Original Investigation

Effect of a 24-Month Physical Activity Intervention vs Health Education on Cognitive Outcomes in Sedentary Older Adults
The LIFE Randomized Trial

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IMPORTANCE Epidemiological 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, lower risk of mild cognitive impairment (MCI) or dementia, or both, compared with a health education program.

DESIGN, SETTING, AND PARTICIPANTS A randomized clinical trial, the Lifestyle Interventions and Independence for Elders (LIFE) study, enrolled 1635 community-living participants at 8 US centers from February 2010 until December 2011. Participants were sedentary adults aged 70 to 89 years who were at risk for mobility disability but able to walk 400 m.

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

MAIN OUTCOMES AND MEASURES Prespecified secondary outcomes of the LIFE study included cognitive function measured by the Digit Symbol Coding (DSC) task subtest of the Wechsler Adult Intelligence Scale (score range: 0-133; higher scores indicate better function) and the revised Hopkins Verbal Learning Test (HVLT-R; 12-item word list recall task) assessed in 1476 participants (90.3%). Tertiary outcomes included global and executive cognitive function and incident MCI or dementia at 24 months.

RESULTS At 24 months, DSC task and HVLT-R scores (adjusted for clinic site, sex, and baseline values) were not different between groups. The mean DSC task scores were 46.26 points for the physical activity group vs 46.28 for the health education group (mean difference, −0.01 points [95% CI, −0.80 to 0.77 points], *P* = .97). The mean HVLT-R delayed recall scores were 7.22 for the physical activity group vs 7.25 for the health education group (mean difference, −0.03 words [95% CI, −0.29 to 0.24 words], *P* = .84). No differences for any other cognitive or composite measures were observed. Participants in the physical activity group who were 80 years or older (n = 307) and those with poorer baseline physical performance (n = 328) had better changes in executive function composite scores compared with the health education group (*P* = .01 for interaction for both comparisons). Incident MCI or dementia occurred in 98 participants (13.2%) in the physical activity group and 91 participants (12.1%) in the health education group (odds ratio, 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 with a health education program did not result in improvements in global or domain-specific cognitive function.

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Epidemiological evidence suggests that 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 mouse models, exercise reduces β-amyloid deposition.[6]

Randomized clinical trials (RCTs) 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 intensity of physical activity.[7] Two small RCTs of physical activity[10,11] found no benefit from a structured physical activity program vs no intervention or cognitive training in older adults without dementia, but with cognitive complaints or at risk for cognitive decline. However, a 6-month RCT of a home-based physical activity program vs usual care in participants with memory complaints or mild cognitive impairment (MCI) found a modest cognitive benefit.[12] The Lifestyle Interventions and Independence for Elders (LIFE) pilot study showed a correlation between changes in physical and cognitive performance during a 12-month exercise intervention.[13]

We report the prespecified 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 impairment in sedentary older adults at risk for mobility disability.[14] We hypothesized that compared with health education, physical activity for 24 months would result in better cognitive function and lower risk of incident all-cause MCI or dementia.

Methods

Trial Design and Participants

The LIFE study was a single-blinded RCT of a physical activity intervention compared with a health education control conducted at 8 US field centers; participants were from rural and urban communities. Details of the LIFE study design and results have been published[14,15] and the trial protocol appears in the Supplement. The study included sedentary men and women aged 70 to 89 years who were at high risk for mobility disability based on objectively assessed lower-extremity functional limitations defined by a Short Physical Performance Battery[16] score of 9 or less (of 12 points), but who could walk 400 m (without assistance) within 15 minutes at baseline.

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 less than 9 years of education were excluded if the screening 3MSE score was less than 70 for black individuals and native Spanish speakers or less than 76 for English-speaking nonblack individuals. Participants with 9 or more years of education were excluded if their 3MSE score was less than 76 for black individuals and less than 80 for native Spanish speakers and English-speaking nonblack individuals. Race/ethnicity was 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 8 sites and monitored by a data and 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 2 center-based visits per week and perform home-based activity 3 to 4 times per week. The physical activity sessions progressed toward a goal of 30 minutes of walking at moderate intensity, 10 minutes of primarily lower-extremity strength training with ankle weights, and 10 minutes 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 to 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 and financial issues, and nutrition. The intervention committee ensured that health education activities were consistent across sites and unlikely to increase physical activity.

