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The Relationship Between Cognitive Function and Physical Performance in Older Women: Results From the Women's Health Initiative Memory Study

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Background. Cognitive function and physical performance are associated, but the common sequence of cognitive and physical decline remains unclear.

Methods. In the Women's Health Initiative Memory Study (WHIMS) clinical trial, we examined associations at baseline and over a 6-year follow-up period between the Modified Mini-Mental State (3MS) Examination and three physical performance measures (PPMs): gait speed (meters/second), chair stands (number of stands in 15 seconds), and grip strength (kilograms). Using mixed models, we examined the baseline 3MS as predictor of change in PPM, change in the 3MS as predictor of change in PPM, and baseline PPM as predictors of 3MS change.

Results. Among 1,793 women (mean age = 70.3 years, 89% white, and mean 3MS score = 95.1), PPM were weakly correlated with 3MS—gait speed: $r = .06$, $p = .02$; chair stands: $r = .09$, $p < .001$; and grip strength: $r = .10$, $p < .001$. Baseline 3MS score was associated with subsequent PPM decline after adjustment for demographics, comorbid conditions, medications, and lifestyle factors. For every *SD* (4.2 points) higher 3MS score, 0.04 *SD* (0.04 m/s) less gait speed and 0.05 *SD* (0.29 kg) less grip strength decline is expected over 6 years ($p \leq .01$ both). Changes in 3MS and PPM were associated, particularly with chair stands and grip strength ($p < .003$ both). Baseline PPMs were not associated with subsequent 3MS change.

Conclusions. Baseline global cognitive function and change in global cognitive function were associated with physical performance change, but baseline physical performance was not associated with cognitive change in this cohort. These analyses support the hypothesis that cognitive decline on average precedes or co-occurs with physical performance decline.

Key Words: Cognitive function—Physical performance—Cognition—Physical function.

MULTIPLE studies have established relationships between cognitive function and muscle-based physical performance in older adults. Longitudinal relationships between cognitive function and physical performance in older adults have been demonstrated in three ways: (a) cognitive measures as predictors of physical performance decline (1–7), (b) physical measures as predictors of cognitive decline or persistent cognitive impairment (8–13), and (c) concurrent declines in cognitive and physical measures (6,7,10,14). An important unanswered question is whether one direction of longitudinal association is more consistent, and the prior studies are limited in addressing this question because they only focus on one or two of the above types of predictive models. Understanding the dominant direction of association would be helpful in understanding mechanisms and planning interventions to slow declines in both cognitive and physical domains.

We hypothesized that on average, cognitive function decrements would precede or co-occur with declines in physical performance more consistently than physical performance decrements would precede declines in cognitive function. Three main mechanisms make this hypothesis biologically plausible. First, cognitive function is likely to be equally or more sensitive to degenerative insults to the brain than to the motor function. This is supported by the observation that many individuals with dementia continue to ambulate even into more severe stages of cognitive impairment (15). Second, older adults may rely on cognitive processes

to perform simple physical performance tasks, as evidenced by a recent functional magnetic resonance imaging study (fMRI) (16). Therefore, declines in cognitive function over time might be expected to precede or co-occur with decreased physical performance because of greater reliance on cognition for physical performance. Third, because decreased motivation may accompany deficits in cognitive function, this may lead to further declines in physical performance due to decreased physical activity over time.

The purpose of the present study was to explore the longitudinal relationship between cognitive and physical performance by utilizing three approaches to the association in a cohort of older women participating in the Women's Health Initiative Memory Study (WHIMS). Utilizing 6 years of repeated measures of cognitive function and physical performance, we compare baseline cognitive function as a predictor of physical performance change, baseline physical performance as a predictor of cognitive change, and change in cognitive function as a predictor of change in physical performance.

