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Effect of a 24-month physical activity intervention compared to health education on cognitive outcomes in sedentary older adults: the LIFE Randomized Trial

Kaycee M. Sink, MD, MAS[1], **Mark A. Espeland, PhD**[2], **Cynthia M. Castro, PhD**[3], **Timothy Church, MD, PhD, MPH**[4], **Ron Cohen, PhD**[5], **John A. Dodson, MD**[6], **Jack Guralnik, MD, PhD**[7], **Hugh C. Hendrie, MB, ChB, D.Sc**[8], **Janine Jennings, PhD**[9], **Jeffery Katula, PhD, MA**[10], **Oscar L. Lopez, MD**[11], **Mary M. McDermott, MD**[12], **Marco Pahor, MD**[5], **Kieran F. Reid, PhD; MPH**[13], **Julia Rushing, MS**[2], **Joe Verghese, MBBS**[14], **Stephen Rapp, PhD**[15], and **Jeff D. Williamson, MD, MHS**[1] **for the LIFE Study investigators**

Kaycee M. Sink: kmsink@wakehealth.edu; Mark A. Espeland: mespelan@wakehealth.edu; Cynthia M. Castro: Cynthia.Castro@stanford.edu; Timothy Church: tim.church@pbrc.edu; Ron Cohen: roncohen@ufl.edu; John A. Dodson: john.dodson@nyumc.org; Jack Guralnik: jguralnik@epi.umaryland.edu; Hugh C. Hendrie: hhendri@iupui.edu; Janine Jennings: jjennings@wfu.edu; Jeffery Katula: katulaj@wfu.edu; Oscar L. Lopez: lopezol@upmc.edu; Mary M. McDermott: mdm608@northwestern.edu; Marco Pahor: mpahor@ufl.edu; Kieran F. Reid: Kieran.reid@tufts.edu; Julia Rushing: jrushing@wakehealth.edu; Joe Verghese: joe.verghese@einstein.yu.edu; Stephen Rapp: srapp@wakehealth.edu; Jeff D. Williamson: jwilliam@wakehealth.edu

[1]Department of Internal Medicine, Section on Gerontology and Geriatric Medicine, Wake Forest School of Medicine, Winston-Salem, NC 27157

[2]Department of Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, NC 27157

[3]Stanford Prevention Research Center, Stanford University School of Medicine, Palo Alto, CA 94304

[4]Pennington Biomedical Research Center, Baton Rouge, LA 70808

[5]College of Medicine, University of Florida, Gainesville, FL, 32608

[6]Leon H. Charney Division of Cardiology, Department of Medicine, New York University School of Medicine, New York, NY 10016

[7]Department of Epidemiology and Public Health, Division of Gerontology, University of Maryland School of Medicine, Baltimore, MD 21201

[8]Department of Psychiatry and Center for Aging Research, Indiana University

[9]Department of Psychology, Wake Forest University, Winston-Salem, NC, 27109

[10]Department of Health and Exercise Sciences, Wake Forest University, Winston-Salem, NC, 27109

Correspondence: Kaycee Sink, MD, MAS, Wake Forest School of Medicine, Sticht Center on Aging, One Medical Center Blvd, Winston-Salem, NC 27157, 336-713-8558; kmsink@wakehealth.edu.

Disclosures:
Dr. Lopez is a consultant for Baxter, Lilly, Grifols, and Lundbeck

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[11]Departments of Neurology and Psychiatry, University of Pittsburgh, Pittsburgh, PA 15213

[12]Department of Medicine, Northwestern University Fienberg School of Medicine, Chicago, IL

[13]Nutrition, Exercise Physiology and Sarcopenia Laboratory, Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, Boston, MA 02111

[14]Departments of Neurology and Medicine, Albert Einstein College of Medicine, Bronx, NY

[15]Department of Psychiatry, Wake Forest School of Medicine, Winston-Salem, NC 27157

Abstract

Importance—Epidemiologic evidence suggests that physical activity benefits cognition, but results from randomized trials are limited and mixed.

Objective—To determine whether a 24-month physical activity program results in better cognitive function and/or lower risk of mild cognitive impairment (MCI) or dementia compared to a health education program.

Design, Setting, and Participants—The Lifestyle Interventions and Independence for Elders (LIFE) study was a multicenter, randomized clinical trial that enrolled 1635 community-living participants at 8 centers in the U.S. from February 2010 until December 2011. Participants were sedentary adults aged 70–89 years at risk for mobility disability, but able to walk 400m.

Intervention—Participants were randomized to a structured, moderate-intensity physical activity program (n=818) that included walking, resistance training, and flexibility exercises or to a health education program (n=817) of educational workshops and upper extremity stretching.

Outcomes and Measures—Pre-specified secondary outcomes of the LIFE study included cognitive function measured by the Digit Symbol Coding task (0–133 scale, higher=better) and Hopkins Verbal Learning Test-Revised (12-word list recall) assessed in 1,476 (90.3%) participants. Tertiary outcomes included global and executive cognitive function and incident MCI or dementia at 24 months. Pre-specified subgroups analyses were performed based on age, sex, baseline physical performance, and baseline Modified Mini-Mental State Examination score.

Results—At 24 months, DSC and HVLT-R scores (adjusted for clinic site, gender, and baseline values) were not different between groups. Mean DSC scores were 46.26 points for physical activity vs. 46.28 for health education; mean difference −0.014 points, 95% CI −0.80 to 0.77, p= 0.97. Mean HVLT-R delayed recall scores were 7.22 for physical activity vs. 7.25 for health education; mean difference −0.03 words, 95% CI −0.29 to 0.24, p= 0.84.

No differences for any other cognitive or composite measures were observed. Participants randomized to physical activity who were ≥80 years (n=307) and those with poorer baseline physical performance (n=328) had better changes in executive function composite scores vs. those randomized to health education (interaction p=0.01, respectively). Incident MCI or dementia occurred in 98 (13.2%) participants randomized to physical activity and 91 (12.1%) participants randomized to health education (OR 1.08, 95% CI 0.80 to 1.46).

Conclusions and Relevance—Among sedentary older adults, a 24-month moderate intensity physical activity program, compared to a health education program, did not result in improvements in global or domain-specific cognitive function.

Introduction

Epidemiologic evidence suggests that regular physical activity is associated with lower rates of cognitive decline. Exercise is associated with improved cerebral blood flow and neuronal connectivity,[1] maintenance or improvement in brain volume,[2;3] and favorable changes in brain-derived neurotrophic factor and neurogenesis.[4;5] In transgenic Alzheimer's mouse models, exercise reduces beta-amyloid deposition.[6]

Randomized clinical trials (RCT) assessing the effect of physical activity on cognitive function are equivocal,[7–9] perhaps due to small sample sizes, short intervention periods, and differences in cohorts and protocols, particularly physical activity intensity.[7] Two recent small RCTs of physical activity found no benefit of a structured physical activity program vs. no intervention or cognitive training in non-demented older adults with cognitive complaints or at risk of cognitive decline.[10;11] However, a 6-month RCT of a home-based physical activity program vs. usual care in participants with memory complaints or mild cognitive impairment found a modest cognitive benefit.[12] The LIFE Pilot study showed a correlation between changes in physical and cognitive performance in a 12 month exercise trial.[13]

Here we report the pre-specified secondary cognitive outcomes of the LIFE Study, the largest and longest RCT to assess the effect of a standardized physical activity intervention on cognitive function and cognitive impairment in sedentary older adults at risk for mobility disability.[14] We hypothesized that compared to health education, physical activity for 24 months would result in better cognitive function and lower risk of incident all-cause mild cognitive impairment (MCI) or dementia.

