Original Investigation

Effect of Structured Physical Activity on Prevention of Major Mobility Disability in Older Adults
The LIFE Study Randomized Clinical Trial

Marco Pahor, MD; Jack M. Guralnik, MD, PHD; Walter T. Ambrosius, PhD; Steven Blair, PED; Denise E. Bonds, MD; Timothy S. Church, MD, PhD, MPH; Mark A. Espeland, PhD; Roger A. Fielding, PhD; Thomas M. Gill, MD; Erik J. Groessl, PhD; Abby C. King, PhD; Stephen B. Kritchevsky, PhD; Todd M. Manini, PhD; Mary M. McDermott, MD; Michael E. Miller, PhD; Anne B. Newman, MD, MPH; W. Jack Rejeski, PhD; Kaycee M. Sink, MD, MAS; Jeff D. Williamson, MD, MHS; for the LIFE study investigators

IMPORTANCE In older adults reduced mobility is common and is an independent risk factor for morbidity, hospitalization, disability, and mortality. Limited evidence suggests that physical activity may help prevent mobility disability; however, there are no definitive clinical trials examining whether physical activity prevents or delays mobility disability.

OBJECTIVE To test the hypothesis that a long-term structured physical activity program is more effective than a health education program (also referred to as a successful aging program) in reducing the risk of major mobility disability.

DESIGN, SETTING, AND PARTICIPANTS The Lifestyle Interventions and Independence for Elders (LIFE) study was a multicenter, randomized trial that enrolled participants between February 2010 and December 2011, who participated for an average of 2.6 years. Follow-up ended in December 2013. Outcome assessors were blinded to the intervention assignment. Participants were recruited from urban, suburban, and rural communities at 8 centers throughout the United States. We randomized a volunteer sample of 1635 sedentary men and women aged 70 to 89 years who had physical limitations, defined as a score on the Short Physical Performance Battery of 9 or below, but were able to walk 400 m.

INTERVENTIONS Participants were randomized to a structured, moderate-intensity physical activity program (n = 818) conducted in a center (twice/wk) and at home (3-4 times/wk) that included aerobic, resistance, and flexibility training activities or to a health education program (n = 817) consisting of workshops on topics relevant to older adults and upper extremity stretching exercises.

MAIN OUTCOMES AND MEASURES The primary outcome was major mobility disability objectively defined by loss of ability to walk 400 m.

RESULTS Incident major mobility disability occurred in 30.1% (246 participants) of the physical activity group and 35.5% (290 participants) of the health education group (hazard ratio [HR], 0.82 [95% CI, 0.69-0.98], P = .03). Persistent mobility disability was experienced by 120 participants (14.7%) in the physical activity group and 162 participants (19.8%) in the health education group (HR, 0.72 [95% CI, 0.57-0.91]; P = .006). Serious adverse events were reported by 404 participants (49.4%) in the physical activity group and 373 participants (45.7%) in the health education group (risk ratio, 1.08 [95% CI, 0.98-1.20]).

CONCLUSIONS AND RELEVANCE A structured, moderate-intensity physical activity program compared with a health education program reduced major mobility disability over 2.6 years among older adults at risk for disability. These findings suggest mobility benefit from such a program in vulnerable older adults.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01072500

JAMA. 2014;311(23):2387-2396. doi:10.1001/jama.2014.5616
Published online May 27, 2014.

Author Video Interview at jama.com

Supplemental content at jama.com

CME Quiz at jamanetworkcme.com and **CME Questions** page 2436

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The LIFE investigators are listed at the end of this article.

Corresponding Author: Marco Pahor, MD, Department of Aging and Geriatric Research, University of Florida, PO Box 100107, Gainesville, FL 32610-0107 (mpahor@ufl.edu).

Copyright 2014 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 10/01/2014

The life expectancy of older Americans continues to increase, with persons 65 years or older representing the fastest growing segment of the US population.[1] Although prolongation of life remains an important public health goal, of even greater significance is the preservation of the capacity to live independently and to function well during late life.[2] Identification of proven interventions to prevent disability is an important public health challenge.[3]

Mobility—the ability to walk without assistance—is a critical characteristic for functioning independently.[4,5] Those who lose mobility have higher rates of morbidity, disability, and mortality[6-13] and yet are often excluded from clinical trials. Preserving the ability to walk 400 m, an excellent proxy for community ambulation, is central to maintaining a high quality of life and independence in the community.

To our knowledge, no trial has conclusively tested that physical activity can prevent or delay the onset of mobility disability over an extended follow-up. Therefore, we conducted the Lifestyle Interventions and Independence for Elders (LIFE) pilot study from 2004 to 2006 to plan for the phase 3 randomized trial.[14] As hypothesized, the LIFE pilot study (N = 424) showed significant improvements in walking speed and physical performance measures. The pilot was not powered for a disability end point, but showed a nonsignificant reduction in risk of major mobility disability in the physical activity group compared with the health education group (also referred to as the successful aging group). In the LIFE study, we hypothesized that a long-term structured physical activity program would reduce the risk of major mobility disability compared with a health education program.

Methods

Trial Design and Participants

The study protocol was approved by the institutional review boards at all participating sites. Written informed consent was obtained from all study participants. The trial was monitored by a data and safety monitoring board appointed by the National Institute on Aging. The LIFE study was a multicenter, single-blind, parallel randomized trial conducted at 8 centers across the United States (University of Florida, Gainesville and Jacksonville, Florida; Northwestern University, Chicago, Illinois; Pennington Biomedical Research Center, Baton Rouge, Louisiana; University of Pittsburgh, Pittsburgh, Pennsylvania; Stanford University, Stanford, California; Tufts University, Boston, Massachusetts; Wake Forest School of Medicine, Winston-Salem, North Carolina; and Yale University, New Haven, Connecticut) between February 2010 and December 2013. The Administrative Coordinating Center was located at the University of Florida and the Data Management, Analysis, and Quality Control Center at Wake Forest School of Medicine. The centers included rural, suburban, and urban communities.

Details of the methods were published previously.[15] Briefly, the eligibility criteria consisted of men and women aged 70 to 89 years who (1) were sedentary (reporting <20 min/wk of performing regular physical activity in the past month and <125 min/wk of moderate physical activity); (2) were at high risk for mobility disability based on lower extremity functional limitations measured by the Short Physical Performance Battery (SPPB)[16] with a score of 9 or lower out of 12 (45% of participants were targeted to have a score <8); (3) could walk 400 m in less than 15 minutes without sitting, leaning, or the help of another person or walker; (4) had no major cognitive impairment (measured by the Modified Mini-Mental State Examination[17] [3MSE] with a score of no more than 1.5 standard deviations below education- and race-specific norms); and (4) could safely participate in the intervention as determined by medical history, physical examination, and resting electrocardiography. Persons with 9 or more years of education who scored less than 80 (<76 if African American) and those with less than 9 years of education who scored less than 76 (<70 if African American or Spanish speaking) on the 3MSE were excluded.

Targeted mass mailings to the community was the primary recruitment strategy.[18]

Randomization

Participants were randomized to a physical activity group or to a health education program group (**Figure 1**) via a secure, web-based data management system using a permuted block algorithm (with random block lengths) stratified by field center and sex. Both groups received an initial individual 45-minute face-to-face introductory session by a health educator who described the intervention, communicated expectations, and answered questions.

