) *	0.32 (1.63)	0.27 (1.65)	
3	3.98 (1.69) *	2.14 (1.64)	1.71 (1.67)	
4 (most active)	5.53 (1.67) **	2.11 (1.69)	1.82 (1.73)	.17
Trailmaking Test				
Part A				
1 (least active)	(Reference)	(Reference)	(Reference)	
2	−10.97 (3.52) **	−5.71 (3.43)	−6.15 (3.50)	
3	−11.48 (3.56) **	−8.82 (3.44) *	−8.89 (3.52) *	
4 (most active)	−18.16 (3.54) ***	−11.62 (3.57) **	−11.78 (3.67) **	.001
Part B				
1 (least active)	(Reference)	(Reference)	(Reference)	
2	−13.68 (8.90)	−1.62 (8.29)	−0.60 (8.37)	
3	−30.72 (9.05) **	−24.25 (8.38) **	−21.54 (8.46) *	
4 (most active)	−34.95 (8.95) ***	−17.30 (8.68) [†]	−15.91 (8.82)	.009
Delta				
1 (least active)	(Reference)	(Reference)	(Reference)	
2	−3.82 (7.41)	3.34 (7.13)	4.70 (7.21)	
3	−20.10 (7.54) **	−17.04 (7.21) *	−14.36 (7.29) *	
4 (most active)	−19.19 (7.45) *	−8.41 (7.47)	−6.89 (7.60)	.06
Hopkins Verbal Learning Test				

Test and PASE Quartile	Beta (Standard Error)			Trend Model 3 <i>P</i> -value [‡]
	Model 1	Model 2	Model 3	
Encoding				
1 (least active)	(Reference)	(Reference)	(Reference)	
2	0.09 (0.25)	−0.25 (0.25)	−0.23 (0.25)	
3	0.41 (0.25)	0.20 (0.25)	0.16 (0.25)	
4 (most active)	0.80 (0.25) **	0.37 (0.26)	0.31 (0.26)	.07
Delayed recall				
1 (least active)	(Reference)	(Reference)	(Reference)	
2	0.17 (0.39)	−0.43 (0.39)	−0.42 (0.40)	
3	0.54 (0.40)	0.10 (0.39)	0.01 (0.40)	
4 (most active)	1.27 (0.40) **	0.52 (0.40)	0.44 (0.41)	.13

Model 1 presents the unadjusted regression coefficients for each PASE quartile from linear regression models.

Model 2 presents the mean effects for the PASE quartiles adjusted for age, sex, education, race, and total number of medications.

Model 3 presents mean effects for the PASE quartiles adjusted for the same variables as Model 2 plus cardiovascular disease (CVD) and CVD risk factors (heart disease, diabetes mellitus, stroke, and hypertension), pain categories, and depressive symptoms.

Pairwise comparisons with reference groups, *P*-value of regression coefficient <

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[†] PASE is scored 0 to 559; quartile cutpoints 52, 89, 136.

* .05

** .01

*** .001.

[‡] Test for linear trend (1 degree of freedom) for Model 3.