Methods

Trial design and participants

The LIFE study was a multicenter, single-blinded, randomized clinical trial of a physical activity intervention versus a health education control conducted at 8 field centers across the U.S. Participants were from rural and urban communities. (See acknowledgment section for the field centers.) Details of the LIFE Study design and results have been published.[14;15] The study included sedentary men and women aged 70–89 years who were at high risk for mobility disability based on objectively assessed lower extremity functional limitations defined as a Short Physical Performance Battery (SPPB)[16] score ≤9 (out of 12), but who could walk 400 m in 15 minutes at baseline without assistance. Eligible participants had no diagnosis of dementia or significant cognitive impairment on the Modified Mini-Mental State Examination[17] (3MSE) based on education- and race-specific norms. Participants with <9 years of education were excluded if the screening 3MSE score was <70 for African Americans and Spanish Speakers or <76 for English-speaking non-African Americans. Participants with ≥9 years of education were excluded if their 3MSE score was <76 for African Americans and <80 for Spanish speakers and English-speaking non-African Americans. Race and ethnicity were self-reported and collected as required by the National Institutes of Health.

Recruitment was predominantly by mass mailing to age-eligible residents. Additional strategies included newspaper, radio and television advertisements, and presentations at health fairs, senior centers, medical clinics, and churches.

The LIFE study was approved by the institutional review boards at all participating sites and monitored by a data safety monitoring board appointed by the National Institute on Aging. Written informed consent was obtained from all participants.

Interventions

Participants were randomly assigned, using a secure web-based data management system (permuted block algorithm with random block lengths), with equal probability to either a physical activity intervention or a successful aging health education program, stratifying by field center and sex. The physical activity intervention focused on walking, strength, flexibility, and balance training. Participants were expected to attended two center-based visits per week and perform home-based activity 3–4 times per week. The physical activity sessions progressed towards a goal of 30 min of walking at moderate intensity, 10 min of primarily lower extremity strength training with ankle weights, 10 min of balance training, and large muscle group flexibility exercises.

The health education group attended weekly health education workshops during the first 26 weeks of the intervention and at least monthly sessions thereafter. Sessions lasted 60–90 minutes and consisted of interactive and didactic presentations, facilitator demonstrations, guest speakers, or field trips. Sessions included approximately 10 minutes of group discussion and interaction and 5- to 10-minutes of upper extremity stretching and flexibility exercises. Example topics included travel safety, age appropriate preventive services, legal/ financial issues, and nutrition. The intervention committee ensured that health education activities were consistent across sites and unlikely to increase physical activity.

Measurements

Outcome assessments were conducted in person by masked staff every six months. Home, telephone, and proxy assessments were attempted if participants could not attend clinic visits. Information on demographics, medical and hospitalization history, medication inventory, quality of well-being, and functional limitation was based on self-report.[18] Usual physical activity was assessed by self-report using the CHAMPS questionnaire to measure total weekly minutes in walking and strength training[19] and objectively using an Actigraph accelerometer to measure total minutes of at least moderate activity (>760 counts/minute) over seven days[14].

Cognitive assessment

A previously described neuropsychological battery of tests was administered by trained and certified examiners at baseline and 24 months post-randomization.[20] Three computerized tasks were administered at baseline and either 18 or 30 months depending on when the participant was enrolled.[20]

Neuropsychological battery—Cognitive tests at baseline included the Modified Mini-Mental State Examination (3MSE),[17] a 100-point test of global cognitive function; the Wechsler Adult Intelligence Scale-III Digit Symbol Coding (DSC),[21] a test of psychomotor speed, attention, and working memory; the Hopkins Verbal Learning Test-Revised (HVLT-R),[22] a 12-item word list learning and recall task; and a modified version of the Rey-Osterrieth Complex Figure to assess visuospatial function (copy) and figural memory (immediate recall). At 24 months these measures were repeated along with the Boston Naming Test, a measure of language;[23] the Trail Making Test[24] parts A (measuring attention, concentration, and psychomotor speed) and B (executive function); and Category Fluency for animals, a measure of executive function. In all tests except Trail Making, higher scores indicate better performance.

Computerized battery—Using a laptop computer, participants were administered 3 tasks that were chosen for added sensitivity in assessing speed of processing and executive function: the n-back (1-back and 2-back) task,[25] the Eriksen Flanker task,[26] and a task switching paradigm.[27]

Mild Cognitive Impairment (MCI) and Dementia outcome determinations

At baseline and 24 months post-randomization, all participants were assigned one of the following cognitive classifications: No Cognitive Impairment, MCI, or Dementia. Participants who scored ≤88 on the 3MSE were sent for central adjudication by a panel of eight clinical experts in the diagnosis of late life cognitive impairment, blinded to treatment assignment.[20] Each case was assigned to 2 independent adjudicators; disagreements were resolved by the full panel. Adjudicators reviewed data from the neuropsychological battery, medical history, medications, discharge diagnoses for hospitalizations during the trial, Center for Epidemiology Studies-Depression (CESD) scores,[28] self-reported disability, and informant-reported functional status (Functional Assessment Questionnaire, FAQ).[29] The FAQ is a 10-item interviewer-administered questionnaire assessing degree of dependence in cognitively challenging activities of daily living such as preparing balanced meals, traveling outside the neighborhood, and managing finances. The FAQ was administered to the participant's proxy for all participants with a 3MSE score ≤88 at baseline and 24 months. MCI and dementia were adjudicated based on the 2011 National Institute on Aging/Alzheimer's Association criteria.[30;31]

Statistical analyses

The LIFE protocol specified DSC (total score) and HVLT-R (mean of the immediate and delayed recall subscales) as the two primary cognitive outcomes for assessing cognitive decline, each tested according to the intention to treat principle with analysis of covariance using 24-month data and covariate adjustment for field center, gender, and the baseline value. Additional pre-specified cognitive outcomes were based on scores from the computerized battery. Raw scores from this battery were first winsorized to limit the influence of extreme values: this was done by replacing scores less than the 1st percentile of the cohort wide distribution with the value of the 1st percentile and replacing scores greater than the 99th percentile with the 99th percentile value. Z-scores were formed for each cognitive test score by dividing their difference from the baseline mean by the baseline standard deviation. Composite scores for the HVLT-R (immediate and delayed recall scores), n-back (1- and 2-back scores), task switching (no switch and switch reaction times), and flanker tasks (congruent and incongruent reaction times) were formed by averaging the z-scores for their two individual components. The global cognitive function score was the average of scores from these composites and the z-transformed DSC, renormalized to have mean 0 and standard deviation 1 at baseline. The executive function composite score was the renormalized average of scores from the n-back, task switching, and Flanker tasks. In creating these composite scores, averages were taken of all available data, i.e., missing data if participants did not complete the full battery were ignored. Supporting analyses were conducted using multiple imputation in which missing measures and exam scores were imputed to create five databases that were analyzed in parallel.[32]

Subgroup comparisons using interaction terms were pre-specified for gender and baseline SPPB (<8 versus ≥8), 3MSE (<90 versus ≥90), and age (70–79 years versus ≥80 years). Associations between changes in cognitive function and changes in objective and subjective physical activity were assessed using linear regression and tests of interactions.