Interventions

The physical activity intervention involved walking, with a goal of 150 min/wk, strength, flexibility, and balance training.[15] The intervention included attendance at 2 center-based visits per week and home-based activity 3 to 4 times per week for the duration of the study. A protocol was in place to restart the intervention for the participants who suspended the physical activity for medical reasons. The physical activity sessions were individualized and progressed toward a goal of 30 minutes of walking daily at moderate intensity, 10 minutes of primarily lower extremity strength training by means of ankle weights (2 sets of 10 repetitions), 10 minutes of balance training, and large muscle group flexibility exercises. The participants began with lighter intensity and gradually increased intensity over the first 2 to 3 weeks of the intervention. The Borg scale of self-perceived exertion,[19] which ranges from 6 to 20, was used to measure intensity of activity. Participants were asked to walk at an intensity of 13 (activity perception "somewhat hard"), and lower extremity strengthening exercises were performed at an intensity of 15 to 16.

The health education program focused on successful aging (termed *the successful aging group* in previous publications). The health education group attended weekly workshops of health education during the first 26 weeks, and then monthly sessions thereafter (bimonthly attendance was optional). Workshops included topics relevant to older adults, such as how to effectively negotiate the health care system, how to travel safely, preventive services and screenings rec-

Copyright 2014 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 10/01/2014

ommended at different ages, where to go for reliable health information, nutrition, etc. The workshops did not include any physical activity topics. The program also included a 5- to 10-minute instructor-led program of gentle upper extremity stretching or flexibility exercises.

Measurements

Participants were assessed every 6 months at clinic visits. Home, telephone, and proxy assessments were attempted if the participants could not come to the clinic. The assessment staff was blinded to the intervention and remained separate from the intervention team. Participants were asked not to disclose their assigned group and not to talk about their interventions during the assessment. Self-reported physical activity was ascertained by a separate set of unblinded assessors.

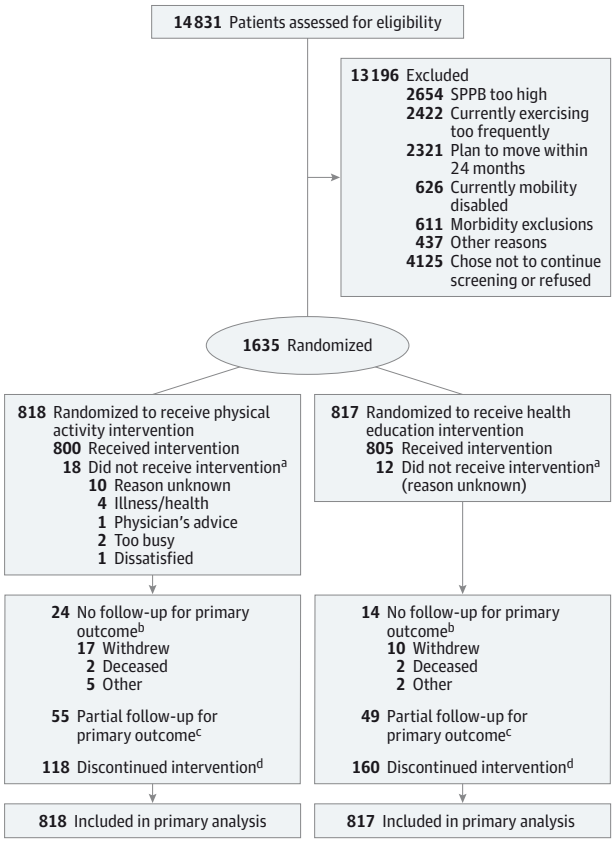
The main baseline assessments included self-reported demographic and contact information, medical and hospitalization history, medication inventory, electrocardiography, physical examination, Quality of Well-Being questionnaire,[20] health care utilization, physical activity assessed with the Community Healthy Activities Model Program for Seniors (CHAMPS) questionnaire,[21] and with accelerometry over 7-day periods (Actigraph Inc), cognitive testing, 400-m walk test,[22] the SPPB, body weight, blood pressure, and pulse rate. These measures were repeated during follow-up at varied intervals. Details of these measures and their frequency are described elsewhere.[15] The SPPB consisted of 4-m walk at usual pace, a timed repeated chair stand, and 3 increasingly difficult standing balance tests.[16,23] Each measure was assigned a categorical score ranging from 0 (inability to complete the test) to 4 (best performance). A summary score ranging from 0 (worst performers) to 12 (best performers) was calculated by summing the 3 component scores. Race and ethnicity were reported by the participants and were collected according to National Institutes of Health requirements. To minimize reporting bias, adverse events originating from the blinded assessments are presented.

Outcome Assessment

The primary outcome of major mobility disability was defined as the inability to complete a 400-m walk test within 15 minutes without sitting and without the help of another person or walker.[15] Use of a cane was acceptable. Participants were asked to walk 400 m at their usual pace, without overexerting, on a 20-m course for 10 laps (40 m/lap). Participants were allowed to stop for up to 1 minute for fatigue or related symptoms. When major mobility disability could not be objectively measured because of the inability of the participant to come to the clinic and absence of a suitable walking course at the participant's home, institution, or hospital, an alternative adjudication of the outcome was based on objective inability to walk 4 m in less than 10 seconds, or self-, proxy-, or medical record-reported inability to walk across a room. If participants met these alternative criteria, they would not be able to complete the 400-m walk within 15 minutes. Reports of death were tracked through regular surveillance. Two consecutive major mobility disability assessments or major mobility disability followed by death defined persistent mobility disability. Censoring was defined at the time of the last definitive assessment for major mobility disability.

At each contact, participants (or proxies, if the participant was not available) were questioned about outcomes and hospitalizations since the last visit. All records for hospitalizations were obtained and outcomes were reviewed and adjudicated independently by 2 experts who were blinded to the group randomization. If the 2 reviewers disagreed, the information was forwarded to the adjudication committee and a determination was made by consensus.

Figure 1. Flow of Participants Through the Study



SPPB indicates Short Physical Performance Battery.

[a] Participants who did not receive the allocated intervention (ie, attended no intervention sessions).

[b] For participants who did not have any major mobility disability assessments, we assigned 1 hour of follow-up time, because we knew that they were able to do the 400-m walk at baseline.

[c] Partial follow-up indicates participants who had censoring times prior to the last planned follow-up visit.

[d] Discontinuation of the intervention was operationalized as participants who did not attend at least 1 intervention session during their last 6 months of follow-up prior to the last planned follow-up visit date. Deaths and intervention withdrawals are included in these numbers. As an example, a participant may have discontinued the intervention in the initial 6 months of follow-up due to illness and then died prior to the 6-month assessment for the primary outcome. This participant would be reflected as missing the primary outcome due to death and also discontinuing the intervention.

Copyright 2014 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 10/01/2014

Statistical Considerations

Power calculations for the primary outcome, time until the first postrandomization occurrence of major mobility disability, were based on a log-rank test with a 2-sided, .05 significance level. Based on the LIFE pilot study,[14] the annual incidence rate of major mobility disability in the health education group was assumed to increase from 18% in the first year to 21% after 2 years. We further assumed that recruitment would be uniform over 21 months, follow-up would average 31 months, and loss to follow-up would be 8% per year. Under these assumptions, randomization of 1600 participants provides 80% power to detect a 21% reduction, and 90% power to detect a 24% reduction in the hazard for major mobility disability in the physical activity participants. These effect-size targets were determined based on consistency with effects derived from observational research, the LIFE pilot experience, clinical relevance (around 20% reduction), and available funding resources.

