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Changes in Cognitive Function in a Randomized Trial of Physical Activity: Results of the Lifestyle Interventions and Independence for Elders Pilot Study

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Background. Cognitive impairment is an important contributor to disability. Limited clinical trial evidence exists regarding the impact of physical exercise on cognitive function (CF). We report results of a pilot study to provide estimates of the relative impact of physical activity (PA) on 1-year changes in cognitive outcomes and to characterize relationships between changes in mobility disability and changes in cognition in older adults at increased risk for disability.

Methods. Sedentary persons (102) at increased risk for disability (aged 70–89 years) were randomized to moderate-intensity PA or health education. Participants were administered the Digit Symbol Substitution Test (DSST), Rey Auditory Verbal Learning Test (RAVLT), modified Stroop test, and Modified Mini-Mental State Examination at baseline and 1 year.

Results. Group differences were not significant but improvements in cognitive scores were associated with improvements in physical function. Specifically, the DSST significantly correlated with change in the Short Physical Performance Battery score ($r = .38$, $p = .0002$), in chair stand score ($r = .26$, $p = .012$), in balance score ($r = .21$, $p = .046$), and in 400-m gait speed ($r = .15$, $p = .147$). Change recall on the RAVLT and in the Stroop test was also positively correlated with changes in chair stand and balance, respectively.

Conclusions. These results provide further support for the benefits of exercise on CF in older adults. An adequately powered clinical trial of PA involving older adults at increased risk for cognitive disability is needed to expand the indications for prescribing exercise for prevention of decline in brain function.

Key Words: Exercise—Cognition—Aging—Prevention—LIFE study.

COGNITIVE impairment (CI) is a prevalent condition in older adults, which significantly affects independent function and incident disability (1–4). CI can also advance to dementia, a leading cause of long-term care placement (1,3,4). Physical exercise may have a beneficial effect on cognitive functioning and the brain and be a potential pathway to reducing age-related disability. Observational studies have shown that higher levels of self-reported physical activity (PA) were predictive of lower rates of dementia (5,6) and cognitive decline (7–9) Conversely, other investigators have found no relationship (10,11). Randomized trials of aerobic exercise in sedentary older adults have demonstrated selective improvement in executive control processes (12) and positive effects of exercise on brain volume (13). However, the evidence is limited due to the existing randomized controlled trial's (RCT) short interventions (6 months) and focus on generally healthy older adults (12,14,15,16).

To address further the need for more knowledge regarding the relationship between exercise and cognitive function (CF) in humans, we report the results from the cognitive substudy (CS) of the Lifestyle Interventions and Independence for Elders pilot (LIFE-P) study. This trial (LIFE-P cognition) adds two important contributions to the current knowledge base: inclusion of a physically "at-risk" population defined by mobility disability measures and a longer follow-up than most prior trials. CF was assessed at two sites to examine the potential of incorporating cognitive outcomes in a larger trial using this intervention and to obtain important benchmarks for designing such a trial. We provide estimates of the relative impact of the PA program on

**The list of the LIFE study investigators is in the Appendix.*

1-year changes in cognitive outcomes. We also characterize relationships that changes in measures of mobility disability have with changes in these outcomes, both overall and separately within each intervention condition. We use results from these analyses to examine more critically the feasibility of preventing cognitive decline by using PA interventions.

Methods

Study Design

The design and primary results of the LIFE-P study have been reported elsewhere (17). Briefly, the LIFE-P study was a single-blind multicenter RCT of a PA intervention compared with a "successful aging" (SA) health education–based intervention in sedentary older adults who were at higher risk for disability. An additional goal of the pilot study was to assess the feasibility of testing the effect of exercise on other potential outcomes, including cognition. The overall study was conducted at four field centers (Cooper Institute, Stanford University [SU], University of Pittsburgh, and Wake Forest University [WFU]) and the cognitive substudy was conducted at two of the four: SU and WFU.