Progression in cognitve impairment (i.e., from baseline normal cognitive function to either MCI or dementia or from baseline MCI to dementia), was a tertiary outcome. Logistic regression was used to compare progression rates between intervention groups. Participants with prevalent MCI (n=141) at baseline were not included in the incidence of MCI, but were included in the incident dementia outcome if they progressed to dementia at 24 months. Seven participants were adjudicated to have dementia at the baseline visit (in spite of otherwise meeting LIFE entry criteria). These participants were excluded from the incident dementia outcome analysis.

Analyses were conducted using SAS 9.4; two-sided inferences with $p \leq 0.05$ were considered statistically significant. The targeted sample size (N=1600) was expected to provide 87% power to detect mean differences between groups of 0.15 SD for cognitive tests. This was projected to correspond to mean differences of 1.8 units for DSC scores and 0.8 units for HVLT immediate memory scores.

Results

From February 2010 to December 2011, 1,635 participants were randomized (818 to physical activity and 817 to health education) (Figure 1). Analyses are limited to the 1476 (90.3%) participants with cognitive data during follow-up. Compared to participants without follow-up cognitive data, included participants had faster gait speeds (p<0.001). 24-month retention rates were 89.8% in the physical activity and 90.7% in the health education group (p=0.56).

Table 1 shows characteristics of participants. Overall, mean (SD) age was 78.9 (5.2) years, 68% were women, and 67% had a college education. The mean 3MSE score was 91.7 (5.4) (range 71 to 100). There were more African-Americans in the physical activity than the health education group.

Intervention adherence

Based on accelerometry data, and compared to the health education group, the physical activity group maintained moderate/vigorous physical activity between baseline and 24-month follow-up (mean −2.1 minutes/week (95% CI −9.7 to 13.9) vs −40.4 minutes/week (95% CI −29.4 to −51.4), p<0.001). Based on CHAMPS questionnaire data, and compared to the health education group, the physical activity group had greater increase in self-reported physical activity from baseline to 24 months (mean +130.4 min/week (95% CI 116.7 to 144.1) vs +30.5 min/week (95% CI 18.9 to 42.1), p<0.001). The median attendance at physical activity sessions was 71%, excluding medical leave.

Cognitive function results

At baseline, interviewer-administered cognitive assessments were collected on all participants. Computer-based assessments were collected on 85.5% (2-back) to 96.2% (Flanker) of participants. There were no differences between groups on any cognitive tests at baseline.

Table 2 presents the raw scores and z-transformed cognitive outcomes, adjusting for clinic site, gender, and baseline values. Z-scores are interpreted as the change from baseline in standard deviations. The adjusted mean raw DSC scores (range 1–133) at follow up were not different between groups (46.26 points (95% CI 45.71 to 46.82) in the physical activity group and 46.28 (95% CI 45.73 to 46.83) in the health education; mean difference −0.01 points, 95% CI −0.80 to 0.77, p= 0.97). Similarly, adjusted mean HVLT-R delayed recall scores (range 0–12) were not different between groups (7.22 words (95% CI 7.03 to 7.41) for physical activity vs. 7.25 (95% CI 7.06 to 7.44) for health education; mean difference −0.03 words, 95% CI −0.29 to 0.24, p= 0.84). There were no between-group differences in the executive function composite z-score (p=0.59) or mean global composite score (p=0.40). Additional adjustment for race/ethnicity and education did not change the results.

Figure 2 shows results of pre-specified subgroup comparisons. Intervention effects did not vary by gender or baseline 3MSE. For the executive function composite, however, there was heterogeneity in intervention effects, suggesting benefit in executive function associated with the physical activity intervention (p=0.01 for tests of interaction) for participants with baseline SPPB <8 or age ≥80. Details of the scores for all subgroups and outcomes can be found in the supplemental table.

Relationships with changes in physical activity

24-month changes in the four cognitive function measures were not correlated with changes in moderate physical activity as measured by accelerometry (p>0.30) among the 697 participants with 24-month data. 24-month changes in weekly walking and strength training from the CHAMPS were modestly associated with global cognitive function (r=0.07; p=0.006) and executive function (r=0.06; p=0.04). These relationships were not different between the two intervention groups (interaction tests p>0.70). Results were unchanged when using 12 month change in physical activity.

Incident MCI or Dementia

There was no difference between groups in the incidence of MCI, dementia, or both combined; 13.2% of participants randomized to physical activity developed MCI or dementia by 24 months compared to 12.1% randomized to health education (unadjusted OR [95% CI] 1.08 [0.80 to 1.46]; p=0.61) (Table 3). There were no between group differences within MCI subtypes: incident amnestic MCI was 5.5% for physical activity and 5.7% for health education (p= 0.85); non-amnestic MCI was 4.6% and 3.2% (p=0.16), respectively.

Discussion

The LIFE Study's structured, 24-month moderate-intensity physical activity intervention did not result in better global or domain-specific cognition compared with a health education program in older, sedentary adults. There was also no difference between groups in the incidence of MCI or dementia, though this was an exploratory outcome with limited statistical power. However, participants randomized to the physical activity group who were ≥80 years old and those with lower baseline physical functioning levels experienced benefits in executive functioning compared to the health education group. Cognitive function remained stable over 2 years for all participants. We cannot rule out that both interventions were successful at maintaining cognitive function.

Despite epidemiologic evidence supporting benefits of exercise and physical activity on cognition, the results of the LIFE Study are consistent with some other randomized trials.[7] In the MAX trial,[10] a structured aerobic physical activity intervention was not superior to a stretching exercise control or mental activity control in sedentary older adults. The Look AHEAD trial found no benefit of diet plus physical activity on cognitive function over 8 years.[33] A large trial of a multifactorial intervention including diet, physical activity, cognitive training, social activity, and management of metabolic and vascular risk factors showed a small, statistically significant benefit on global and executive cognitive function at 2 years.[34] However, it is difficult to compare this trial with the LIFE Study because the population was 10 years younger, physically active at baseline, and had a multi-factorial intervention.