Baseline characteristics were summarized by intervention group using mean and standard deviation, or percentages. Intervention adherence was calculated as the percentage of scheduled intervention sessions attended by participants. Self-reported minutes of activity and minutes spent in activity associated with more than 760 counts/min (by accelerometry)[24] were analyzed using mixed-effects analysis of covariance models for repeatedly measured outcomes with an unstructured parameterization for longitudinal covariance. Models contained the following terms: field center and sex (both used to stratify randomization), baseline value of the relevant physical activity measure, intervention, clinic visit, and intervention-by-visit interaction. Least squares means were obtained from these models and contrasts were used to estimate the average effects (95% CI) over the follow-up period. Risk ratios (95% CI) were calculated to determine the relative effect of the intervention on the proportion of participants reporting adverse effects. A test of equality of the risk ratios for hospitalization between baseline subgroups defined by SPPB levels (<8 vs ≥8) was performed using Poisson regression.

The effect of the intervention on the primary outcome (ie, time until the initial ascertainment of major mobility disability) was tested based on a 2-tailed significance of .05 using the intention-to-treat approach in which participants are grouped according to randomization assignment. To compare interventions, we used a likelihood ratio test from a Cox regression model, stratified by field center and sex. Failure time was measured from the time of randomization; follow-up was censored at the last successfully completed 400-m walk test. For participants who did not have any outcome assessments, we assigned 1 hour of follow-up time, because we knew that they completed the 400-m walk at baseline. An assessment for nonproportionality of hazards was made with the addition of the interaction between log (time) and intervention.[25] Interaction terms were entered into these Cox models and likelihood ratio tests were used to assess the consistency of the intervention effect across levels of baseline subgroups (ethnicity/race, sex, cardiovascular disease, diabetes, walking speed, and physical performance). The secondary end points were analyzed using the same approach as used for the primary outcome.

Sensitivity analyses were performed to investigate the effect of loss to follow-up on major mobility disability. These analyses used stabilized inverse probability weights that were a function of baseline covariates hypothesized to be predictive of loss-to-follow-up (ie, sex, race/ethnicity, age [≥80], history of diabetes, gait speed <0.8 m/s, low SPPB score [<8], 3MSE <90, clinical site, and living alone [yes/no]) and follow-up gait speed and SPPB scores to explore how the estimated hazard ratios and CIs may have been altered under these missing data assumptions. Statistical analyses were performed in SAS (SAS Institute), version 9.3, and R (Institute for Statistics and Mathematics).[26]

Results

Study Participants

From February 2010 to December 2011, we screened 14 831 participants; of these, 1635 were eligible and randomized (818 to the physical activity group and 817 to the health education group; Figure 1). Details regarding screening, recruitment yields, and baseline characteristics have been published.[18] Baseline characteristics were similar in the 2 groups (**Table 1**). The mean age was 78.9 years, 67.2% were women, 17.6% were African American, the average body mass index (calculated as weight in kilograms divided by height in meters squared) was 30.2, and the average SPPB score was 7.4. The mean follow-up for any contact (including telephone) was 2.6 years (median, 2.7 years; interquartile range [IQR], 2.3-3.1 years). The trial ended in December 2013, as planned in the study protocol.

Intervention Adherence

The physical activity group attended 63% of the scheduled sessions after excluding medical leave (SD, 27%; median [IQR], 71% [50%-83%]). A total of 479 participants (58.6%) went on medical leave at least once and 210 participants (25.7%) went more than once. The mean duration of medical leave was 135 days (SD, 203 days; median [IQR], 49 days [21-140]). Health education participants attended 73 of the scheduled sessions (SD, 25%; median [IQR], 82% [63%-90%]). Based on CHAMPS questionnaires, through the 24-month follow-up visit (the minimum planned intervention duration for all participants), the physical activity group maintained an average of 218 min/wk (95% CI, 210-227; average change from baseline, 138 minutes [95% CI, 129-146]) in walking and weight training activities, whereas the health education group maintained an average of 115 min/wk (95% CI, 106-123; average change from baseline, 34 minutes [95% CI, 24-42]; **Figure 2**). Thus, the physical activity intervention maintained a 104-minute difference (95% CI, 92-116; $P < .001$) in walking and weight training activities compared with the health education group during the initial 2 years in which all participants were followed up.

Based on accelerometry using a definition of more than 760 counts/min for moderate activity,[24] through follow-up,

Copyright 2014 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 10/01/2014

on average, the physical activity group participated in 213 min/wk (95% CI, 205 to 221; average change from baseline, 15 minutes [95% CI, 7 to 23]) of moderate activity. The health education group maintained 173 min/wk (95% CI, 165 to 181; average change from baseline, −25 minutes [95% CI, −33 to −17]; Figure 2). Thus, the physical activity intervention maintained a 40-min/wk difference (95% CI, 29 to 52; $P < .001$) in moderate physical activity assessed with accelerometry, compared with the health education group during 2 years of follow-up.

Major Mobility Disability

Data for major mobility disability were obtained for 794 participants (97.1%) in the physical activity group and 803 participants (98.3%) in the health education group. Loss to follow-up was 4.0% annually. Major mobility disability was experienced by 246 participants (30.1%) in the physical activity group and 290 participants (35.5%) in the health education group (HR, 0.82 [95% CI, 0.69-0.98]; $P = .03$; **Figure 3**). Of the 246 and 290 physical activity and health education participants classified with major mobility disability, 42 participants (17%) of the physical activity group and 32 participants (11%) of the health education group resulted from alternative adjudications. The sensitivity analyses exploring the effect of loss to follow-up on conclusions altered the estimates of the HR and CI limits by less than 0.016 for all analyses (eAppendix in the Supplement). Persistent mobility disability was experienced by 120 participants (14.7%) in the physical activity group and 162 participants (19.8%) in the health education group (HR, 0.72 [95% CI, 0.57-0.91]; $P = .006$). Major mobility disability or death was experienced by 264 participants (32.3%) in the physical activity group and 309 participants (37.8%) in the health education group (HR, 0.82 [95% CI, 0.70-0.97]; $P = .02$).

In prespecified subgroup analyses, results for major mobility disability did not significantly differ when participants were categorized by ethnicity/race, sex, history of cardiovascular disease, history of diabetes, baseline walking speed, and baseline physical performance (**Figure 4**). The subgroup with lower physical function at baseline (SPPB <8), representing 44.7% of the study population and 71% of major mobility disability events (283 of 536 total events), received considerable benefit (HR, 0.75). In post-hoc analyses, the benefit of physical activity on major mobility disability was similar in participants with a 3MSE score of less than 90 and in those with a score of 90 or higher (Figure 4).

Safety

Serious adverse events were reported by 404 participants (49.4%) in the physical activity group and 373 participants (45.7%) in the health education group (risk ratio [RR], 1.08 [95% CI, 0.98-1.20], **Table 2**). For inpatient hospitalizations, 396 of 818 participants (48.4%) in the physical activity group and 360 of 817 participants (44.1%) in the health education group reported an event (RR, 1.10 [95% CI, 0.99-1.22]). The reasons for hospitalization were highly heterogeneous, most of them deemed unrelated to the intervention.