Methods

The WHIMS Clinical Trials

WHIMS is a pair of randomized, placebo-controlled double-blind clinical trials designed to assess the effect of postmenopausal hormone therapy on the incidence of probable dementia and other cognitive outcomes. Participants between 65 and 80 years old were recruited from the Women's Health Initiative (WHI) and randomly assigned with equal probability to receive 0.625 mg/day conjugated equine estrogens (CEE) alone (if prior hysterectomy) or CEE in combination with 2.5 mg/day of medroxyprogesterone acetate (MPA; if no prior hysterectomy) versus matching placebo. The WHIMS study design, eligibility criteria, and recruitment procedures have been reported previously (17). Briefly, exclusion criteria were based on competing risks (medical conditions with a predicted survival of less than 3 years), safety (e.g., prior breast or other invasive cancer within the past 10 years), adherence and retention factors (e.g., unwillingness or inability to complete study requirements, alcoholism, performance during a pill run-in), probable dementia, history of mental illness (including severe depression), or evidence of drug dependence. The National Institutes of Health and Institutional Review Boards for all participating institutions approved the study, and all participants provided written informed consent.

Study Population

A total of 7,479 women aged 65–80 years old were enrolled in the WHIMS clinical trials in 39 WHI clinical centers throughout the United States. These women were assessed annually for global cognitive function using the Modified Mini-Mental State Examination (3MS) (18). Of the 7,479 WHIMS participants, 25% had also been randomly selected within WHI to have physical performance repeatedly measured using a timed walk, chair stands, and grip strength (19). This limited our potential study population to 1,873 participants with data on physical performance. Additionally, 80 participants were excluded due to a lack of any follow-up cognitive or physical measures over the 6-year follow-up; these 80 individuals had lower cognitive function and physical performance at baseline than participants included in this analysis. Thus, the final sample comprised the 1,793 participants with baseline and at least one follow-up cognitive and physical performance measure (PPM).

Follow-up and Retention

Following discovery of an unfavorable risk-to-benefit ratio of its noncognitive end points for CEE + MPA therapy, the WHI trial of this regimen was discontinued in July 2002 (20). The WHI trial of CEE therapy was discontinued in February 2004 due to an increased risk of stroke and embolic events and the lack of any favorable effect on cardiovascular disease for CEE therapy (21). Mean WHIMS follow-up was 4.4 (range: 0–8) years.

Global Cognitive Function Measure

The 3MS consists of 15 items that when summed range from 0 to 100 with higher scores reflecting better cognitive functioning (18). Test items measure temporal and spatial orientation, immediate and delayed recall, executive function, naming, verbal fluency, abstract reasoning, praxis, writing, and visuoconstructional abilities. The proportions of women who provided 3MS data at annual examinations were 97% (Year 1), 94% (Year 2), 90% (Year 3), 86% (Year 4), 81% (Year 5), and 81% (Year 6).

Physical Performance Measures

Physical performance (gait speed, chair stands, and grip strength) was assessed at baseline and at Years 1, 3, and 6. *Gait speed* (meters/second) was assessed using a timed walk over a marked 6-m course at usual pace. Timing began at the initiation of walking and ended when one of the participant's feet was completely across the finish line. The *chair stand test* (number of stands in 15 seconds) was conducted using a standard, straight-backed, flat-seated (nonpadded), and armless chair. Participants were instructed to stand up and sit down with arms folded across the chest as many times as possible in a 15-second period. *Grip strength* (kilograms) was tested in the dominant hand using a standard hydraulic handgrip dynamometer. The participant was instructed to squeeze the handle of the dynamometer as hard as she could for two trials. For all PPMs, we utilized the better of two trials for these analyses. The PPM data was slightly less complete than the 3MS data, declining to

76% (gait speed), 69% (chair stands), and 76% (grip strength) at Year 6.

Covariates

We considered as covariates any measures or characteristics present at baseline that may potentially confound the relationship between cognitive and physical function. Data collection methods and reporting for these variables for the WHI are described more fully elsewhere (17,22). Briefly, data on baseline demographic and health habits were collected via standard self-report assessments (age, ethnicity, educational level, family income, smoking status, and alcohol consumption). Total exercise in the previous week was also assessed by questionnaire, and metabolic equivalents of each type of physical activity were assigned to calculate the total kilocalories per kilogram of body weight expended (23). Other covariates included trial treatment assignment (CEE alone, CEE + MPA, or placebo), body mass index (calculated as measured weight in kilograms divided by measured height in meters squared), depressive symptoms (measured by Centers for Epidemiological Studies-Depression 10-item scale score) (24), hemoglobin level, systolic and diastolic blood pressure (average of two measurements), self-report history of physician diagnosis of specific diseases (hypertension, diabetes mellitus, coronary artery disease, cerebrovascular disease, peripheral arterial disease, and nondermatological cancer), and self-reported medications that might affect the central nervous system (sedatives [benzodiazepines and barbiturates], narcotics, anticholinergics, serotonin selective reuptake inhibitors, and tricyclic antidepressants).