Possible explanations for the lack of cognitive benefit of the LIFE physical activity intervention include: a) the dose of physical activity may have been insufficient to produce changes in the cognitive measures despite its effect on physical function;[14] b) improvements in cognitive function in some shorter clinical trials, including the LIFE pilot,[13] may dissipate by 24 months and thus may have been missed in LIFE, especially if adherence to the physical activity intervention wanes over time;[14] c) the LIFE population was not specifically selected for cognitive vulnerability, though poor physical function, especially gait speed, has been shown to be a risk for cognitive decline;[35;36] d) LIFE participants were well educated, with over 2/3 having gone to college, and high cognitive reserve may have protected against cognitive decline over 2 years;[39] and e) the health education intervention may have benefited cognition.[10;37] The LIFE health education group consisted of interactive seminars providing both cognitive and social stimulation. Both cognitive and social stimulation have been shown to preserve cognition in older adults.[10;37]

The dose-response relationship between physical activity and cognition is not well-understood.[7;38] The LIFE physical activity intervention was designed to provide moderate-intensity aerobic walking activity and was consistent with American College of Sports Medicine recommendations. However, we recruited a population with limited physical ability. It is possible that impaired lower extremity functioning and the high prevalence of comorbidities limited participants' ability to exercise at sustained levels sufficient to improve cognition. Nonetheless, the LIFE physical activity group had significantly greater physical activity levels than controls, and a more intensive, sustained intervention that could be translatable at the population level would be difficult to achieve.

Despite the lack of overall benefit, our pre-specified subgroup analyses of participants ≥80 years and those with lower baseline physical performance demonstrated that the physical activity group had better performance on executive function tasks than those in the health education group at 24 months. This finding is important because executive function is the most sensitive cognitive domain to exercise interventions[40] and preserving executive function is required for independence in instrumental activities of daily living. Future physical activity interventions in particularly vulnerable older adult groups (e.g., those 80 years and older and those with especially diminished physical functioning levels) may be warranted.

To our knowledge, the LIFE Study is the largest, longest randomized clinical trial of a physical activity intervention in sedentary older adults at increased risk for mobility disability. Other strengths include high retention rates, without differential loss to follow-up in the 2 groups; comprehensive standardized, well-validated cognitive assessments; and blinded adjudication of MCI and dementia. However, there are several limitations. First, while cognitive function and incident MCI/dementia were *a priori* outcomes for the LIFE Study, the LIFE Study was not specifically powered for these outcomes and may have been too short to affect incident events. Second, the intensity of the physical activity intervention was moderate by design. While sufficient to increase physical activity and reduce incident mobility disability,[14] it may have been insufficient to produce cognitive effects. Third, the components of the health education intervention, including the cognitive and social components, may have improved or prevented cognitive decline. Fourth, we did not measure changes in mechanistic surrogate outcomes, such as brain volumes or cerebrospinal fluid amyloid beta levels.

Conclusions

Among sedentary older adults, a 24-month moderate intensity physical activity program, compared to a health education program, did not result in improvements in global or domain-specific cognitive function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Mark Espeland had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Valerie K. Wilson, MD (Adjunct Instructor, Wake Forest School of Medicine, Winston Salem, NC and Staff physician, Veterans Affairs, Johnson City, TN) contributed to the work reported in this manuscript as an adjudicator of cognitive outcomes. She received compensation for her effort.

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Appendix: Research Investigators for the LIFE Study

Northwestern University, Chicago, IL

Mary M. McDermott, MD – Field Center Principal Investigator

Bonnie Spring, PhD – Field Center Co-Principal Investigator

Joshua Hauser, MD

Martha Gulati, MD

Sanjiv Shah, MD

Kathryn Domanchuk

Rex Graff

Kasia Kadela

Alvito Rego

Pennington Biomedical Research Center, LA

Timothy Church, MD, PhD, MPH – Field Center Principal Investigator

Steven Blair, PED (University of South Carolina)

Valerie Myers, PhD

Ron Monce, PA-C

Nathan Britt, NP

Melissa Nauta, BS

Ami Parks, MPA, BS

Ruben Rodarte, MBA, MS, BS

Heidi Millet, BS

Catrine Tudor-Locke, PhD, FACSM

Ben Butitta, BS

Sheletta Donatto, MS, RD, LDN, CDE

National Heart, Lung and Blood Institute, Bethesda, MD

Denise Bonds, MD

National Institute on Aging, Bethesda, MD

Evan C. Hadley, MD

Kushang V. Patel, PhD

Sergei Romashkan, MD, PhD

Office of Behavioral and Social Sciences Research, National Institutes of Health

Robert M. Kaplan, PhD

Stanford University, Palo Alto, CA

Abby C. King, PhD – Field Center Principal Investigator

Cynthia M. Castro, PhD

William L. Haskell, PhD

Randall S. Stafford, MD, PhD

Veronica Yank, MD

Leslie A. Pruitt, PhD

Kathy Berra, MSN, NP-C, FAAN

Carol Bell, NP

Rosita Thiessen

Kate P. Youngman, MA

Selene B. Virgen, BAS

Kristina N. Tarin, MS, CSCS

Heather Klaftenegger

Carolyn A. Prosak, RD

Ines Campero, BA

Dulce M. Garcia

José Soto, BA

Linda Chio

David Hoskins, MS

Tufts University, Boston, MA

Roger Fielding, PhD – Field Center Principal Investigator

Miriam Nelson, PhD

Sara Folta, PhD

Edward Phillips, MD

Christine Liu, MD

Erica Cifarelli, MS

Kieran Reid, MSc, MPH

Paige Lacasse, BS

Dylan Kirn, BS

Evan Pasha, BS

Sonnly Ribourg, BS

Karen Ruais, NP

Won Kim, BS

Gregory Cloutier, BS

University of Florida, Gainesville, FL

- Todd Manini, PhD

Field Center Principal Investigator

Marco Pahor, MD – Field Center Co-Principal Investigator

Stephen Anton, PhD

Thomas Buford, PhD

Susan Nayfield, MD, MSc

Joe Nocera, PhD

Michael Marsiske, PhD

Bhanu Sandesara, MD

Jocelyn Lee, PhD

Deborah Hiatt-Jensen, ARNP, MPH

Mieniecia Black, MS

Kimberly Case, PhD

Katherine Herring, BS

Amber Schwier-Delvisco, BS

Bill Burk

Brian Hoover, BS

Jeffrey Knaggs, BS

Allison Martin, MS, RCEP

Brooks Center for Rehabilitation Studies (Satellite Site)

Chonglun Xie, MD

Holly Morris, RN

Flo Singletary, MS, CCC-SLP

Jackie Causer

Susan Yonce, RN

Christine Del Boccio

Charles Gay, D.C.