Table 1. Baseline Characteristics of the Participants

Characteristic	No. (%)[a] Physical Activity (n = 818)	Health Education (n = 817)
Age, mean (SD), y	78.7 (5.2)	79.1 (5.2)
Women	547 (66.9)	551 (67.4)
Ethnicity/race		
Hispanic	31 (3.8)	30 (3.7)
White	604 (73.8)	635 (77.7)
African American	163 (19.9)	125 (15.3)
SPPB score		
Mean (SD)	7.4 (1.6)	7.3 (1.6)
<8	353 (43.3)	378 (46.2)
400-m walking speed, mean (SD), m/s	0.83 (0.17)	0.82 (0.17)
BMI, mean (SD)	30.1 (5.7)	30.3 (6.2)
Walking/weight training activities, mean (SD), min/wk[b]	75.1 (125.6)	86.7 (134.5)
Median (IQR)	0 (0-105)	30 (0-105)
Accelerometry of moderate physical activity, mean (SD), min/wk[c]	193.7 (155.3)	202.1 (186.5)
Median (IQR)	161 (80-257) (n = 590)	153 (85-266) (n = 581)
3MSE score, 0-100 scale, mean (SD)	91.5 (5.5)	91.6 (5.3)
Conditions, No./total (%)		
Hypertension[b]	573/813 (70.5)	578/808 (71.5)
Diabetes[b]	199/815 (24.4)	216/813 (26.6)
Myocardial infarction[b]	60/815 (7.4)	69/812 (8.5)
Stroke[b]	57/814 (7.0)	52/814 (6.4)
Cancer[b]	178/814 (21.9)	192/815 (23.6)
Chronic pulmonary disease[b]	130/815 (16.0)	123/812 (15.2)

Abbreviations: 3MSE, Modified Mini-Mental State Examination; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); SPPB, Short Physical Performance Battery.

[a] Some values may slightly differ from those previously published[18] due to data updates.

[b] Self-reported.

[c] Moderate physical activity was defined for accelerometry based on the 760 counts/min cut point.[24]

Among those with SPPB score lower than 8, the RR was 1.04 (95% CI, 0.90-1.20); and among those with SPPB score of 8 or higher, the RR was 1.17 (95% CI, 1.00-1.36). The test of equality of RRs for hospitalization for physical activity vs health education between the 2 baseline SPPB subgroups was not significant ($P = .44$).

Discussion

The LIFE study showed that, over 2.6 years of follow-up, the physical activity intervention compared with the health education intervention significantly reduced major mobility disability (HR, 0.82; $P = .03$), persistent mobility disability (HR, 0.72; $P = .006$), and the combined outcome of major mobility disability or death (HR, 0.82; $P = .02$). The subgroup with lower physical function at baseline (SPPB <8),

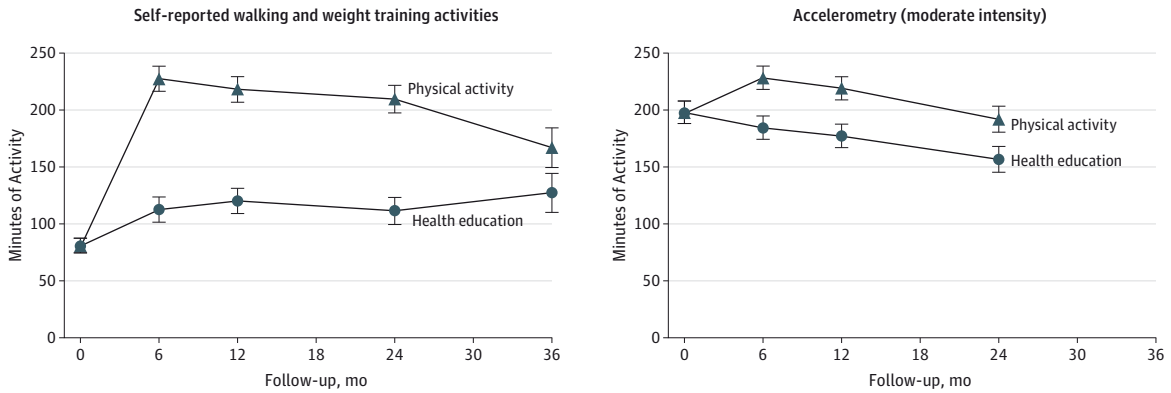
Copyright 2014 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 10/01/2014

representing 44.7% of the study population and 71% of major mobility disability events (283 of 536 total events), received considerable benefit (HR, 0.81). These results suggest the potential for structured physical activity as a feasible and effective intervention to reduce the burden of disability among vulnerable older persons, in spite of functional decline in late life. To our knowledge, the LIFE study is the largest and longest duration randomized trial of physical activity in older persons.

The LIFE study has important strengths, including the objectively measured primary outcome of major mobility disability that is a reliable,[22] well-validated, and important clinical and public health outcome in older people.[11] Participants at high risk for disability were recruited from 8 field centers spanning the United States, including urban, suburban, and rural settings, and included a high proportion of older adults from African American and Hispanic backgrounds. Although highly prevalent and increasing in size,

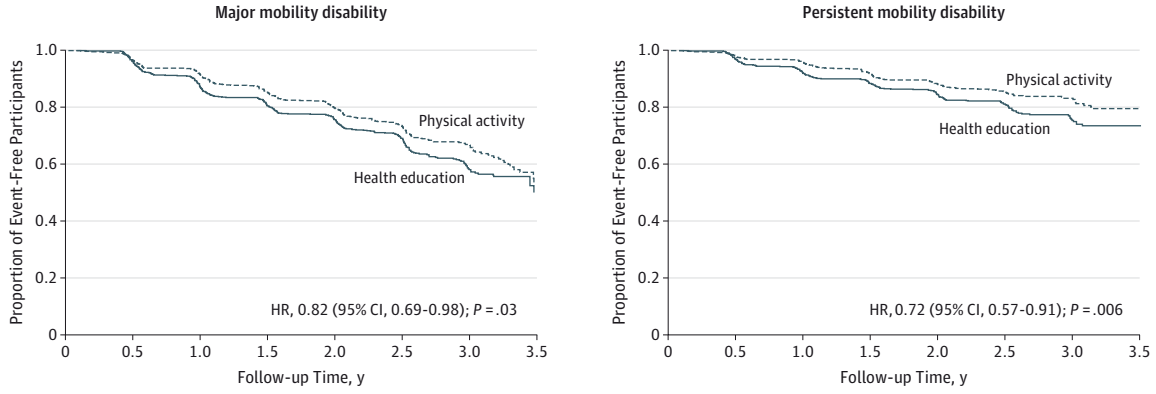
Figure 2. Self-reported and Accelerometry-Derived Physical Activity by Treatment Group



No. of participants									
Physical activity	818	774	761	724	292	590	423	420	349
Health education	817	796	777	738	295	581	422	425	346

Plotted values represent least squares means (95% CI) from a mixed-effects model adjusting for clinical site and sex (both used to stratify randomization) and the baseline self-reported walking/weight training activities or accelerometry counts. In addition to the above-mentioned terms, the model contained a term for the intervention group, follow-up clinic visit, and the intervention × visit interaction. All participants had expected follow-up through 24 months and approximately 47% of randomized participants had expected visits at 36 months. Accelerometry data were not collected at the 36-month visit. Baseline values represent the overall mean of both groups combined (a standard practice when using the analysis of covariance method): this is the assumed value for both groups when obtaining least squares means at follow-up using mixed-effects analysis of covariance. The baseline, prerandomization value is reflected by follow-up time 0. The *P* value is less than .001 for the average intervention effect.