Measurements

Assessments were conducted every 6 months in person by staff masked to treatment group assignment. 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 Community Healthy Activities Model Program for Seniors questionnaire[19] to measure total weekly minutes of walking and performing strength training exercises and objectively using an Actigraph accelerometer to measure total minutes of at least moderate activity (>760 counts/min) over 7 days.[14]

Cognitive Assessment

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

Neuropsychological Battery

Cognitive tests at baseline included (1) the 3MSE,[17] which is a 100-point test of global cognitive function, (2) the Digit Symbol Coding (DSC) task subtest of the Wechsler Adult Intelligence Scale Third Edition,[21] which is a test of psychomotor speed, attention, and working memory, (3) the revised Hopkins Verbal Learning Test (HVLT-R),[22] which is a 12-item word list learning and recall task, and (4) a modified version of the Rey-Osterrieth Complex Figure, which assesses visuospatial function (copy) and figural memory (immediate recall). At 24 months, these measures were repeated along with (1) the Boston Naming Test, which is a measure of language,[23] (2) the Trail Making Test[24] part A, which is a measure of attention, concentration, and psychomotor speed, and part B, which is a measure of executive function, and (3) the category fluency test for animals, which is a measure of executive function. In all tests, except parts A and B of the Trail Making Test, 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 task,[25] the Eriksen Flanker task,[26] and a task switching exercise.[27]

Outcome Determinations for MCI and Dementia

At baseline and 24 months after randomization, all participants were assigned 1 of the following cognitive classifications: no cognitive impairment, MCI, or dementia. Participants who scored 88 points or less on the 3MSE were sent for central adjudication by a panel (blinded to treatment assignment) of 8 clinical experts in the diagnosis of late-life cognitive impairment.[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 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. For all those who had a 3MSE score of 88 or less, the FAQ was administered either at baseline or at 24 months, or both, to the participant's proxy. Based on 2011 criteria from the National Institute on Aging and the Alzheimer's Association,[30,31] MCI and dementia were adjudicated.

Statistical Analyses

The LIFE protocol specified DSC (total score) and HVLT-R (immediate and delayed recall subscales mean) as the 2 primary cognitive outcomes for assessing cognitive decline. Outcomes were tested according to the intention-to-treat principle with analysis of covariance using 24-month data and covariate adjustment for field center, sex, and the baseline value. Additional prespecified 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 first percentile of the cohortwide distribution with the value of the first percentile and replacing scores greater than the 99th percentile with the 99th percentile value. The *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 2 individual components. The global cognitive function score was the average of scores from these composites and the *z*-transformed DSC, renormalized to have a mean of 0 and an SD of 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 (ie, missing data if participants did not complete the full battery were ignored). Supporting analyses were conducted using multiple imputation for which missing measures and examination scores were imputed to create 5 databases that were analyzed in parallel.[32]

Subgroup comparisons using interaction terms were prespecified for sex and baseline Short Physical Performance Battery score (<8 vs ≥8), 3MSE score (<90 vs ≥90), and age (70-79 years vs ≥80 years). Associations between changes in cognitive function and changes in objective and subjective physical activity level were assessed using linear regression and tests of interactions.