Participants

Participants were recruited in the age range of 70–89 years. Additional inclusion criteria included a sedentary life style (< 20 min/wk spent in structured PA), able to walk 400 m within 15 minutes without sitting and without use of any assistive device, and Short Physical Performance Battery (SPPB) (18) score 9 or less (of 12). Participants with severe heart failure, uncontrolled angina, severe pulmonary disease, severe arthritis, cancer requiring treatment in the past 3 years, Parkinson's disease or other serious neurological disorders, life expectancy of less than 12 months, or a Mini-Mental State Examination score less than 21 were ineligible. Recruitment strategies and a flow diagram of reasons for exclusion have been described previously (19). Per protocol, the first 50 participants at each participating site were administered the cognitive battery (final $n = 102$) at baseline for the cognitive substudy pilot.

Physical Activity Intervention

The PA intervention (16) consisted of a combination of aerobic, strength, balance, and flexibility exercises divided into three phases: adoption (weeks 1–8), transition (weeks 9–24), and maintenance (week 25 to the end of the trial). Each participant in the PA group received a 45-minute individualized, introductory session to describe the intervention and to provide individual counseling to optimize safety and participation. For the first 2 months (adoption), three center-based exercise sessions (40–60 minutes) per week were conducted in a supervised setting. During the next 4 months (transition), the number of center-based sessions was reduced (two per week) and home-based endurance, strengthening, or flexibility exercises (three or more per week) were begun. The subsequent maintenance phase consisted of the home-based intervention, optional once to twice per week center-based sessions, and monthly telephone contacts. The PA intervention focused on walking as the primary mode of exercise with a goal of progressively building to at least 150 minutes weekly (20).

SA Intervention

An SA health education intervention was used as the active control and was designed to provide attention and health education to participants. Participants met in small groups weekly for the first 26 weeks and then monthly. Sessions included health topics relevant to older adults such as nutrition, medications, foot care, and recommended preventive services at different ages. Basic educational information related to PA was provided, but there was no content provided describing the PA intervention.

Measurements

The cognitive assessment battery was administered at the baseline and 12-month clinic visits. To ensure blinding, participants were instructed not to discuss their intervention during the outcome assessments conducted by blinded staff members at locations other than the intervention sites. Prevalence of clinical conditions was determined using self-reported physician-diagnosed disease information, electrocardiogram, and a physician-led clinical exam. The Community Healthy Activities Model Program for Seniors questionnaire was used to assess self-reported PA in all participants at baseline and follow-up. Depressive symptoms were assessed using the Center for Epidemiological Studies-Depression scale.

Outcomes

Cognitive.—The LIFE-P assessed CF using a battery adapted from the Action to Control Cardiovascular Risk in Diabetes (ACCORD)—Memory in Diabetes trial (21). This battery was developed specifically for the purpose of incorporating cognitive assessment as a secondary outcome in a large cardiovascular clinical trial (ACCORD). It was chosen by the LIFE study investigators based on its broad assessment of domains of cognition likely to be affected by the intervention plus our experience from ACCORD on its ease of administration and time required in a large trial. Additionally, this battery facilitated balancing the desire to incorporate cognitive assessment with the overall intervention and outcome ascertainment burden to participants in LIFE. The cognitive battery consisted of four primary components:

1. *Digit Symbol Substitution Test* (DSST) (22) as a measure of psychomotor speed and working memory (23).

The DSST has proven to be feasible in aging studies and large multicenter clinical trials (15,23,24), has been validated in similar populations, and is modifiable by exercise interventions (25). Participants are given a series of numbered symbols and then asked to draw the appropriate symbols below a list of random numbers. The score is the number of correctly made matches in 1 minute.