Statistical Analysis

Baseline characteristics were reported as mean ± *SD* unless otherwise stated. Correlation coefficients were used to summarize baseline relationships between the 3MS and each PPM. To analyze the cross-sectional and longitudinal relationships between cognition and physical performance, a series of linear regression and mixed effects models were used. First, linear regression models were used to assess the baseline cross-sectional relationships that 3MS, as the independent variable, had with each of the physical measures (gait speed, chair stands, and grip strength), as dependent variables. Second, mixed effects models (SAS Proc Mixed) were used to assess whether baseline 3MS score predicted declines in each of the physical measures over the 6-year follow-up and whether baseline physical measures predicted changes in 3MS scores. Finally, the associations that changes in cognitive function (independent variable) had with changes in each PPM over time (dependent variables) were assessed with three additional mixed effects models. Two levels of covariate adjustment were used in each case: (a) a *limited adjustment model* including clinic site, age, ethnicity, education, income, and trial treatment assignment (and baseline outcome variable for longitudinal models) as covariates and (b) a *full adjustment model* that added smoking status; alcohol consumption; exercise in the previous week; body mass index; depressive symptoms; hemoglobin level; history of hypertension, diabetes mellitus, coronary artery disease, cerebrovascular disease, peripheral arterial disease, and nondermatological cancer; and medications to the covariates in the limited adjustment model.

Table 1. Baseline Characteristics of Study Participants (n = 1,793)

Characteristic	$M \pm SD$ or %
Age (y)	70.3 ± 3.7
% White	89%
Less than high school education	7.0%
Family income	
Do not know	2.3%
$19,999 or less	24.5%
$20,000–49,999	51.8%
$50,000 or greater	21.4%
% Assigned to active treatment (CEE alone or CEE + MPA)	49.6%
Smoking status	
Current	6.7%
Past	37.5%
Self-reported alcohol intake	
None or past drinker	34.1%
Less than 1 per wk	33.2%
1–6 drinks per wk	21.9%
7 drinks or more per wk	10.8%
Total weekly exercise (kcal/kg/wk)	11.4 ± 13.6
Body mass index (kg/m^2)	28.5 ± 5.7
Hypertension	38.0%
Diabetes mellitus	8.4%
Cardiovascular disease	16.7%
Cerebrovascular disease	4.0%
Peripheral arterial disease	2.1%
History of nondermatologic cancer	3.6%
Hemoglobin (gm/dL)	13.6 ± 1.0
Medications	
Sedatives	4.6%
Narcotics	1.7%
Anticholinergics	12.4%
Serotonin selective reuptake inhibitors	3.1%
Tricyclic antidepressants	2.3%
Baseline shortened CESD score	0.025 ± 0.09
Baseline 3MS score	95.1 ± 4.4
Gait speed (m/s)	1.22 ± 0.97
Chair stands (number of stands in 15 s)	6.8 ± 1.8
Grip strength (kg)	24.2 ± 5.9

Notes: 3MS = Modified Mini-Mental State Examination; CEE = conjugated equine estrogens; CESD = Centers for Epidemiological Studies-Depression; MPA = medroxyprogesterone acetate.

Results

The characteristics of the 1,793 women included in the analysis are presented in Table 1. The mean age of the study group was 70.3 years, 89% were white, and 7% had less than a high school education. The average 3MS score of 95.1 and average gait speed of 1.22 m/s indicates high functioning in this cohort. Overall, the mean scores for each

Table 2. Baseline Cross-Sectional Associations Between the 3MS score and PPMs

	Regression Coefficient for Baseline PPMs per *SD* Increment* of 3MS					
	Gait Speed		Chair Stands		Grip Strength	
Model	Coefficient (*SE*)	*p* Value	Coefficient (*SE*)	*p* Value	Coefficient (*SE*)	*p* Value
Limited adjustment	.012 (0.029)	.67	.030 (0.048)	.55	.330 (0.158)	.04
Full adjustment	−.013 (0.031)	.69	.041 (0.050)	.41	.420 (.165)	.02

Notes: 3MS = Modified Mini-Mental State Examination; PPMs = physical performance measures.