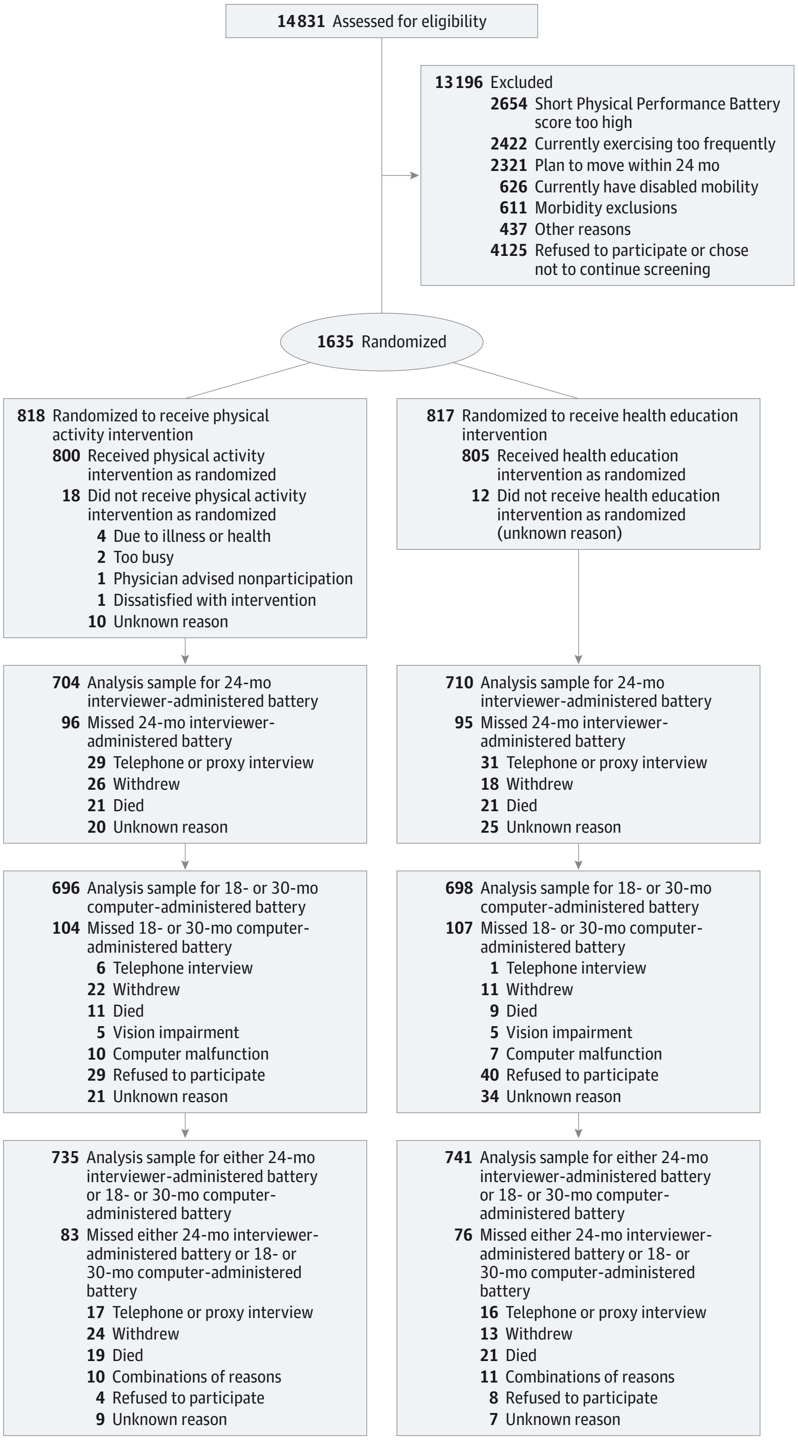
Progression in cognitive impairment (ie, from baseline normal cognitive function to either MCI or dementia or from baseline MCI to dementia) was a tertiary outcome. Logistic regression was used to compare progression rates between intervention groups. Participants with prevalent MCI (n = 141) at baseline 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 (despite otherwise meeting LIFE study entry criteria). These participants were excluded from the incident dementia outcome analysis.

Statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc). Two-sided inferences with $P < .05$ were considered statistically significant. The targeted sample size of 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-R immediate memory scores.

Results

From February 2010 until December 2011, 1635 participants were randomized (818 to physical activity group and 817 to health education group; **Figure 1**). Analyses are limited to 1476 participants (90.3%) with cognitive data during follow-up. Compared with participants without cognitive follow-up data, the participants included in the analyses had faster gait speeds

Figure 1. Flow of Participants in the Lifestyle Interventions and Independence for Elders (LIFE) Study



($P < .001$). The 24-month retention rates were 89.8% for the physical activity group and 90.7% for the health education group ($P = .56$).