2. *Modified Stroop test* as a measure of processing speed, cognitive flexibility, and inhibition or disinhibition. It was successfully administered to older persons in cardiovascular determinants of dementia (CASCADE) (24), and the performance on this test correlates with aerobic capacity and has shown responsiveness to exercise in a small RCT (25). This test consists of three subtasks: color word naming, color naming, and naming of color words printed in a different color from the color word (interference component). Participant score is the difference between tests 2 and 3.
3. *Modified Mini-Mental State Examination* (3MSE) (26) is a widely used measure of global cognitive functioning. This is an expanded 100-point version of the original Folstein Mini-Mental State Examination.
4. *The Rey Auditory Verbal Learning Test (RAVLT)* (27), a test of short- and long-term verbal memory assessing the ability to learn a list of 15 common words. The study participant is read this list five times, and after each time, he or she immediately recalls as many words as possible. Following the fifth recall, an interference list is presented after which the participant is asked to spontaneously recall words from the original list. Then, a 10-minute interval passes and he or she is asked again to remember spontaneously as many words as possible from the first list (delayed recall). Scoring is based on total correct words across all components.

Functional.—The SPPB score is based on timed measures of standing balance, walking speed, and ability to rise from a chair and has been extensively described (18,28). For the balance test, participants were asked to maintain their feet in side-by-side, semitandem (heel of one foot beside the big toe of the other foot), and tandem (heel of one foot in front and touching the other foot) positions for 10 seconds each. Walking speed was assessed by asking participants to walk at their usual pace for a 4-m course. For the chair test, participants were asked to stand up from a sitting position with their arms folded across the chest five times as quickly as possible and the time to perform the test was recorded. Each of the three performance measures was assigned a score ranging from 0 to 4, with 4 indicating the highest level of performance and 0 the inability to complete the test. A summary score (range 0–12) was subsequently calculated by adding the three scores.

For comparability to other populations, four categories were computed for walking speed and chair stands, according to cut points based on quartiles of the time to perform each task assessed in the Established Populations for Epidemiologic Studies of the Elderly (29). The speed was scored as follows: less than 0.42 m/s = 1; 0.41–0.59 m/s = 2; 0.58–0.75 m/s = 3; and more than 0.75 m/s = 4. The time required to perform five chair stands was scored as follows: less than 16.7 seconds = 1; 13.7–16.6 seconds = 2; 11.2–13.6 seconds = 3; and more than 11.1 seconds = 4.

For the 400 m walk (30,31), participants were asked to walk 10 laps of a 20-m course at their usual pace. Participants were allowed to stop and rest if necessary but without sitting. For the follow-up visits (but not for screening), participants were allowed to use a cane. For individuals who did not complete the 400-m walk, the distance completed and the total time used to complete that distance was used to calculated gait speed. Handgrip strength was measured using a handheld isometric dynamometer (Jaymar; JLW Instruments, Chicago, IL). Grip strength was determined by the maximum performance in four trials, two using the left hand and two using the right and calculated as the average grip strength for left and right hands.

Statistical Analysis

To characterize the sample in this pilot study, means or proportions and standard deviations (*SD*s) were calculated by randomization group for multiple baseline demographic and medical history variables. Because this was a pilot study, it was not powered to detect meaningful differences between groups for the cognition measures. However, the information on means, *SD*s, and correlations that we obtained were used to determine the feasibility of using these outcomes in a proposed larger and more definitive main trial (Life-M) study. We calculated unadjusted means and *SD*s for each cognition measure obtained at the baseline and follow-up visits. Analysis of covariance, controlling for clinical site and baseline cognition measure, was used to estimate the mean difference between intervention groups at the 12-month follow-up. Ninety-five percent confidence intervals were calculated for each intervention difference. Finally, Spearman correlation coefficients were used to investigate associations between changes (Month 12 − baseline) in cognition test scores and changes in physical performance measures, after adjusting for intervention group random assignment. Because this is an exploratory pilot study, we have not controlled Type I error across inferences. With 90 participants having data on each variable, we have approximately 80% power to detect correlations of 0.29 or larger, assuming a .05 two-sided alpha level.