Limited adjustment: clinic site, age, ethnicity, education, income, and trial treatment assignment. *Full adjustment*: *Adds* smoking status, alcohol consumption, exercise in the previous week, body mass index, depressive symptoms (Centers for Epidemiological Studies-Depression 10-item scale score), hemoglobin level, hypertension, diabetes mellitus, coronary artery disease, cerebrovascular disease, peripheral arterial disease, cancer, and medications.

* *SD* = 4.4 points.

physical measure declined over the 6 years, however, mean 3MS scores did not.

At baseline, each PPM was modestly but significantly correlated with 3MS scores: gait speed: $r = .06$, $p = .02$; chair stands: $r = .09$; $p < .001$; and grip strength: $r = .10$, $p < .001$. In both limited and full covariate adjusted regression models with baseline 3MS as the independent variable and each PPM as the dependent variable, significant relationships were found only for grip strength (Table 2). In the fully adjusted model, a 1 *SD* higher 3MS score (4.4 points) was associated with a 0.420 kg higher mean grip strength (corresponding to 0.07 *SD* of grip strength).

Table 3 shows the results of mixed effects models relating baseline 3MS and change in 3MS over the 6-year follow-up to change in each PPM. Baseline 3MS significantly predicted subsequent change in grip strength; in the fully adjusted model, 1 *SD* higher score on the baseline 3MS was associated with 0.05 *SD* (0.289 kg) less average decline in grip strength over the follow-up. After full adjustment, a similar relationship was found for gait speed. The relationship for chair stands was in the same direction but not statistically significant in either the limited or full adjustment models ($p = .08$ after full adjustment).

Also in Table 3, the relationship between change in 3MS and change in PPMs is shown. In the limited adjustment models, less decline in 3MS was significantly associated with less decline in each of gait speed, chair stands, and grip strength. These associations remained significant for chair stands and grip strength with full adjustment: 1 *SD* less decline in 3MS was associated with 0.06 *SD* (0.101) less decline in the number of chair stands in 15 seconds and 0.04 *SD* (0.258 kg) less decline in grip strength. For gait speed, the magnitude of the association with change in 3MS was decreased slightly and the relationship was no longer significant after full adjustment ($p = .08$).

Table 4 presents the results of the separate mixed effects models with baseline gait speed, chair stands, and grip strength as independent variables and subsequent declines in the 3MS as the dependent variable. No significant relationships were found.

Discussion

In this high-functioning cohort of 65- to 80-year-old women, we found that baseline global cognitive function and global cognitive decline independently predicted declines in specific physical measures but that none of our

Table 3. Relationship Between Baseline 3MS Score and Change in 3MS to Average Change in Physical Performance Over 6-Year Follow-up

		Regression coefficient for change in PPMs per *SD* increment* of *baseline* 3MS					
		Δ Gait speed		Δ Chair stands		Δ Grip strength	
Predictor variable	Model	Coefficient (*SE*)	*p* Value	Coefficient (*SE*)	*p* Value	Coefficient (*SE*)	*p* Value
Baseline 3MS	Limited adjustment	.029 (0.017)	.09	.053 (0.038)	.16	.309 (0.110)	.005
	Full adjustment	.037 (0.019)	.05	.069 (0.040)	.08	.289 (0.118)	.02
		Regression coefficient for change in PPMs per *SD* increment* of 3MS *change over 6 y*					
		Δ Gait speed		Δ Chair stands		Δ Grip strength	
Predictor variable	Model	Coefficient (*SE*)	*p* Value	Coefficient (*SE*)	*p* Value	Coefficient (*SE*)	*p* Value
Change in 3MS	Limited adjustment	.039 (0.018)	.03	.118 (0.032)	<.001	.271 (0.092)	.003
	Full adjustment	.034 (0.019)	.08	.101 (0.033)	.002	.258 (0.098)	.003

Notes: 3MS = Modified Mini-Mental State Examination; PPMs = physical performance measures.