Tangerica Peavy Alexander

Administrative Coordinating Center

Marco Pahor, MD – Principal Investigator of the LIFE Study

Stephen Anton, PhD

Thomas Buford, PhD

Christiaan Leeuwenburgh, PhD

Susan Nayfield, MD, MSc

Todd Manini, PhD

Connie Caudle

Lauren Crump, MPH

Latonia Holmes

Jocelyn Lee, PhD

Ronald Lester, PhD, MBA

Ching-ju Lu, MPH

Ryan O'Mara

Electrocardiogram Reading Center

Carl J. Pepine MD, MACC

Mario Ariet, PhD

Eileen Handberg, PhD, ARNP

Daniel Deluca, BS

James Hill, MD, MS, FACC

University of Maryland School of Medicine, Baltimore, MD

Jack M. Guralnik, MD, PhD – Co-Principal Investigator of the LIFE Study

University of Pittsburgh, Pittsburgh, PA

Anne B. Newman, MD, MPH – Field Center Principal Investigator

Stephanie A. Studenski, MD, MPH – Field Center Co-Principal Investigator

Bret H. Goodpaster, PhD

Oscar Lopez, MD

Nancy W. Glynn, PhD

Janet T. Bonk, MPH, RN

Jennifer Rush, MPH

Piera Kost, BA

Allison Gerger, BS

Pamela Vincent, CMA

LaTisha Davis, BS

Mark A. Newman, PhD

George Grove, MS

Kathy Williams, RN, BSEd, MHSA

VA San Diego Healthcare System and University of California, San Diego, San Diego, CA

Erik J. Groessl, PhD

Wake Forest University, Winston-Salem, NC

Stephen B. Kritchevsky, PhD – Field Center Principal Investigator

Anthony Marsh, PhD – Field Center Co-Principal Investigator

Tina Brinkley, PhD

Jamehl Demons, MD

Kaycee Sink, MD, MAS

Kimberly Kennedy, BA, CCRC

Rachel Shertzer-Skinner, MA, CCRC

Abbie Wrights, MS

Rose Fries, RN, CCRC

Deborah Barr, MA, RHEd, CHES

Cognition Reading Center

Jeff Williamson, MD, MHS – Center Principal Investigator

Kaycee M Sink, MD, MAS – Center Co-Principal Investigator

Hugh C. Hendrie, MB, ChB, DSc (Indiana University)

Stephen R. Rapp, PhD

Joe Verghese, MBBS (Albert Einstein College of Medicine of Yeshiva University)

Nancy Woolard

Valerie K Wilson, MD

Data Management, Analysis and Quality Control Center (DMAQC)

Michael E. Miller, PhD – DMAQC Principal Investigator

Mark Espeland, PhD – DMAQC Co-Principal Investigator

Walter Ambrosius, PhD

Don Babcock, BSEE, PE

Daniel Beavers, PhD, MS

Robert P. Byington, PhD, MPH, FAHA

Delilah Cook

Curt Furberg, MD, PhD

Candace Goode

Jason Griffin, BS

Lea Harvin, BS

Leora Henkin, MPH, Med

John Hepler, BFA

Fang-Chi Hsu, PhD

Kathy Joyce

Laura Lovato, MS

Wesley Roberson, BSBA

Julia Robertson, BS

Julia Rushing, BSPH, MStat

Scott Rushing, BS

Cynthia L. Stowe, MPM

Michael P. Walkup, MS

Don Hire, BS

Jack Rejeski, PhD

Jeff Katula, PhD, MA

Peter H. Brubaker, PhD

Shannon Mihalko, PhD

Janine M. Jennings, PhD

Kathy Lane, BA

Yale University, New Haven, CT

Thomas M. Gill, MD – Field Center Principal Investigator

Robert S. Axtell, PhD, FACSM – Field Center Co-Principal Investigator (Southern Connecticut State University, Exercise Science Department)

Susan S. Kashaf, MD, (VA Connecticut Healthcare System)

Nathalie de Renekeire, MD

Joanne M. McGloin, MDiv, MS, MBA

Raeleen Mautner, PhD

Sharon M. Huie-White, MPH

Luann Bianco, BA

Janice Zocher

Denise M. Shepard, RN, MBA

Barbara Fennelly, MA, RN

Sean Halpin, MA

Theresa Barnett, MS, APRN

Karen C. Wu, RN

Lynne P. Iannone, MS

Julie A. Bugaj, MS

Christine Bailey, MA

Spirometry Reading Center

Geoffrey Chupp, MD

Gail Flynn, RCP, CRFT

Thomas M. Gill, MD

John Hankinson, PhD (Hankinson Consulting, Inc.)

Carlos A. Vaz Fragoso, MD

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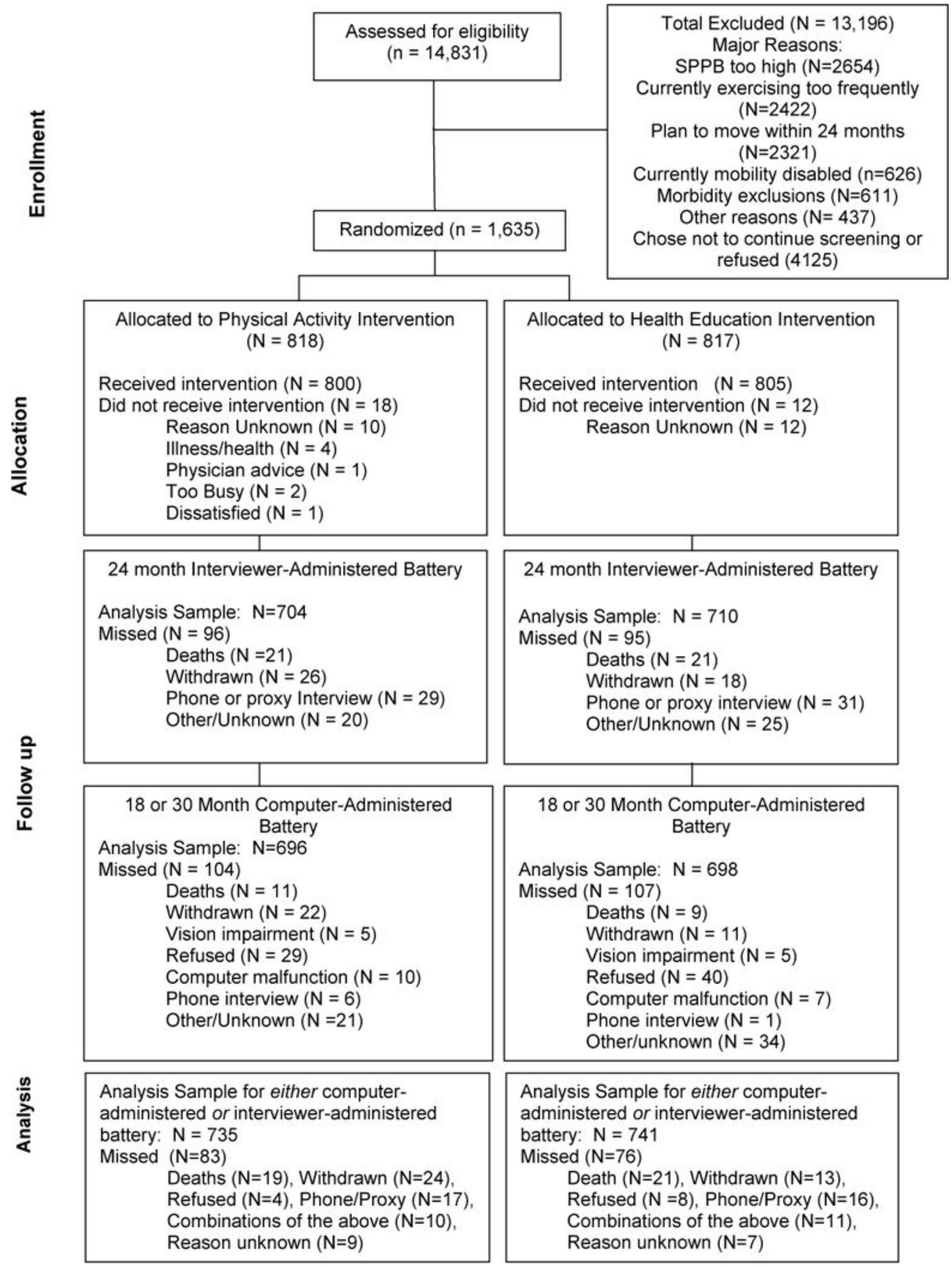
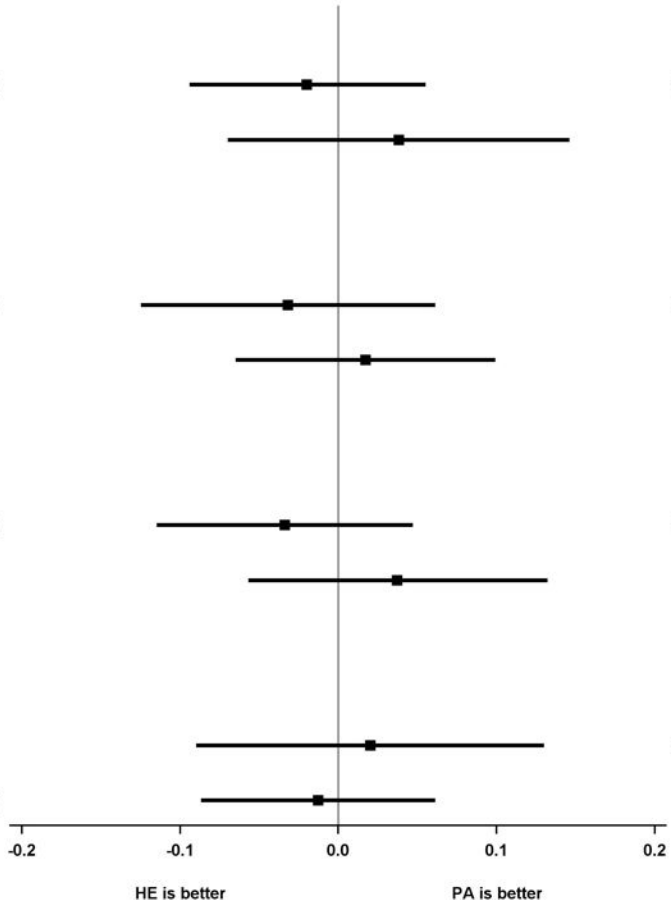