Results

A total of 102 participants were administered the cognitive battery at the baseline examination. Participants' mean age was 77.4 years (*SD* 4.3), 70.6% were women, 17.7%

Table 1. Baseline Characteristics of Study Participants

Variable	Total Randomized ($N=102$)	Physical Activity Group ($N=50$)	Successful Aging Group ($N=52$)	p Value
Age, y	77.44 ± 4.26	76.80 ± 4.37	78.06 ± 4.11	.1371
Race/ethnicity, *n* (%)				.2613
African American/black	14 (13.7)	7 (14.0)	7 (13.5)	
Caucasian/white	83 (81.4)	39 (78.0)	44 (84.6)	
Latino, Hispanic, or Spanish	2 (2.0)	2 (4.0)	0 (0.0)	
Other/mixed	2 (2.0)	2 (4.0)	0 (0.0)	
Gender, *n* (%)				.7590
Female	72 (70.6)	36 (72.0)	36 (69.2)	
Education, *n* (%)				.4037
High school or equivalency	23 (22.5)	13 (26.0)	10 (19.2)	
More than high school	78 (76.5)	36 (72.0)	42 (80.8)	
Self-reported health, *n* (%)				.6068
Excellent	7 (6.9)	4 (8.0)	3 (5.8)	
Very good	21 (20.6)	7 (14.0)	14 (26.9)	
Good	58 (56.9)	31 (62.0)	27 (51.9)	
Fair	14 (13.7)	7 (14.0)	7 (13.5)	
Poor	2 (2.0)	1 (2.0)	1 (1.9)	
Body mass index	28.97 ± 5.08	28.80 ± 5.03	29.14 ± 5.17	.7328
Depression scale	8.49 ± 6.64	8.94 ± 7.18	8.06 ± 6.12	.5051
Hypertension, *n* (%)	77 (75.49)	39 (78.00)	38 (73.08)	.5634
Diabetes, *n* (%)	18 (17.65)	10 (20.00)	8 (15.38)	.5410
Any ADL difficulty, *n* (%)	90 (88.24)	44 (88.00)	46 (88.46)	.9423
Difficulty walking quarter mile, *n* (%)	3 (2.94)	1 (2.00)	2 (3.85)	.5812
Difficulty walking 1 mile, *n* (%)	48 (47.06)	20 (40.00)	28 (53.85)	.1613
SPPB score	7.79 ± 1.27	7.82 ± 1.16	7.77 ± 1.38	.8411

Note: ADL = activity of daily living; SPPB = Short Physical Performance Battery.

were racial or ethnic minorities, and 31.4% had a SPPB score of 7 or less. The baseline demographic and health characteristics are shown in Table 1.

Of the 102 baseline participants, 98 (96.1%) remained in the study through the Month 12 visit (1 death, 2 study withdrawals from the overall study, and 1 refused to complete the cognition questionnaires during a closeout home visit), 93 (91.2%) completed some component of the cognitive questionnaire battery at the 12-month follow-up, and 92 (90.2%) completed the Month 12 DSST questionnaire, the prespecified primary outcome for this pilot. Of the 5 remaining participants with missing data on CF, 4 participants did not receive cognitive testing because a certified tester was not available at the time of follow-up at the clinical site and 1 participant was in a board-and-care facility and unable to be scheduled for a cognition substudy interview before study closeout.

Unadjusted means for cognition measures at baseline, 12-month follow-up, and the 12-month change from baseline are presented in Table 2. The PA intervention resulted in slightly improved scores at Month 12 for DSST, but there were no meaningful differences in the remaining tests. Although the unadjusted means presented in Table 2 are similar at 12 months for the DSST score, the adjusted mean difference between groups is 1.7 because the SA group had a higher baseline mean DSST level. As expected from this pilot study, for all outcomes, the adjusted mean differences are small relative to the width of the 95% confidence intervals placed around them.