Limited adjustment: clinic site, age, ethnicity, education, income, trial treatment assignment, and baseline PPM. The model with change in 3MS as the independent variable is also includes baseline 3MS. *Full adjustment*: *Adds* smoking status, alcohol consumption, exercise in the previous week, body mass index, depressive symptoms (Centers for Epidemiological Studies-Depression 10-item scale score), hemoglobin level, hypertension, diabetes mellitus, coronary artery disease, cerebrovascular disease, peripheral arterial disease, cancer, and medications.

* *SD* = 4.4 points.

Table 4. Relationship Between Baseline PPMs and Change in 3MS Score over the 6-Year Follow-up

	Regression Coefficient for Change in 3MS per *SD* Increment of Baseline PPM			
	Limited Adjustment		Full Adjustment	
Baseline Physical Function Measure (*SD*)	Coefficient (*SE*)	*p* Value	Coefficient (*SE*)	*p* Value
Gait speed (.97 m/s)	−.088(0.074)	.23	−.081 (0.074)	.27
Chair stands (1.8/15 s)	−.100 (0.081)	.22	−.077 (0.086)	.37
Grip strength (5.9 kg)	.144 (0.081)	.08	.064 (0.085)	.45

Notes: 3MS = Modified Mini-Mental State Examination; PPMs = physical performance measures.

Limited adjustment: clinic site, age, ethnicity, education, income, trial treatment assignment, and baseline 3MS score. *Full adjustment*: *Adds* smoking status, alcohol consumption, exercise in the previous week, body mass index, depressive symptoms (Centers for Epidemiological Studies-Depression 10-item scale score), hemoglobin level, hypertension, diabetes mellitus, coronary artery disease, cerebrovascular disease, peripheral arterial disease, cancer, and medications.

physical measures predicted cognitive change. These findings support our hypothesis that cognitive function decrements in older adults on average precede or co-occur with physical performance declines. Although these findings need to be confirmed in broader populations of older adults, the main implication of these analyses is that older adults with declining global cognitive function are at risk for muscle-based physical declines over time and interventions in those with decreased cognitive function such as physical activity might be considered to preserve muscular and cognitive function. Our finding of a more consistent association of cognitive function with grip strength suggests that this simple measure may be useful to include in future studies of the relationship between cognitive function and physical performance.

The result that baseline global cognitive function and change in global cognitive function were associated with declines in physical performance is consistent with prior studies (1–7,14). Several studies have previously demonstrated that baseline physical performance predicts declines in cognitive function (10–13,25) and/or incident cognitive impairment or dementia (7–9,26,27), but we could not confirm these findings, possibly due to a lower relative strength of the predictive association of baseline PPMs with subsequent global cognitive function change or possibly due to measurement limitations with our cognitive function measure. It is also possible that the lack of overall cognitive decline in our sample may have limited our ability to detect a relationship.

There are several mechanisms to explain the longitudinal relationships that we observed between global cognitive function and physical performance. It is possible that increased cognitive monitoring is required for physical performance as individuals age, and when cognitive function declines, the ability to monitor physical performance may therefore decline. Supporting this concept, a recent fMRI study demonstrated greater activation in areas of the brain reflecting increased cognitive monitoring of even simple hand and foot movements in older adults versus younger adults (e.g., the presupplementary motor area, predorsal motor area, rostral cingulate, and prefrontal cortex) (16). Another potential mechanism is that vascular or degenerative insults to the brain may affect both cognitive and motor areas, which would then explain a link between cognitive function and physical performance over time. Additionally, comorbid factors and health behaviors could affect the brain, peripheral nerves, skeletal muscle, and their connections individually. For example, we have previously observed that combined declines in cognitive and physical performance are associated with lower hemoglobin levels and current smoking (14). It is therefore possible that such systemic factors as smoking and low hemoglobin could contribute to lower cognitive function and physical performance through directly impacting the oxygen supply to the brain, peripheral nerves, and skeletal muscle. Physical activity could also affect both cognition and muscular function individually (28,29). However, we found significant longitudinal relationships between cognitive function and physical performance even after adjustment for smoking status, hemoglobin level, and many other potential confounders.