Figure 1.
Consort Diagram

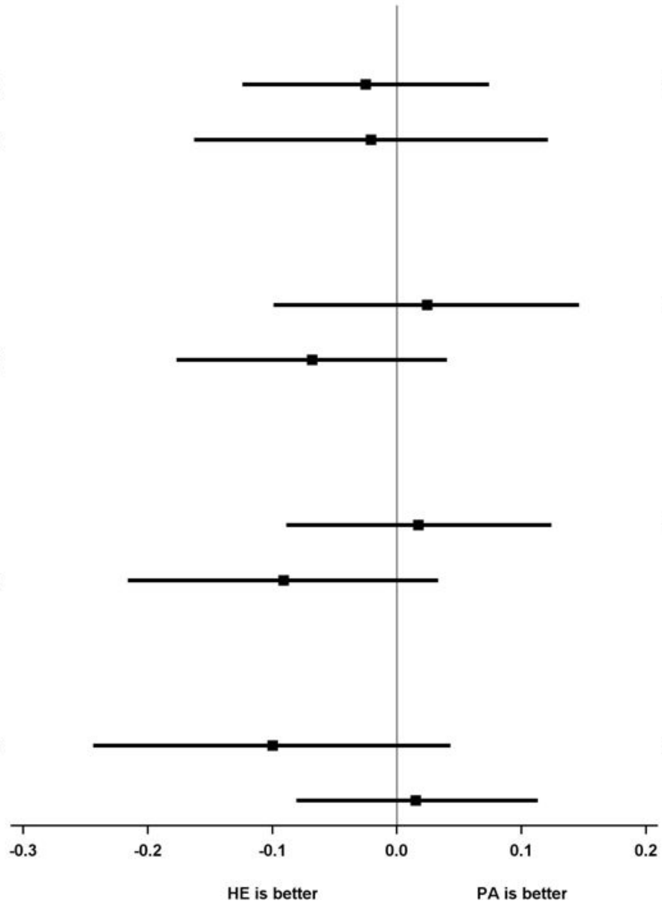
(a)

Subgroup	Physical Activity Mean (95% CI)	Health Education Mean (95% CI)	Intervention Effect Mean (95% CI)	p-value
Gender				
Female	0.004 (-0.050, 0.057)	0.024 (-0.029, 0.076)	-0.020 (-0.094, 0.055)	0.39
Male	-0.018 (-0.093, 0.058)	-0.055 (-0.133, 0.029)	0.038 (-0.070, 0.146)	
SPBB				
<8	-0.060 (-0.127, 0.008)	-0.027 (-0.091, 0.036)	-0.032 (-0.125, 0.061)	0.44
8-9	0.038 (-0.019, 0.095)	0.021 (-0.039, 0.080)	0.017 (-0.065, 0.099)	
Age, years				
70-79	0.013 (-0.044, 0.069)	0.047 (-0.011, 0.105)	-0.034 (-0.115, 0.047)	0.26
80-89	-0.026 (-0.095, 0.042)	-0.064 (-0.130, 0.002)	0.037 (-0.057, 0.132)	
3MSE				
<90	-0.054 (-0.134, 0.026)	-0.074 (-0.153, 0.005)	0.020 (-0.090, 0.130)	0.63
90-100	0.020 (-0.033, 0.073)	0.032 (-0.021, 0.086)	-0.013 (-0.087, 0.061)	



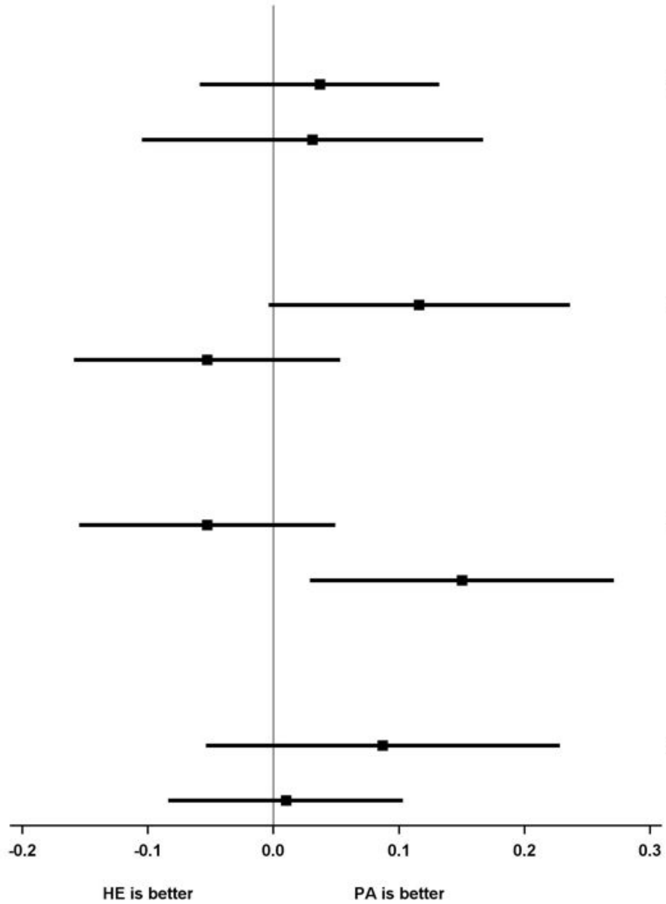
(b)