Characteristics of the participants appear in **Table 1**. The mean (SD) age was 78.9 (5.2) years, 68% were women, and 67% had a college education. The mean (SD) 3MSE score was 91.7 (5.4) (range, 71-100). There were more black participants in the physical activity group vs the health education group.

Intervention Adherence

Based on accelerometry data, the physical activity group maintained moderate to vigorous physical activity levels between

Table 1. Baseline Characteristics of Participants in the Lifestyle Interventions and Independence for Elders (LIFE) Study[a]

	Physical Activity (n = 735)	Health Education (n = 741)
Age group, y		
70-79	428 (58.2)	413 (55.7)
80-89	307 (41.8)	328 (44.3)
Women	496 (67.5)	503 (67.9)
Education[b]		
≤High school	249 (33.9)	237 (32.1)
≥College	485 (66.1)	501 (67.9)
Race[b]		
Black	148 (20.2)	112 (15.2)
Non-Hispanic white	542 (73.9)	580 (78.5)
Other[c]	43 (5.9)	47 (6.4)
Short Physical Performance Battery score[d]		
<8	309 (42.0)	341 (46.0)
8-9	426 (58.0)	400 (54.0)
400-m walking speed, mean (SD), m/s	0.83 (0.16)	0.82 (0.16)
Body mass index, mean (SD)[e]	30.2 (5.8)	30.2 (6.1)
Walking and strength training, mean (SD), min/wk	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)
Apolipoprotein E ε4 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)
Modified Mini-Mental State Examination score, mean (SD)[f]	91.61 (5.54)	91.71 (5.28)
Score <90	230 (31.3)	236 (31.8)
Digit Symbol Coding task score, mean (SD)[g]	45.99 (13.04)	47.01 (12.72)
No. correct on revised Hopkins Verbal Learning Test, mean (SD)		
Sum of 3 immediate word recall trials[h]	23.44 (5.12)	23.18 (5.44)
Delayed word recall[i]	7.79 (2.73)	7.70 (2.92)
Percentage correct on n-back task, mean (SD)[j]		
1-back	81.58 (17.85)	82.11 (16.30)
2-back	51.04 (19.84)	50.68 (21.47)
Reaction time on task switching, mean (SD), s[k]		
No switch	1.46 (0.73)	1.41 (0.69)
Switch	2.44 (1.04)	2.35 (1.01)
Reaction time on Eriksen Flanker task, mean (SD), s[k]		
Congruent	0.65 (0.19)	0.65 (0.20)
Incongruent	0.72 (0.22)	0.73 (0.24)

[a] Data are expressed as No. (%) unless otherwise indicated.

[b] Missing data for 4 participants.

[c] Included participants who self-identified as Asian, Native American, Alaskan Native, Pacific Islander, Hispanic white, other, or who refused to respond.

[d] Score range: 0-12 (higher scores indicate better performance).

[e] Calculated as weight in kilograms divided by height in meters squared.

[f] Score range: 0-100 (higher scores indicate better performance).

[g] Score range: 0-133 (higher scores indicate better performance).

[h] Score range: 0-36 (higher scores indicate better performance).

[i] Score range: 0-12 (higher scores indicate better performance).

[j] Score range: 0-100 (higher scores indicate better performance).

[k] Higher values indicate slower (worse) performance.

baseline and 24-month follow-up (mean difference, −2.1 min/wk [95% CI, −9.7 to 13.9 min/wk]) compared with the health education group (mean difference, −40.4 min/wk [95% CI, −29.4 to −51.4 min/wk]; $P < .001$). Based on data from the Community Healthy Activities Model Program for Seniors questionnaire, the physical activity group had a greater increase in self-reported physical activity level from baseline to 24 months (mean difference, 130.4 min/wk [95% CI, 116.7 to 144.1 min/wk]) compared with the health education group (mean difference, 30.5 min/wk [95% CI, 18.9 to 42.1 min/wk]; $P < .001$). The median attendance at physical activity sessions was 71%, excluding medical leave.