The stronger relationship of global cognitive function with the grip strength measurement is a notable finding of this study, and we offer a few potential reasons for this possible selective association. First, the strongest relationship between cognition and physical performance could truly be with strength, and this could possibly be related to denervation of skeletal muscle that could accompany neural aging (30). Second, grip strength could be considered a more novel cognitively demanding task than the other measures as it involves the use of an instrument and is a test of maximal performance. Lastly, there was a greater variance in the sample for performance on the grip strength measure, which could have accounted for greater sensitivity to detect a relationship.

This study has several strengths, including the large sample size, concurrent cognitive and physical assessments using validated measures, and a number of lifestyle and health variables available. Some strengths of this study can also be considered limitations. Women participating in a clinical trial are likely to be healthier than the general population, which limits confounders but constrains the generalizability of our results. The lack of overall cognitive decline in the sample likely limited our ability to detect a relationship

between baseline physical measures and cognitive decline; examining these relationships in a larger sample with overall cognitive decline would be informative. It is also possible that the 3MS, as a measure of global cognitive function, was not as sensitive to change as the PPMs, which had greater variance in our sample and are less prone to ceiling effects. If other measures of cognitive function had been available for the cohort that focused on executive function or cognitive processing speed, we may have found a relationship between baseline physical measures and declines in these specific cognitive functions. Other PPMs (such as quantitative gait analyses) could also be more sensitive to cognitive function, but the physical measures used in this study are easy to perform in a clinical setting and predict important clinical outcomes, including disability and mortality (31,32). Lastly, some factors that we considered as confounders in our full adjustment models could also be considered mediators of the association between cognitive function and physical performance, such as depressive symptoms and physical activity level. However, results from our fully adjusted models were not meaningfully changed, and in post hoc analyses, we found that removing physical activity from the models with baseline 3MS and change in 3MS as predictors did not change the estimates or significance.

In summary, this study investigated the association between cognitive function and physical performance bidirectionally and our findings suggest that global cognitive function decrements more consistently precede or co-occur with physical performance decline among older women. Although there are likely to be individual differences in the temporal sequence of cognitive and physical decline, it is worthwhile to consider the predominant direction of association in future research to add to our understanding of the mechanisms of the relationship between cognitive and physical performance.

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References

1. Atkinson HH, Rosano C, Simonsick EM, et al. Cognitive function, gait speed decline, and comorbidities: the health, aging and body composition study. *J Gerontol A Biol Sci Med Sci*. 2007;62(8):844–850.
2. Inzitari M, Baldereschi M, Di CA, et al. Impaired attention predicts motor performance decline in older community-dwellers with normal baseline mobility: results from the Italian Longitudinal Study on Aging (ILSA). *J Gerontol A Biol Sci Med Sci*. 2007;62(8): 837–843.
3. Raji MA, Ostir GV, Markides KS, Goodwin JS. The interaction of cognitive and emotional status on subsequent physical functioning in older mexican americans: findings from the Hispanic established population for the epidemiologic study of the elderly. *J Gerontol A Biol Sci Med Sci*. 2002;57(10):M678–M682.
4. Seeman TE, Charpentier PA, Berkman LF, et al. Predicting changes in physical performance in a high-functioning elderly cohort: MacArthur studies of successful aging. *J Gerontol*. 1994;49(3):M97–M108.