Subgroup	Physical Activity Mean (95% CI)	Health Education Mean (95% CI)	Intervention Effect Mean (95% CI)	p-value
Gender				
Female	-0.096 (-0.166, -0.025)	-0.070 (-0.140, -0.001)	-0.025 (-0.124, 0.074)	0.96
Male	-0.199 (-0.300, -0.099)	-0.178 (-0.281, -0.076)	-0.021 (-0.163, 0.121)	
SPBB				
<8	-0.158 (-0.247, -0.069)	-0.182 (-0.266, -0.097)	0.024 (-0.099, 0.146)	0.27
8-9	-0.109 (-0.184, -0.033)	-0.040 (-0.118, 0.037)	-0.068 (-0.177, 0.040)	
Age, years				
70-79	-0.044 (-0.119, 0.031)	-0.062 (-0.138, 0.015)	0.017 (-0.089, 0.124)	0.19
80-89	-0.253 (-0.343, -0.163)	-0.161 (-0.248, -0.075)	-0.091 (-0.216, 0.033)	
3MSE				
<90	-0.354 (-0.460, -0.248)	-0.254 (-0.361, -0.148)	-0.100 (-0.244, 0.043)	0.19
90-100	-0.023 (-0.094, 0.047)	-0.039 (-0.109, 0.031)	0.015 (-0.081, 0.113)	



(c)

Subgroup	Physical Activity Mean (95% CI)	Health Education Mean (95% CI)	Intervention Effect Mean (95% CI)	p-value
Gender				
Female	0.037 (-0.031, 0.106)	0.001 (-0.066, 0.068)	0.037 (-0.059, 0.132)	0.95
Male	-0.017 (-0.113, 0.080)	-0.048 (-0.145, 0.049)	0.031 (-0.105, 0.167)	
SPBB				
<8	0.026 (-0.061, 0.113)	-0.090 (-0.173, -0.007)	0.116 (-0.004, 0.236)	0.01
8-9	-0.023 (-0.098, 0.051)	0.030 (-0.046, 0.105)	-0.053 (-0.159, 0.053)	
Age, years				
70-79	0.020 (-0.051, 0.091)	0.073 (-0.000, 0.146)	-0.053 (-0.155, 0.049)	0.01
80-89	0.019 (-0.069, 0.107)	-0.131 (-0.215, -0.047)	0.150 (0.029, 0.271)	
3MSE				
<90	-0.059 (-0.164, 0.045)	-0.146 (-0.247, -0.045)	0.087 (-0.054, 0.228)	0.37
90-100	0.054 (-0.014, 0.120)	0.044 (-0.023, 0.111)	0.010 (-0.084, 0.103)	



(d)

Subgroup	Physical Activity Mean (95% CI)	Health Education Mean (95% CI)	Intervention Effect Mean (95% CI)	p-value
Gender				
Female	-0.027 (-0.084, 0.031)	-0.043 (-0.100, 0.014)	0.016 (-0.064, 0.097)	0.60
Male	-0.103 (-0.186, -0.020)	-0.157 (-0.240, -0.074)	0.054 (-0.063, 0171)	
SPBB				
<8	-0.049 (-0.122, 0.024)	-0.141 (-0.021, -0.072)	0.092 (-0.008, 0.193)	0.08
8-9	-0.054 (-0.116, 0.008)	-0.029 (-0.093, 0.035)	-0.026 (-0.114, 0.063)	
Age, years				
70-79	-0.018 (-0.079, 0.044)	-0.017 (-0.080, 0.047)	-0.001 (-0.089, 0.087)	0.37
80-89	-0.100 (-0.174, -0.027)	-0.160 (-0.231, -0.090)	0.060 (-0.041, 0.161)	
3MSE				
<90	-0.115 (-0.205, -0.025)	-0.132 (-0.219, -0.044)	0.017 (-0.102, 0.135)	0.83
90-100	-0.024 (-0.082, 0.035)	-0.056 (-0.114, 0.002)	0.032 (-0.048, 0.113)	

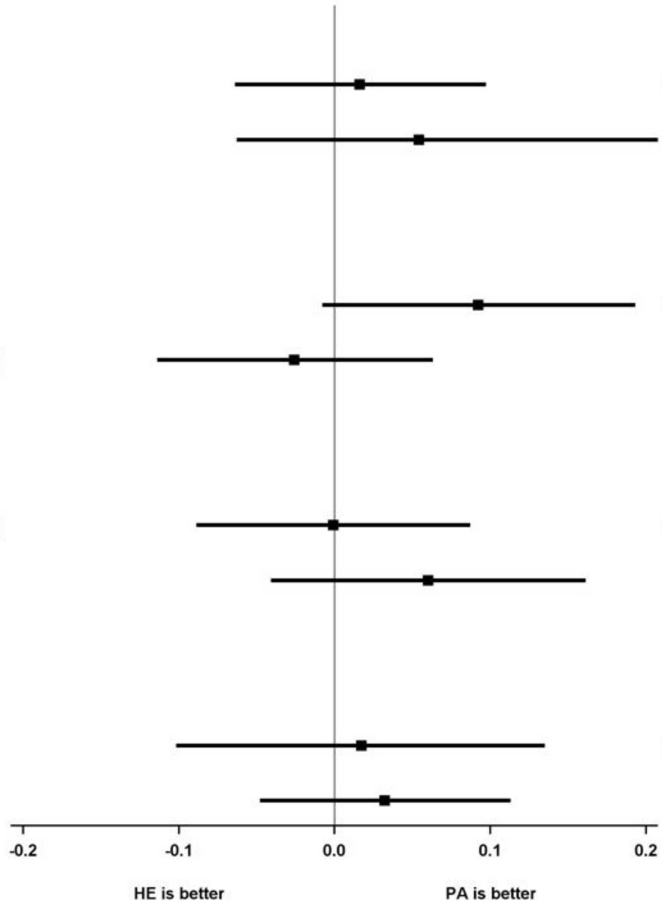


Figure 2.

a) Forest plot of intervention effects on Z-transformed Digit Symbol Coding

b) Forest plot of intervention effects on z-transformed Hopkins Verbal Learning Test

c) Forest plot of intervention effects on z-transformed executive function composite

d) Forest plot of intervention effects on z-transformed cognitive function composite

P values represent test of interaction in all plots

Table 1

Baseline characteristics: The Lifestyle Interventions and Independence of Elders (LIFE) Study.