Table 2. Adjusted Raw and *z*-Transformed Follow-up Cognitive Function Scores

	Mean (95% CI)			
	Physical Activity (n = 735)[a]	Health Education (n = 741)[a]	Difference Between Groups	*P* Value
Digit Symbol Coding task				
Raw score	46.26 (45.75 to 46.82)	46.28 (45.72 to 46.83)	−0.01 (−0.80 to 0.77)	.97
z Score	−0.003 (−0.046 to 0.040)	−0.002 (−0.045 to 0.041)	−0.001 (−0.063 to 0.060)	
Revised Hopkins Verbal Learning Test				
Immediate word recall				
Raw score	22.83 (22.52 to 23.14)	22.97 (22.67 to 23.28)	−0.14 (−0.58 to 0.29)	.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 word recall				
Raw score	7.22 (7.03 to 7.41)	7.25 (7.06 to 7.44)	−0.03 (−0.29 to 0.24)	.84
z Score	−0.167 (−0.234 to −0.100)	−0.157 (−0.224 to −0.090)	−0.010 (−0.103 to 0.084)	
Composite *z* score[b]	−0.130 (−0.187 to −0.073)	−0.106 (−0.163 to −0.049)	−0.024 (−0.105 to 0.057)	.56
Executive function				
Percentage correct on n-back task				
1-back	83.7 (82.5 to 84.9)	82.9 (81.8 to 84.1)	0.7 (−0.9 to 2.4)	.39
2-back	53.2 (51.6 to 54.8)	51.9 (50.4 to 53.5)	1.3 (−0.9 to 3.5)	.26
Reaction time on task switching, s				
No	1.47 (1.42 to 1.51)	1.46 (1.42 to 1.51)	0.01 (−0.06 to 0.07)	.86
Yes	2.43 (2.37 to 2.49)	2.39 (2.33 to 2.45)	0.04 (−0.05 to 0.13)	.37
Reaction time on Flanker task, s				
Congruent	0.65 (0.64 to 0.67)	0.67 (0.66 to 0.68)	−0.02 (−0.03 to −0.01)	.04
Incongruent	0.73 (0.72 to 0.74)	0.75 (0.73 to 0.76)	−0.02 (−0.04 to 0)	.07
Composite *z* score[b]	−0.003 (−0.060 to 0.054)	−0.025 (−0.080 to 0.030)	0.022 (−0.057 to 0.101)	.59
Mean global composite *z* score[b,c]	−0.052 (−0.099 to −0.005)	−0.081 (−0.128 to −0.034)	0.029 (−0.038 to 0.095)	.40

[a] Adjusted for sex, clinic site, and baseline values.

[b] Ordered so that positive values reflect better performance on tasks.

[c] Includes Digit Symbol Coding task, revised Hopkins Verbal Learning Test immediate and delayed recall, n-back task, and reaction time on task switching and Flanker tasks.

Cognitive Function Results

At baseline, interviewer-administered cognitive assessments were collected on all participants. Computer-based assessments were collected on 85.5% (2-back task) to 96.2% (Flanker task) 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, sex, and baseline values. The *z* scores are interpreted as the change from baseline in standard deviations. The adjusted mean raw DSC task scores (score range, 0-133) at follow-up were not different between the 2 groups (46.26 points [95% CI, 45.75 to 46.82 points] in the physical activity group vs 46.28 points [95% CI, 45.72 to 46.83 points] in the health education group; mean difference, −0.01 points [95% CI, −0.80 to 0.77 points]; *P* = .97). Similarly, the adjusted scores for mean HVLT-R delayed word recall (score range, 0-12) were not different between groups (7.22 words [95% CI, 7.03 to 7.41 words] for the physical activity group vs 7.25 words [95% CI, 7.06 to 7.44 words] for the health education group; mean difference, −0.03 words [95% CI, −0.29 to 0.24 words]; *P* = .84). There were no between-group differences in the executive function composite *z* score (*P* = .59) or the mean global composite *z* score (*P* = .40). Additional adjustment for race/ethnicity and education did not change the results.

The results of prespecified subgroup comparisons appear in **Figure 2**. Intervention effects did not vary by sex or baseline 3MSE score. However, for participants with a baseline Short Physical Performance Battery score of less than 8 or age of 80 years or older, there was heterogeneity in the intervention effects for the executive function composite, suggesting benefit in executive function associated with physical activity (*P* = .01 for interaction).