Results of correlation analyses between changes in cognition test scores and changes in physical performance measures are provided in Table 3. These correlation coefficient estimates adjust for an intervention effect, that is, intervention assignment. A positive correlation between change (follow-up minus baseline) in any of the cognition scores, with the exception of the Stroop test, and change in the physical performance measures is indicative that improvements (or declines) in both measurements track together. For the Stroop test, larger values are associated with poorer performance, so negative correlations between the change measurements are indicative that improvements track. Improvements in DSST were significantly associated with improvements in total SPPB score, chair stand score, and balance score. The estimated correlation between the change in the DSST score and the change in the 400-m gait speed was positive, as expected ($r = .15$), but not statistically significant ($p = .147$). Changes in the remaining components of the battery were generally in the same direction as the lower extremity functional changes. The RAVLT was positively correlated with change in the chair stand test ($r = .21$, $p = .042$) and the Stroop test was marginally associated with the balance score ($r = -.20$, $p = .059$).

Discussion

These results from the LIFE-P CF substudy show that the positive effect of physical exercise on physical function may also extend into some domains of CF. To our knowledge, this is the first multicenter randomized clinical trial

Table 2. Baseline and Follow-Up Results for Cognition Measures

		Physical Activity			Successful Aging				
Description	Outcome	*N*	Unadjusted Mean (*SD*)	Adjusted Mean* (*SE*)	*N*	Unadjusted Mean (*SD*)	Adjusted Mean* (*SE*)	Difference in Unadjusted Means	Difference in Adjusted Means (95% CI)
Baseline visit	DSST	50	45.70 (12.12)		52	47.69 (12.51)		−1.99	
	Rey	50	49.82 (14.23)		52	50.85 (14.55)		−1.03	
	Stroop	49	40.41 (21.90)		52	40.63 (22.90)		−0.23	
	3MSE	50	89.88 (6.19)		52	90.67 (6.66)		−0.79	
12-month visit	DSST	44	46.84 (15.31)	47.58 (1.44)	48	46.50 (13.37)	45.84 (1.38)	0.34	1.74 (−2.22 to 5.70)
	Rey	44	54.30 (14.55)	55.12 (1.35)	47	56.23 (14.34)	55.55 (1.31)	−1.94	−0.43 (−4.17 to 3.31)
	Stroop	45	40.36 (18.92)	39.61 (2.59)	47	39.09 (24.92)	39.50 (2.51)	1.27	0.11 (−7.06 to 7.27)
	3MSE	45	90.33 (7.07)	90.65 (0.83)	48	91.79 (6.12)	91.51 (0.80)	−1.46	−0.86 (−3.16 to 1.44)
Change from baseline	DSST	44	0.68 (11.32)	0.56 (1.44)	48	−1.31 (7.61)	−1.18 (1.38)	1.99	1.74 (−2.22 to 5.70)
	Rey	44	4.73 (8.89)	4.49 (1.35)	47	4.62 (10.12)	4.92 (1.31)	0.11	−0.43 (−4.17 to 3.31)
	Stroop	44	−1.23 (16.43)	−0.95 (2.59)	47	−0.74 (21.12)	−1.06 (2.51)	−0.48	0.11 (−7.06 to 7.27)
	3MSE	45	0.69 (6.10)	0.44 (0.83)	48	1.04 (6.34)	1.30 (0.80)	−0.35	−0.86 (−3.16 to 1.44)

Notes: 3MSE = Modified Mini-Mental State Examination; CI = confidence interval; DSST = Digit Symbol Substitution Test; SE = standard error.
*Obtained from analysis of covariance with baseline measurements and sites included as covariate.

evaluating the effect of long-term exercise on measures of CF and physical function together in a population targeted specifically for its increased risk for disability and whose mean age is more than 70.

Preservation of CF in aging is essential to the maintenance of independence and the prevention of institutionalization. A 5-year delay in the onset of dementia would result in an approximate 50% decrease in the number of dementia cases after several decades (32). Even smaller delays in onset, assuming normal rate of decline in CF after onset, would still result in substantially lower numbers of cases. Therefore, testing interventions such as exercise with the potential to prevent or reduce the loss of CF is of high public health importance.