5. Wang L, van Belle G, Kukull WB, Larson EB. Predictors of functional change: a longitudinal study of nondemented people aged 65 and older. *J Am Geriatr Soc*. 2002;50(9):1525–1534.
6. Tabbarah M, Crimmins EM, Seeman TE. The relationship between cognitive and physical performance: MacArthur studies of successful aging. *J Gerontol A Biol Sci Med Sci*. 2002;57(4):M228–M235.
7. Buchman AS, Wilson RS, Boyle PA, Bienias JL, Bennett DA. Grip strength and the risk of incident Alzheimer's disease. *Neuroepidemiology*. 2007;29(1–2):66–73.
8. Verghese J, Lipton RB, Hall CB, Kuslansky G, Katz MJ, Buschke H. Abnormality of gait as a predictor of non-Alzheimer's dementia. *N Engl J Med*. 200228;347(22):1761–1768.
9. Marquis S, Moore MM, Howieson DB, et al. Independent predictors of cognitive decline in healthy elderly persons. *Arch Neurol*. 2002; 59(4):601–606.
10. Alfaro-Acha A, Al Snih S, Raji MA, Kuo YF, Markides KS, Ottenbacher KJ. Handgrip strength and cognitive decline in older Mexican Americans. *J Gerontol A Biol Sci Med Sci*. 2006;61(8):859–865.
11. Alfaro-Acha A, Al Snih S, Raji MA, Markides KS, Ottenbacher KJ. Does 8-foot walk time predict cognitive decline in older Mexicans Americans? *J Am Geriatr Soc*. 2007;55(2):245–251.
12. Inzitari M, Newman AB, Yaffe K, et al. Gait speed predicts decline in attention and psychomotor speed in older Adults: The Health Aging and Body Composition Study. *Neuroepidemiology*. 2007;29 (3-4):156–162.
13. Wang L, Larson EB, Bowen JD, van Belle G. Performance-based physical function and future dementia in older people. *Arch Intern Med*. 2006;166(10):1115–1120.
14. Atkinson HH, Cesari M, Kritchevsky SB, et al. Predictors of combined cognitive and physical decline. *J Am Geriatr Soc*. 2005;53(7): 1197–1202.
15. Njegovan V, Hing MM, Mitchell SL, Molnar FJ. The hierarchy of functional loss associated with cognitive decline in older persons. *J Gerontol A Biol Sci Med Sci*. 2001;56(10):M638–M643.
16. Heuninckx S, Wenderoth N, Debaere F, Peeters R, Swinnen SP. Neural basis of aging: the penetration of cognition into action control. *J Neurosci*. 2005;25(29):6787–6796.
17. Shumaker SA, Reboussin BA, Espeland MA, et al. The Women's Health Initiative Memory Study (WHIMS): a trial of the effect of estrogen therapy in preventing and slowing the progression of dementia. *Control Clin Trials*. 1998;19(6):604–621.
18. Teng EL, Chui HC. The Modified Mini-Mental State (3MS) examination. *J Clin Psychiatry*. 1987;48(8):314–318.
19. The Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. *Control Clin Trials*. 1998;19(1):61–109.
20. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288(3):321–333.
21. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA*. 2004;291(14):1701–1712.
22. Anderson GL, Manson J, Wallace R, et al. Implementation of the Women's Health Initiative study design. *Ann Epidemiol*. 2003;13 (9 suppl):S5–S17.
23. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc*. 2000;32(9 suppl):S498–S504.
24. Andresen EM, Malmgren JA, Carter WB, Patrick DL. Screening for depression in well older adults: evaluation of a short form of the CES-D (Center for Epidemiologic Studies Depression Scale). *Am J Prev Med*. 1994;10(2):77–84.
25. Verghese J, Wang C, Lipton RB, Holtzer R, Xue X. Quantitative gait dysfunction and risk of cognitive decline and dementia. *J Neurol Neurosurg Psychiatry*. 2007;78(9):929–935.
26. Louis ED, Tang MX, Mayeux R. Parkinsonian signs in older people in a community-based study: risk of incident dementia. *Arch Neurol*. 2004;61(8):1273–1276.
27. Waite LM, Grayson DA, Piguet O, Creasey H, Bennett HP, Broe GA. Gait slowing as a predictor of incident dementia: 6-year longitudinal data from the Sydney Older Persons Study. *J Neurol Sci*. 2005;229–230:89–93.
28. Heyn P, Abreu BC, Ottenbacher KJ. The effects of exercise training on elderly persons with cognitive impairment and dementia: a meta-analysis. *Arch Phys Med Rehabil*. 2004;85(10):1694–1704.
29. Kramer AF, Colcombe SJ, McAuley E, et al. Enhancing brain and cognitive function of older adults through fitness training. *J Mol Neurosci*. 2003;20(3):213–221.
30. Delbono O. Neural control of aging skeletal muscle. *Aging Cell*. 2003;2(1):21–29.
31. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol*. 1994;49(2):M85–M94.
32. Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. *N Engl J Med*. 1995;332(9):556–561.

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