Figure 3. Effect of a Moderate Physical Activity Intervention on the Onset of Major Mobility Disability and Persistent Mobility Disability



No. at risk															
Physical activity	818	758	706	646	559	378	182	11	818	761	726	673	579	393	188	12
Health education	817	765	680	617	540	358	162	13	817	762	707	655	567	371	178	10
Events																
Physical activity	0	29	67	115	155	197	224	246	0	18	32	64	88	104	113	120
Health education	0	33	105	155	190	232	277	286	0	25	64	91	118	138	158	162

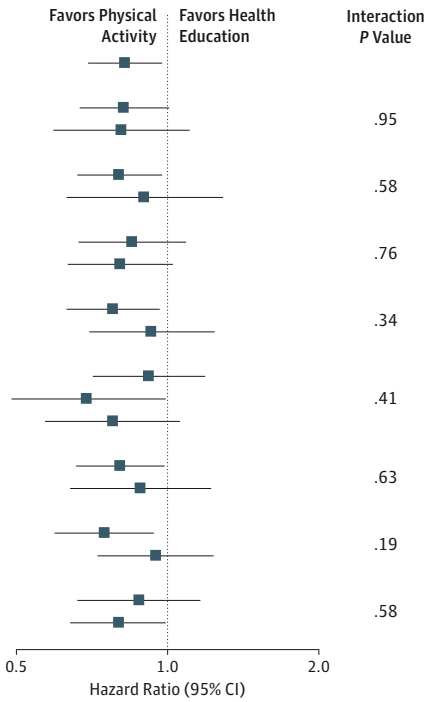
HR indicates hazard ratio. The graph for major mobility disability was truncated at 3.5 years and the health education group had 4 additional failures between 3.5 and 3.6 years of follow-up. Number of events represents cumulative events and adjusted HRs and *P* values are from proportional hazards regression models defined in the Methods section.

Copyright 2014 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 10/01/2014

Figure 4. Hazard Ratio of Major Mobility Disability for Physical Activity vs Health Education According to Subgroups

Subgroup	Physical Activity Events, No.	Physical Activity Total Participants	Health Education Events, No.	Health Education Total Participants	Hazard Ratio (95% CI)	Interaction *P* Value
Overall	246	818	290	817	0.82 (0.69-0.98)	
Sex						
Women	171	547	204	551	0.82 (0.67-1.01)	.95
Men	75	271	86	266	0.81 (0.59-1.11)	
Ethnicity/race						
Non-Hispanic white	182	604	234	635	0.80 (0.66-0.98)	.58
Other	64	211	56	180	0.90 (0.63-1.29)	
Age, y						
70-79	123	477	138	455	0.85 (0.67-1.09)	.76
≥80	123	341	152	362	0.81 (0.63-1.03)	
History of CVD						
No CVD	155	582	187	563	0.78 (0.63-0.97)	.34
CVD	91	236	103	254	0.93 (0.70-1.24)	
History of diabetes						
None	114	406	126	414	0.92 (0.71-1.19)	
Impaired fasting glucose	59	192	68	165	0.69 (0.49-0.99)	.41
Diabetes	73	220	96	238	0.78 (0.57-1.06)	
Gait speed						
<0.8 m/s	173	485	210	508	0.81 (0.66-0.99)	.63
≥0.8 m/s	73	333	80	309	0.88 (0.64-1.22)	
SPPB						
<8	135	353	177	378	0.75 (0.60-0.94)	.19
8 or 9	111	465	113	439	0.95 (0.73-1.23)	
3MSE (post hoc)						
<90	95	261	108	261	0.88 (0.66-1.16)	.58
≥90	151	557	182	556	0.80 (0.64-0.99)	



3MSE indicates Modified Mini-Mental State Examination; CVD, cardiovascular disease; SPPB, Short Physical Performance Battery. *P* values were obtained from likelihood ratios tests of the interaction terms added to the Cox regression model.

the older, more vulnerable population has been understudied and typically is not included in large randomized trials. Retention throughout the follow-up was excellent. The adherence rates to the physical activity intervention were similar or higher than those achieved in other much shorter studies involving older adults.[27-29] The physical activity program was likely successful in part because of the adherence and lifestyle motivation procedures.[30] The participants were reimbursed for their transportation costs, which added to the cost of the intervention, but likely contributed to the high levels of attendance. According to initial cost data collected in the LIFE study, the physical activity intervention cost, including transportation, was approximately $4900 per participant over the 2.6 years of average participation ($1815/year). The physical activity intervention was designed to be simple for widespread implementation in a variety of communities and settings, because it does not require any special equipment.

The LIFE study has limitations. We could not ascertain whether participants who were excluded because of their high level of physical function or severe cognitive deficits would also benefit from physical activity. The participants were recruited from the community, but may have been self-referred, so they may not be fully representative of all people in the community. The average follow-up duration of 2.6 years was relatively short vs the estimated average 9-year life expectancy of the LIFE cohort.[31] Ideally, it would be useful to assess the effect of the intervention on the quality of the remaining years of life. The study, which was powered based on assumptions of 21% to 24% risk reduction, achieved an HR of 0.82 and an absolute risk difference of 5.4%. Although the effect size was slightly lower than planned, we believe that it is clinically relevant given the major health effect of mobility disability and the lack of proven interventions to avert mobility disability in vulnerable older populations. In addition, persistent mobility disability was significantly reduced by a larger degree in the physical activity group (HR, 0.72), indicating that physical activity not only prevents the onset of major mobility disability, but also favors improved recovery in those who lose mobility.

Based on observational cohorts,[32] we expected a lower hospitalization rate in the physical activity group. In the LIFE study, physical activity did not decrease the hospitalizations rate. We found a higher rate of hospitalizations in the physical activity group that did not reach statistical significance. The hospitalizations comprised a range of heterogeneous diagnoses mostly deemed unrelated to the intervention. Our finding may have several explanations. First, physical activity may unmask symptoms resulting in earlier detection of underlying medical conditions. For example, sedentary older persons with subclinical left ventricular dysfunction may observe heart failure symptoms when they start moderate physical activity. Second, the physical activity group's more frequent contact and testing of vital signs at each intervention session may have led to a higher rate of recognition of health events. Third, the stress of exercise in

Copyright 2014 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 10/01/2014

Table 2. All Deaths and Number of Participants Reporting Adverse Events at Blinded Assessments