Relationships With Changes in Physical Activity

The 24-month changes in the 4 cognitive function measures were not correlated with changes in moderate physical activity as measured by accelerometry (*P* > .30) among the 697 participants with 24-month data. The 24-month changes in weekly walking and strength training from the Community Healthy Activities Model Program for Seniors questionnaire were modestly associated with global cognitive function (*r* = 0.07; *P* = .006) and executive function (*r* = 0.06; *P* = .04). These relationships were not different between the 2 groups (*P* > .70 for interaction). Results were unchanged when using 12-month change in level of physical activity.

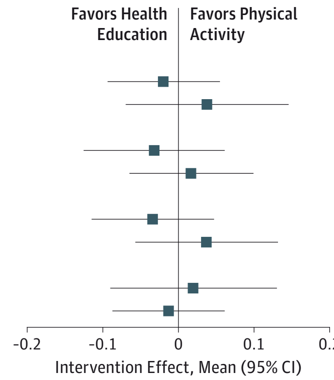
Incident MCI or Dementia

There was no significant difference between groups in the incidence of MCI, dementia, or both combined; 13.2% of the physical

Figure 2. Intervention Effects on *z*-Transformed Scores From 4 Assessment Tools

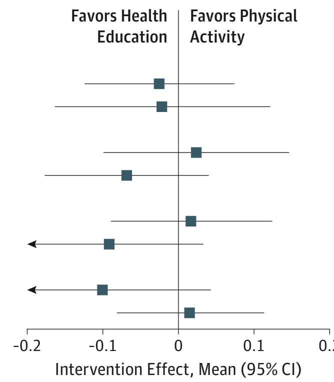
A Digit Symbol Coding task

	Mean *z*-Transformed Score (95% CI) Physical Activity	Mean *z*-Transformed Score (95% CI) Health Education	Intervention Effect, Mean (95% CI)	*P* Value for Interaction
Sex				
Female	0.004 (-0.050 to 0.057)	0.024 (-0.029 to 0.076)	-0.020 (-0.094 to 0.055)	.39
Male	-0.018 (-0.093 to 0.058)	-0.055 (-0.133 to 0.029)	0.038 (-0.070 to 0.146)	
Short Physical Performance Battery score				
<8	-0.060 (-0.127 to 0.008)	-0.027 (-0.091 to 0.036)	-0.032 (-0.125 to 0.061)	.44
8-9	0.038 (-0.019 to 0.095)	0.021 (-0.039 to 0.080)	0.017 (-0.065 to 0.099)	
Age group, y				
70-79	0.013 (-0.044 to 0.069)	0.047 (-0.011 to 0.105)	-0.034 (-0.115 to 0.047)	.26
80-89	-0.026 (-0.095 to 0.042)	-0.064 (-0.130 to 0.002)	0.037 (-0.057 to 0.132)	
Modified Mini-Mental State Examination score				
<90	-0.054 (-0.134 to 0.026)	-0.074 (-0.153 to 0.005)	0.020 (-0.090 to 0.130)	.63
90-100	0.020 (-0.033 to 0.073)	0.032 (-0.021 to 0.086)	-0.013 (-0.087 to 0.061)	