Performance on the DSST has been previously shown to be a reliable cognitive measure for predicting future decline in CF in older adults (33). LIFE-P CS results showed that the DSST was associated with change in physical performance measures such as standing balance, ability to transfer from a chair to standing position, and to some extent walking speed (r = .15). Change in working memory, as measured by the RAVLT, and in cognitive flexibility (Stroop test) was also associated with positive change in chair stand time and balance, respectively. These findings are consistent with past RCTs, which suggest that changes in physiological functioning, aerobic capacity specifically, mediate the influence of exercise on improvements in cognitive functioning (12,14,15,16). Given that persons with evidence for dementia were screened out of this population, it is not surprising that the results showed no effect on the more global cognitive instrument, the 3MSE.

Animal models have shown possible underling mechanisms for these findings. Specifically, exercise decreases amyloid load (34); positively affects hippocampal neuronal function(35–37), hippocampal and parietal cortical cholinergic function, and spatial learning (38); increases levels of brain-derived neurotrophic factors; and may protect against antioxidant and other forms of neuronal damage (39,40).

Although the potentially important relationship of "preclinical" cognitive deficits to decrements in physical functional performance has been shown (41), randomized trials are needed to determine if the effect of an exercise intervention positively affects changes in long-term CF in a high population. These results support the rationale for including cognitive outcomes in randomized trials of exercise to shed further light on the potential of role cognition as an effect modifier of the overall functional effect. The LIFE-P CF substudy results provide estimates of covariance and attrition necessary to design an efficient larger trial. We observed a difference at 12 months in the average DSST scores between groups of 1.7, approximately 15% of a baseline *SD*, and the correlation between baseline and 12-month

Table 3. Spearman Correlation Coefficients for Changes in Cognition Outcomes Adjusted for Intervention Differences (correlation coefficients with p values and sample sizes in parentheses)

Test	Total SPPB	Grip	Chair Stand	Balance	Gait Speed
DSST	0.38 (p=.0002; n=92)	−0.11 (p=.3251; n=88)	0.26 (p=.0117; n=92)	0.21 (p=.0468; n=92)	0.15 (p=.1472; n=91)
Rey short	0.11 (p=.3095; n=91)	0.07 (p=.5283; n=87)	0.22 (p=.0385; n=91)	0.07 (p=.5200; n=91)	0.25 (p=.0193; n=90)
Rey interference	−0.13 (p=.2364; n=91)	0.03 (p=.7811; n=87)	−0.14 (p=.1954; n=91)	0.05 (p=.6101; n=91)	−0.21 (p=.0523; n=90)
Rey long	0.18 (p=.0860; n=90)	−0.01 (p=.8925; n=86)	0.20 (p=.0569; n=90)	0.14 (p=.2025; n=90)	0.01 (p=.9417; n=89)
3MSE	−0.001 (p=.9918; n=93)	0.05 (p=.6599; n=89)	−0.04 (p=.6987; n=93)	0.13 (p=.2122; n=93)	−0.05 (p=.6274; n=92)
Stroop	−0.07 (p=.5222; n=91)	−0.09 (p=.4170; n=87)	0.02 (p=.8798; n=91)	−0.20 (p=.0589; n=91)	−0.11 (p=.2902; n=90)

Note: 3MSE = Modified Mini-Mental State Examination; DSST = Digit Symbol Substitution Test; SPPB = Short Physical Performance Battery.

DSST scores was 0.75. Accounting for 8% per year dropout, results from the LIFE-P CS allowed us to estimate that a total of *N* of 2,000 participants would provide greater than 90% power to detect the effect size we target (0.15 *SD*), assuming a two-sided .05 alpha.

This pilot study of 102 older adults at risk for mobility disability participating in an RCT of a PA intervention showed significant correlations between physical and cognitive performance. Together with previously published literature, these data support the idea that strategies to improve physical performance may improve cognitive performance. A full-scale randomized trial is required to determine whether PA can prevent the onset of severe CI and dementia. If confirmed, health care providers for older adults in the future may recommend a walking program for the preservation of not only physical function but also CF.

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