Event Type	Physical Activity Group (n = 818)		Health Education Group (n = 817)		Risk Ratio (95% CI)[a]
	Participants, No. (%)	Events, No.	Participants, No. (%)	Events, No.	
Serious adverse events					
All serious adverse events	404 (49.4)	879	373 (45.7)	774	1.08 (0.98-1.20)
Death	48 (5.9)	48	42 (5.1)	42	1.14 (0.76-1.71)
Life-threatening event	11 (1.3)	11	8 (1.0)	8	1.37 (0.56-3.40)
Persistent disability/incapacity	33 (4.0)	51	26 (3.2)	45	1.27 (0.77-2.10)
All inpatient hospitalizations	396 (48.4)	777	360 (44.1)	681	1.10 (0.99-1.22)
Any other serious events	7 (0.9)	8	8 (1.0)	10	0.87 (0.32-2.40)
Most frequent hospitalization diagnoses					
Infection	74 (.9.0)	95	57 (7.0)	68	1.30 (0.93-1.81)
Surgical procedure	68 (8.3)	76	73 (8.9)	84	0.93 (0.68-1.28)
Fall, syncope, dizziness, vertigo	54 (6.4)	58	53 (6.5)	62	1.02 (0.71-1.49)
Atrial fibrillation/flutter	24 (2.9)	28	20 (2.4)	23	1.20 (0.67-2.15)
Heart failure	18 (2.2)	21	14 (1.7)	20	1.28 (0.64-2.56)
Stroke/TIA/intracranial hemorrhage	29 (3.5)	33	28 (3.4)	34	1.03 (0.62-1.72)
MI/chest pain/acute coronary syndrome	33 (4.0)	42	25 (3.1)	27	1.32 (0.79-2.20)
Fracture	27 (3.3)	29	26 (3.2)	27	1.04 (0.61-1.76)
Neoplasm	17 (2.1)	17	17 (2.1)	20	1.00 (0.51-1.94)
Arthritis/back, neck, or bone pain	30 (3.7)	31	33 (4.0)	35	0.91 (0.56-1.47)
Symptoms resulting in at least 1 wk of restricted activity[b]					
All cases	198 (24.2)	253	198 (24.2)	249	1.00 (0.84-1.19)
Fall	47 (5.7)	53	71 (8.7)	81	0.66 (0.46-0.94)
Fatigue	38 (4.6)	46	41 (5.0)	45	0.93 (0.60-1.42)
Muscle or joint aching	32 (3.9)	37	40 (4.9)	43	0.80 (0.51-1.26)
Back pain	36 (4.4)	41	33 (4.0)	35	1.09 (0.69-1.73)
Muscle or joint stiffness	26 (3.2)	30	33 (4.0)	35	0.79 (0.48-1.30)
Foot pain	17 (2.1)	17	18 (2.2)	18	0.94 (0.49-1.82)
Dizziness	18 (2.2)	19	14 (1.7)	15	1.28 (0.64-2.56)
Shortness of breath	15 (1.8)	16	20 (2.4)	22	0.75 (0.39-1.45)
Fainting	16 (2.0)	18	10 (1.2)	11	1.60 (0.73-3.50)
Abnormal heart rhythm	9 (1.1)	9	8 (1.0)	8	1.12 (0.44-2.90)
Other symptom	84 (10.3)	96	71 (8.7)	75	1.18 (0.87-1.60)

Abbreviations: MI, myocardial infarction; TIA, transient ischemic attack.

[a] Risk ratio compares the proportion of participants reporting any events in the physical activity group vs the health education group, with asymptomatic 95% CIs.

[b] Symptoms resulting in at least 1 week of restricted activity may also lead to serious adverse events. Thus, events reported in this section of Table 2 may also be reflected as serious adverse events or hospitalizations.

the context of lowered homeostatic reserve in vulnerable participants[33] may have led to a higher risk of adverse events. However, our data do not support this explanation. The hospitalization results were not significantly different among those with SPPB score less than 8, and those with a score 8 or 9. Finally, there may be no causal association between physical activity and hospitalizations.

Physical activity did not decrease the death rate. We found a higher rate of mortality in the physical activity group that did not reach statistical significance, and which was compatible with benefit or harm of physical activity (Table 2). Given the small number of events the data regarding mortality are inconclusive. Further studies are needed to assess the effects of physical activity on mortality and hospitalizations in vulnerable older adults.

Conclusions

A structured moderate-intensity physical activity program compared with a health education program reduced major mobility disability over 2.6 years among older adults at risk of disability. These findings suggest mobility benefit from such a program in vulnerable older adults.

Copyright 2014 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 10/01/2014

ARTICLE INFORMATION

Published Online: May 27, 2014. doi:10.1001/jama.2014.5616.

Author Affiliations: Department of Aging and Geriatric Research, University of Florida, Gainesville (Pahor, Guralnik, Manini); Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore (Guralnik); Department of Internal Medicine, Wake Forest University and School of Medicine, Winston-Salem, North Carolina (Ambrosius, Espeland, Kritchevsky, Miller, Rejeski, Sink, Williamson); Department of Exercise Science, Arnold School of Public Health, University of South Carolina, Columbia (Blair); Division of Cardiac Sciences, National Heart, Lung, and Blood Institute, Bethesda, Maryland (Bonds); Department of Preventative Medicine, Pennington Biomedical Research Center, Louisiana (Church); Jean Mayer United States Department of Agriculture Human Nutrition Research Center on Aging, Tufts University, Boston, Massachusetts (Fielding); Department of Internal Medicine, Yale School of Medicine, New Haven, Connecticut (Gill); Veterans Affairs San Diego Healthcare System, San Diego, California (Groessl); Department of Family and Preventive Medicine, University of California, San Diego, San Diego (Groessl); Department of Health Research and Policy and Department of Medicine, Stanford University, School of Medicine, Stanford, California (King); Department of Medicine and Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois (McDermott); Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania (Newman).

Author Contributions: Dr Miller 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.
Study concept and design: Pahor, Guralnik, Blair, Church, Espeland, Fielding, Gill, Groessl, King, Kritchevsky, Manini, Miller, Newman, Rejeski, Sink, Williamson.
Acquisition, analysis, or interpretation of data: Pahor, Guralnik, Ambrosius, Bonds, Church, Espeland, Fielding, Gill, Manini, McDermott, Miller, Newman, Sink, Williamson.
Drafting of the manuscript: Pahor, Espeland, Fielding, Manini, McDermott, Miller, Rejeski.
Critical revision of the manuscript for important intellectual content: Pahor, Guralnik, Ambrosius, Blair, Bonds, Church, Espeland, Fielding, Gill, Groessl, King, Kritchevsky, Manini, McDermott, Miller, Newman, Sink.
Statistical analysis: Ambrosius, Espeland, Miller.
Obtained funding: Pahor, Guralnik, Church, Fielding, Gill, Groessl, King, Manini, McDermott, Miller, Newman, Rejeski, Williamson.
Administrative, technical, or material support: Pahor, Guralnik, Bonds, Fielding, Gill, King, Manini, Miller, Newman, Williamson.
Study supervision: Pahor, Guralnik, Fielding, Gill, King, Kritchevsky, Manini, McDermott, Rejeski, Williamson.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Blair reports receiving grant funding from BodyMedia, the Coca-Cola Company, and Technogym. Dr Fielding reports receiving grant funding from the Dairy Research Institute, Department of Defense, Nestle, Regeneron Pharmaceuticals, and Unilever; consulting for Dairy Management, Eli Lilly, Essentient, Merck, Nestle, and Regeneron; and serving on the board for Aging in Motion, Ammonett, Cytokinetics, Myosyntax, Nestle, and Segterra. Dr McDermott reports being a medical editor for Informed Medical Decisions Foundation. Dr Sink reports receiving grant funding from the Alzheimer's Association and the Donald W. Reynolds Foundation; and being a site principal investigator for a multicenter trial of medical food for patients with Alzheimer disease. No other disclosures were reported.

Funding/Support: The Lifestyle Interventions and Independence for Elders Study is funded by cooperative agreement U01AG22376 from the National Institutes of Health (NIH) and National Institute on Aging; supplement 3U01AG022376-05A2S from the National Heart, Lung, and Blood Institute; and was sponsored in part by the Intramural Research Program. The research is partially supported by the Claude D. Pepper Older Americans Independence Centers at the University of Florida (1 P30 AG028740), Wake Forest University (1 P30 AG21332),Tufts University (1P30AG031679), University of Pittsburgh (P30 AG024827), and Yale University (P30AG021342) and the NIH/NCRR CTSA at Stanford University (UL1 RR025744), at University of Florida (U54RR025208) and at Yale University (UL1 TR000142). Tufts University is also supported by the Boston Rehabilitation Outcomes Center (1R24HD065688-01A1). LIFE investigators are also partially supported by the following: Dr Thomas Gill (Yale University) is the recipient of an Academic Leadership Award (K07AG3587) from the National Institute on Aging. Dr Carlos Fragoso (Spirometry Reading Center, Yale University) is the recipient of a Career Development Award from the Department of Veterans Affairs. Dr Roger Fielding (Tufts University) is partially supported by the US Department of Agriculture, under agreement 58-1950-0-014.