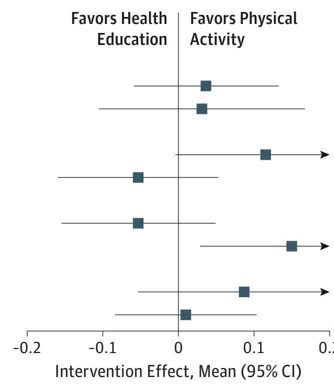
B Revised Hopkins Verbal Learning Test

	Mean *z*-Transformed Score (95% CI) Physical Activity	Mean *z*-Transformed Score (95% CI) Health Education	Intervention Effect, Mean (95% CI)	*P* Value for Interaction
Sex				
Female	-0.096 (-0.166 to -0.025)	-0.070 (-0.140 to -0.001)	-0.025 (-0.124 to 0.074)	.96
Male	-0.199 (-0.300 to -0.099)	-0.178 (-0.281 to -0.076)	-0.021 (-0.163 to 0.121)	
Short Physical Performance Battery score				
<8	-0.158 (-0.247 to -0.069)	-0.182 (-0.266 to -0.097)	0.024 (-0.099 to 0.146)	.27
8-9	-0.109 (-0.184 to -0.033)	-0.040 (-0.118 to 0.037)	-0.068 (-0.177 to 0.040)	
Age group, y				
70-79	-0.044 (-0.119 to 0.031)	-0.062 (-0.138 to 0.015)	0.017 (-0.089 to 0.124)	.19
80-89	-0.253 (-0.343 to -0.163)	-0.161 (-0.248 to -0.075)	-0.091 (-0.216 to 0.033)	
Modified Mini-Mental State Examination score				
<90	-0.354 (-0.460 to -0.248)	-0.254 (-0.361 to -0.148)	-0.100 (-0.244 to 0.043)	.19
90-100	-0.023 (-0.094 to 0.047)	-0.039 (-0.109 to 0.031)	0.015 (-0.081 to 0.113)	



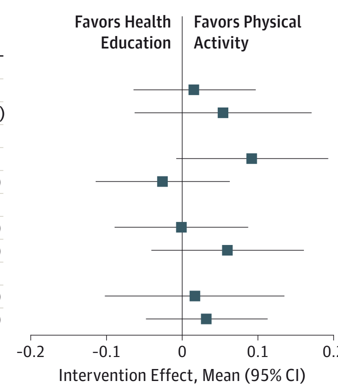
C Executive function composite

	Mean *z*-Transformed Score (95% CI) Physical Activity	Mean *z*-Transformed Score (95% CI) Health Education	Intervention Effect, Mean (95% CI)	*P* Value for Interaction
Sex				
Female	0.037 (-0.031 to 0.106)	0.001 (-0.066 to 0.068)	0.037 (-0.059 to 0.132)	.95
Male	-0.017 (-0.113 to 0.080)	-0.048 (-0.145 to 0.049)	0.031 (-0.105 to 0.167)	
Short Physical Performance Battery score				
<8	0.026 (-0.061 to 0.113)	-0.090 (-0.173 to -0.007)	0.116 (-0.004 to 0.236)	.01
8-9	-0.023 (-0.098 to 0.051)	0.030 (-0.046 to 0.105)	-0.053 (-0.159 to 0.053)	
Age group, y				
70-79	0.020 (-0.051 to 0.091)	0.073 (-0.000 to 0.146)	-0.053 (-0.155 to 0.049)	.01
80-89	0.019 (-0.069 to 0.107)	-0.131 (-0.215 to -0.047)	0.150 (0.029 to 0.271)	
Modified Mini-Mental State Examination score				
<90	-0.059 (-0.164 to 0.045)	-0.146 (-0.247 to -0.045)	0.087 (-0.054 to 0.228)	.37
90-100	0.054 (-0.014 to 0.120)	0.044 (-0.023 to 0.111)	0.010 (-0.084 to 0.103)	



D Global cognitive function composite

	Mean *z*-Transformed Score (95% CI) Physical Activity	Mean *z*-Transformed Score (95% CI) Health Education	Intervention Effect, Mean (95% CI)	*P* Value for Interaction
Sex				
Female	-0.027 (-0.084 to 0.031)	-0.043 (-0.100 to 0.014)	0.016 (-0.064 to 0.097)	.60
Male	-0.103 (-0.186 to -0.020)	-0.157 (-0.240 to -0.074)	0.054 (-0.063 to 0.171)	
Short Physical Performance Battery score				
<8	-0.049 (-0.122 to 0.024)	-0.141 (-0.021 to -0.072)	0.092 (-0.008 to 0.193)	.08
8-9	-0.054 (-0.116 to 0.008)	-0.029 (-0.093 to 0.035)	-0.026 (-0.114 to 0.063)	
Age group, y				
70-79	-0.018 (-0.079 to 0.044)	-0.017 (-0.080 to 0.047)	-0.001 (-0.089 to 0.087)	.37
80-89	-0.100 (-0.174 to -0.027)	-0.160 (-0.231 to -0.090)	0.060 (-0.041 to 0.161)	
Modified Mini-Mental State Examination score				
<90	-0.115 (-0.205 to -0.025)	-0.132 (-0.219 to -0.044)	0.017 (-0.102 to 0.135)	.83
90-100	-0.024 (-0.082 to 0.035)	-0.056 (-0.114 to 0.002)	0.032 (-0.048 to 0.113)	