	Physical Activity N=735	Health Education N=741
Age		
70–79 years	428 (58.2%)	413 (55.7%)
80–89 years	307 (41.8%)	328 (44.3%)
Women	496 (67.5%)	503 (67.9%)
Education, Miss=4		
High School or less	249 (33.9%)	237 (32.1%)
College or more	485 (66.1%)	501 (67.9%)
Race, Miss=4		
African-American	148 (20.2%)	112 (15.2%)
Non-Hispanic White	542 (73.9%)	580 (78.5%)
Other	43 (5.9%)	47 (6.4%)
SPPB score		
<8	309 (42.0%)	341 (46.0%)
8–9	426 (58.0%)	400 (54.0%)
400 m walking speed (m/sec)	0.83 (0.16)	0.82 (0.16)
Body mass index (kg/m^2)	30.2 (5.8)	30.2 (6.1)
Minutes/week walking and strength training	75.1 (125.6)	86.7 (134.4)
History of hypertension	552 (75.1%)	554 (74.8%)
Diabetes status		
None	366 (49.8%)	375 (50.6%)
Impaired fasting glucose	173 (23.5%)	154 (20.8%)
Diabetes	196 (26.7%)	212 (28.6%)
History of cardiovascular disease	210 (28.6%)	225 (30.4%)
History of stroke	53 (7.2%)	48 (6.5%)
ApoE-e4 allele		
0	525 (64.2%)	529 (64.8%)
1	146 (17.8%)	153 (18.7%)
2	10 (1.2%)	9 (1.1%)
Missing	137 (16.8%)	126 (15.4%)
3MSE (0–100)	91.61 (5.54)	91.71 (5.28)
% with score <90	230 (31.3%)	236 (31.8%)
DSC score (0–133)	45.99 (13.04)	47.01 (12.72)

	Physical Activity N=735	Health Education N=741
HVLT-R, number correct		
Sum of 3 Immediate recall trials (0–36)	23.44 (5.12)	23.18 (5.44)
Delayed recall (0–12)	7.79 (2.73)	7.70 (2.92)
N-back, % correct (0–100)		
1-back	81.58 (17.85)	82.11 (16.30)
2-back	51.04 (19.84)	50.68 (21.47)
Task Switching, reaction time (seconds)		
No switch	1.46 (0.73)	1.41 (0.69)
Switch	2.44 (1.04)	2.35 (1.01)
Flanker, reaction time (seconds)		
Congruent	0.65 (0.19)	0.65 (0.20)
Incongruent	0.72 (0.22)	0.73 (0.24)

Data are N (%) or means (standard deviations); SPPB = Short Physical Performance Battery; 3MSE= Modified Mini-Mental State Examination (higher scores indicate better performance); DSC = Digit Symbol Coding (higher scores indicate better performance); HVLT-R = Hopkins Verbal Learning Test-Revised (higher scores indicate better performance); for task switching and flanker reaction times, larger values indicate slower (worse) performance.

Table 2

Mean (95% Confidence Interval) adjusted raw and z-transformed follow-up cognitive function scores by intervention assignment: The LIFE Study

	Physical Activity Mean [95% CI] N=735	Health Education Mean [95% CI] N=741	Mean Difference [95% CI]	p-value
DSC				
Raw	46.26 [45.75 to 46.82]	46.28 [45.72 to 46.83]	−0.01 [−0.80 to 0.77]	0.97
z-score	−0.003 [−0.046 to 0.040]	−0.002 [−0.045 to 0.041]	−0.001 [−0.063 to 0.060]	
HVLT-R				
Immediate				
Raw	22.83 [22.52 to 23.14]	22.97 [22.67 to 23.28]	−0.14 [−0.58 to 0.29]	0.52
z-score	−0.073 [−0.132 to −0.014]	−0.046 [−0.105 to 0.013]	−0.027 [−0.110 to 0.055]	
Delayed				
Raw	7.22 [7.03 to 7.41]	7.25 [7.06 to 7.44]	−0.03 [−0.29 to 0.24]	0.84
z-score	−0.167 [−0.234 to −0.100]	−0.157 [−0.224 to −0.090]	−0.010 [−0.103 to 0.084]	
HVLT-R Composite z-score	−0.130 [−0.187 to −0.073]	−0.106 [−0.163 to −0.049]	−0.024 [−0.105 to 0.057]	0.56
Executive Function N-back				
1-back, % correct	83.7 [82.5 to 84.9]	82.9 [81.8 to 84.1]	0.7 [−0.9 to 2.4]	0.39
2-back, % correct	53.2 [51.6 to 54.8]	51.9 [50.4 to 53.5]	1.3 [−0.9 to 3.5]	0.26
Task Switching reaction time				
no switch, seconds	1.47 [1.42 to 1.51]	1.46 [1.42 to 1.51]	0.01 [−0.06 to 0.07]	0.86
switch, seconds	2.43 [2.37 to 2.49]	2.39 [2.33 to 2.45]	0.04 [−0.05 to 0.13]	0.37
Flanker reaction time				
Congruent, seconds	0.65 [0.64 to 0.67]	0.67 [0.66 to 0.68]	−0.02 [−0.03 to −0.01]	0.04
Incongruent, seconds	0.73 [0.72 to 0.74]	0.75 [0.73 to 0.76]	−0.02 [−0.04 to 0.00]	0.07
Composite z-score	−0.003 [−0.060 to 0.054]	−0.025 [−0.080 to 0.030]	0.022 [−0.057 to 0.101]	0.59
Overall Composite z-score	−0.052 [−0.099 to −0.005]	−0.081 −0.128 to −0.034]	0.029 [−0.038 to 0.095]	0.40

DSC = Digit Symbol Coding; HVLT-R = Hopkins Verbal Learning Test-Revised

Covariate adjustment for sex, clinic site, and baseline value

Composite scores are ordered so that positive values reflect better performance on tasks

Executive function composite: n-back, task switching, and flanker tasks

Overall composite includes: DSC, HVLT-R immediate and delayed recall, n-back, task switching and flanker tasks

Table 3

Incident mild cognitive impairment (MCI) or dementia at 24 months by intervention assignment: The LIFE Study

	Physical Activity	Health Education	OR [95% CI][a]	p-value
MCI[b]	70/686 (10.2%)	62/682 (9.1%)	1.14 [0.79 to 1.62]	0.48
Dementia[c]	28/743 (3.8%)	29/747 (3.9%)	0.96 [0.57 to1.63]	0.88
MCI or Dementia	98/743 (13.2%)	91/747 (12.1%)	1.08 [0.80 to 1.46]	0.61

[a] Odds ratio from unadjusted logistic regression;

[b] Of those free of MCI or dementia at baseline;

[c] Of those free of dementia at baseline; Denominators are slightly larger than in table 1 because some participants were adjudicated, but did not get cognitive testing at 24 months (deaths, for example).