Role of the Sponsors: The NIH sponsor was a voting member (1 of 12 votes) of the LIFE Steering Committee, which approved the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, and approval of the manuscript; and decision to submit the manuscript for publication.

Research Investigators for the LIFE Study: Administrative Coordinating Center, University of Florida, Gainesville, FL: Marco Pahor, MD—Principal Investigator of the LIFE Study; Jack M. Guralnik, MD, PhD—Coinvestigator of the LIFE Study (University of Maryland School of Medicine, Baltimore, MD); Christiaan Leeuwenburgh, PhD; Connie Caudle; Lauren Crump, MPH; Latonia Holmes; Jocelyn Lee, PhD; Ching-ju Lu, MPH. ***Data Management, Analysis and Quality Control Center***: Wake Forest University, Winston Salem, NC: Michael E. Miller, PhD—DMAQC Principal Investigator; Mark A. Espeland, PhD—DMAQC Coinvestigator; Walter T. Ambrosius, PhD; William Applegate, MD; Daniel P. Beavers, PhD, MS; Robert P. Byington, PhD, MPH, FAHA; Delilah Cook, CCRP; Curt D. Furberg, MD, PhD; Lea N. Harvin, BS; Leora Henkin, MPH, Med; John Hepler, MA; Fang-Chi Hsu, PhD; Laura Lovato, MS; Wesley Roberson, BSBA; Julia Rushing, BSPH, MStat; Scott Rushing, BS; Cynthia L. Stowe, MPM; Michael P. Walkup, MS; Don Hire, BS; W. Jack Rejeski, PhD; Jeffrey A. Katula, PhD, MA; Peter H. Brubaker, PhD; Shannon L. Mihalko, PhD; Janine M. Jennings, PhD; National Institutes of Health, Bethesda, MD; Evan C. Hadley, MD (National Institute on Aging); Sergei Romashkan, MD, PhD (National Institute on Aging); Kushang V. Patel, PhD (National Institute on Aging); National Heart, Lung and Blood Institute, Bethesda, MD; Denise Bonds, MD, MPH. ***Field Centers***: Northwestern University, Chicago, IL: Mary M. McDermott, MD—Field Center Principal Investigator; Bonnie Spring, PhD—Field Center Coinvestigator; Joshua Hauser, MD—Field Center Coinvestigator; Diana Kerwin, MD—Field Center Coinvestigator; Kathryn Domanchuk, BS; Rex Graff, MS; Alvito Rego, MA. Pennington Biomedical Research Center, Baton Rouge, LA: Timothy S. Church, MD, PhD, MPH—Field Center Principal Investigator; Steven N. Blair, PED (University of South Carolina); Valerie H. Myers, PhD; Ron Monce, PA-C; Nathan E. Britt, NP; Melissa Nauta Harris, BS; Ami Parks McGucken, MPA, BS; Ruben Rodarte, MBA, MS, BS; Heidi K. Millet, MPA, BS; Catrine Tudor-Locke, PhD, FACSM; Ben P. Butitta, BS; Sheletta G. Donatto, MS, RD, LDN, CDE; Shannon H. Cocreham, BS; 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; Leslie A. Pruitt, PhD; Kathy Berra, MSN, NP-C, FAAN; Veronica Yank, MD; Tufts University, Boston, MA; Roger A. Fielding, PhD—Field Center Principal Investigator; Miriam E. Nelson, PhD—Field Center Coinvestigator; Sara C. Folta, PhD—Field Center Coinvestigator; Edward M. Phillips, MD; Christine K. Liu, MD; Erica C. McDavitt, MS; Kieran F. Reid, PhD, MPH; Won S. Kim, BS; Vince E. Beard, BS; University of Florida, Gainesville, FL; Todd M. Manini, PhD—Field Center Principal Investigator; Marco Pahor, MD—Field Center Coinvestigator; Stephen D. Anton, PhD; Susan Nayfield, MD; Thomas W. Buford, PhD; Michael Marsiske, PhD; Bhanuprasad D. Sandesara, MD; Jeffrey D. Knaggs, BS; Megan S. Lorow, BS; William C. Marena, MT, CCRC; Irina Korytov, MD; Holly L. Morris, MSN, RN, CCRC (Brooks Rehabilitation Clinical Research Center, Jacksonville, FL); Margo Fitch, PT (Brooks Rehabilitation Clinical Research Center, Jacksonville, FL); Floris F. Singletary, MS, CCC-SLP (Brooks Rehabilitation Clinical Research Center, Jacksonville, FL); Jackie Causer, BSH, RN (Brooks Rehabilitation Clinical Research Center, Jacksonville, FL); Katie A. Radcliff, MA (Brooks Rehabilitation Clinical Research Center, Jacksonville, FL); University of Pittsburgh, Pittsburgh, PA; Anne B. Newman, MD, MPH—Field Center Principal Investigator; Stephanie A. Studenski, MD, MPH—Field Center Coinvestigator; Bret H. Goodpaster, PhD; Nancy W. Glynn, PhD; Oscar Lopez, MD; Neelesh K. Nadkarni, MD, PhD; Kathy Williams, RN, BSEd, MHSA; Mark A. Newman, PhD; George Grove, MS; Janet T. Bonk, MPH, RN; Jennifer Rush, MPH; Piera Kost, BA (deceased); Diane G. Ives, MPH; Wake Forest University, Winston Salem, NC; Stephen B. Kritchevsky, PhD—Field Center Principal Investigator; Anthony P. Marsh, PhD—Field Center Coinvestigator; Tina E. Brinkley, PhD; Jamehl S. Demons, MD; Kaycee M. Sink, MD, MAS; Kimberly Kennedy, BA, CCRC; Rachel Shertzer-Skinner, MA, CCRC;

Copyright 2014 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 10/01/2014

Abbie Wrights, MS; Rose Fries, RN, CCRC; Deborah Barr, MA, RHEd, CHES; Yale University, New Haven, CT; Thomas M. Gill, MD—Field Center Principal Investigator; Robert S. Axtell, PhD, FACSM—Field Center Coinvestigator (Southern Connecticut State University, Exercise Science Department); Susan S. Kashaf, MD, MPH (VA Connecticut Healthcare System); Nathalie de Rekeneire, MD, MS; Joanne M. McGloin, MDiv, MS, MBA; Karen C. Wu, RN; Denise M. Shepard, RN, MBA; Barbara Fennelly, MA, RN; Lynne P. Iannone, MS, CCRP; Raeleen Mautner, PhD; Theresa Sweeney Barnett, MS, APRN; Sean N. Halpin, MA; Matthew J. Brennan, MA; Julie A. Bugaj, MS; Maria A. Zenoni, MS; Bridget M. Mignosa, AS. Cognition Coordinating Center, Wake Forest University, Winston Salem, NC; Jeff Williamson, MD, MHS—Center Principal Investigator; Kaycee M Sink, MD, MAS—Center Coinvestigator; Hugh C. Hendrie, MB, ChB, DSc (Indiana University); Stephen R. Rapp, PhD; Joe Verghese, MB, BS (Albert Einstein College of Medicine of Yeshiva University); Nancy Woolard; Mark Espeland, PhD; Janine Jennings, PhD; Electrocardiogram Reading Center, University of Florida, Gainesville, FL; Carl J. Pepine MD, MACC; Mario Ariet, PhD; Eileen Handberg, PhD, ARNP; Daniel Deluca, BS; James Hill, MD, MS, FACC; Anita Szady, MD. Spirometry Reading Center, Yale University, New Haven, CT; Geoffrey L. Chupp, MD; Gail M. Flynn, RCP, CRFT; Thomas M. Gill, MD; John L. Hankinson, PhD (Hankinson Consulting, Inc.); Carlos A. Vaz Fragoso, MD; Cost Effectiveness Analysis Center; Erik J. Groessl, PhD (University of California, San Diego and VA San Diego Healthcare System); Robert M. Kaplan, PhD (Office of Behavioral and Social Sciences Research, National Institutes of Health).