activity group developed MCI or dementia by 24 months compared with 12.1% of the health education group (unadjusted odds ratio, 1.08 [95% CI, 0.80-1.46]; *P* = .61; **Table 3**). There were no between-group differences within MCI subtypes (incident am-

Table 3. Incident Mild Cognitive Impairment or Dementia at 24 Months

	No./Total (%)		Odds Ratio (95% CI)[a]	*P* Value
	Physical Activity	Health Education		
Mild cognitive impairment[b]	70/686 (10.2)	62/682 (9.1)	1.14 (0.79-1.62)	.48
Dementia[c]	28/743 (3.8)[d]	29/747 (3.9)[d]	0.96 (0.57-1.63)	.88
Mild cognitive impairment or dementia	98/743 (13.2)[d]	91/747 (12.1)[d]	1.08 (0.80-1.46)	.61

[a] From unadjusted logistic regression.

[b] Of those free of mild cognitive impairment or dementia at baseline.

[c] Of those free of dementia at baseline.

[d] Denominator is slightly larger than in Table 1 because some participants were adjudicated but did not receive cognitive testing at 24 months (eg, those who died).

nestic MCI was 5.5% for the physical activity group vs 5.7% for the health education group [*P* = .85] and nonamnestic MCI was 4.6% and 3.2%, respectively [*P* = .16]).

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, although this was an exploratory outcome with limited statistical power. However, participants in the physical activity group who were 80 years or older and those with lower baseline physical functioning levels experienced benefits in executive functioning compared with participants in 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 epidemiological evidence supporting the benefits of exercise and physical activity on cognition, the results of the LIFE study are consistent with some other randomized trials.[7] In the Mental Activity and eXercise 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 Action for Health in Diabetes trial[33] found no benefit of diet plus physical activity on cognitive function over 8 years. 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 multifactorial intervention.

Possible explanations for the lack of cognitive benefit of the physical activity intervention include (1) the assigned level of physical activity may have been insufficient to produce changes in the cognitive measures despite its effect on physical function[14]; (2) improvements in cognitive function in some shorter clinical trials, including the LIFE pilot study,[13] may dissipate by 24 months and thus may have been missed, especially if adherence to the physical activity intervention wanes over time[14]; (3) the study population was not specifically selected for cognitive vulnerability, although poor physical function, especially gait speed, has been shown to be a risk for cognitive decline[35,36]; (4) the participants were well educated (>two-thirds went to college), and high cognitive reserve may have protected against cognitive decline over 2 years[37]; and (5) the health education intervention may have benefited cognition.[10,38] The health education group attended interactive seminars providing both cognitive and social stimulation. Both cognitive and social stimulation have been shown to preserve cognition in older adults.[10,38]

The dose-response relationship between physical activity and cognition is not well understood.[7,39] The 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. Impaired lower-extremity functioning and the high prevalence of comorbidities may have limited participants' ability to exercise at sustained levels sufficient to improve cognition. Nonetheless, the physical activity group had significantly greater physical activity levels than the health education group, 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 prespecified subgroup analyses of participants aged 80 years or older 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 it is required for independence in instrumental activities of daily living. Future physical activity interventions, particularly in vulnerable older adult groups (eg, ≥80 years of age and those with especially diminished physical functioning levels), may be warranted.

To our knowledge, the LIFE study is the largest, longest RCT 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, even though cognitive function and incident MCI and dementia were a priori outcomes for the LIFE study, our 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. Although the physical activity intervention was sufficient to increase physical activity level 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 β-amyloid levels.

Conclusions

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

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