Disclaimer: Any opinions, findings, conclusion, or recommendations expressed in this publication are those of the authors and do not necessarily reflect the view of the US Department of Agriculture. Dr McDermott, senior editor at *JAMA*, did not participate in the evaluation of this article or the decision to publish the study.

Additional Contributions: We thank Evan C. Hadley, MD, and Sergei Romashkan, MD, PhD, from the National Institute on Aging (Bethesda, Maryland), for their substantial intellectual contribution to the development and implementation of the LIFE Study. Dr Hadley and Dr Romashkan are federal employees fully paid by the NIH. They did not receive any additional compensation from the study.

REFERENCES

1. Werner CA. The older population. http://www.census.gov/prod/cen2010/briefs/c2010br-09.pdf. Accessed May 7, 2014.

2. Katz S, Branch LG, Branson MH, Papsidero JA, Beck JC, Greer DS. Active life expectancy. *N Engl J Med*. 1983;309(20):1218-1224.

3. Branch LG, Guralnik JM, Foley DJ, et al. Active life expectancy for 10 000 Caucasian men and women in 3 communities. *J Gerontol*. 1991;46(4):M145-M150.

4. Lonergan ET, Krevans JR. A national agenda for research on aging. *N Engl J Med*. 1991;324(25):1825-1828.

5. Guralnik JM, LaCroix AZ, Abbott RD, et al. Maintaining mobility in late life. *Am J Epidemiol*. 1993;137(8):845-857.

6. Branch LG, Jette AM. A prospective study of long-term care institutionalization among the aged. *Am J Public Health*. 1982;72(12):1373-1379.

7. Corti MC, Guralnik JM, Salive ME, Sorkin JD. Serum albumin level and physical disability as predictors of mortality in older persons. *JAMA*. 1994;272(13):1036-1042.

8. Khokhar SR, Stern Y, Bell K, et al. Persistent mobility deficit in the absence of deficits in activities of daily living. *J Am Geriatr Soc*. 2001;49(11):1539-1543.

9. Hirvensalo M, Rantanen T, Heikkinen E. Mobility difficulties and physical activity as predictors of mortality and loss of independence in the community-living older population. *J Am Geriatr Soc*. 2000;48(5):493-498.

10. Lampinen P, Heikkinen E. Reduced mobility and physical activity as predictors of depressive symptoms among community-dwelling older adults. *Aging Clin Exp Res*. 2003;15(3):205-211.

11. Newman AB, Simonsick EM, Naydeck BL, et al. Association of long-distance corridor walk performance with mortality, cardiovascular disease, mobility limitation, and disability. *JAMA*. 2006;295(17):2018-2026.

12. Shumway-Cook A, Patla A, Stewart A, Ferrucci L, Ciol MA, Guralnik JM. Environmental components of mobility disability in community-living older persons. *J Am Geriatr Soc*. 2003;51(3):393-398.

13. Shumway-Cook A, Patla AE, Stewart A, Ferrucci L, Ciol MA, Guralnik JM. Environmental demands associated with community mobility in older adults with and without mobility disabilities. *Phys Ther*. 2002;82(7):670-681.

14. Pahor M, Blair SN, Espeland M, et al. Effects of a physical activity intervention on measures of physical performance: results of the lifestyle interventions and independence for Elders Pilot (LIFE-P) study. *J Gerontol A Biol Sci Med Sci*. 2006;61(11):1157-1165.

15. Fielding RA, Rejeski WJ, Blair S, et al. The Lifestyle Interventions and Independence for Elders Study. *J Gerontol A Biol Sci Med Sci*. 2011;66(11):1226-1237.

16. Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. *N Engl J Med*. 1995;332(9):556-561.

17. Teng EL, Chui HC. The Modified Mini-Mental State (3MS) examination. *J Clin Psychiatry*. 1987;48(8):314-318.

18. Marsh AP, Lovato LC, Glynn NW, et al. Lifestyle interventions and independence for elders study. *J Gerontol A Biol Sci Med Sci*. 2013;68(12):1549-1558.

19. Borg G. *Perceived Exertion and Pain Scales*. Champaign, IL: Human Kinetics; 1988.

20. Andresen EM, Rothenberg BM, Kaplan RM. Performance of a self-administered mailed version of the Quality of Well-Being (QWB-SA) questionnaire among older adults. *Med Care*. 1998;36(9):1349-1360.

21. Stewart AL, Verboncoeur CJ, McLellan BY, et al. Physical activity outcomes of CHAMPS II. *J Gerontol A Biol Sci Med Sci*. 2001;56(8):M465-M470.

22. Rolland YM, Cesari M, Miller ME, Penninx BWJH, Atkinson HH, Pahor M. Reliability of the 400-m usual-pace walk test as an assessment of mobility limitation in older adults. *J Am Geriatr Soc*. 2004;52(6):972-976.

23. Guralnik JM, Ferrucci L, Pieper CF, et al. Lower extremity function and subsequent disability. *J Gerontol A Biol Sci Med Sci*. 2000;55(4):M221-M231.

24. Matthew CE. Calibration of accelerometer output for adults. *Med Sci Sports Exerc*. 2005;37(11)(suppl):S512-S522.

25. Therneau TM, Grambsch PM. *Modeling Survival Data, Extending the Cox Model*. New York, NY: Springer Science; 2000.

26. Van der Wal WM, Geskus RB. An R package for inverse probability weighting. J Stat Softw. 2011;43(13):1-23. http://www.jstatsoft.org/v43/i13/paper. Accessed May 7, 2014.

27. Messier SP, Loeser RF, Miller GD, et al. Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis. *Arthritis Rheum*. 2004;50(5):1501-1510.

28. Ettinger WH Jr, Burns R, Messier SP, et al. A randomized trial comparing aerobic exercise and resistance exercise with a health education program in older adults with knee osteoarthritis: the Fitness Arthritis and Seniors Trial (FAST). *JAMA*. 1997;277(1):25-31.

29. Berry MJ, Rejeski WJ, Adair NE, Ettinger WH Jr, Zaccaro DJ, Sevick MA. A randomized, controlled trial comparing long-term and short-term exercise in patients with chronic obstructive pulmonary disease. *J Cardiopulm Rehabil*. 2003;23(1):60-68.

30. Rejeski WJ, Axtell R, Fielding R, et al. Promoting physical activity for elders with compromised function. *Clin Interv Aging*. 2013;8:1119-1131.

31. Studenski S, Perera S, Patel K, et al. Gait speed and survival in older adults. *JAMA*. 2011;305(1):50-58.

32. Physical Activity Guidelines Advisory Committee. *Physical Activity Guidelines Advisory Committee Report*. Washington, DC: US Dept of Health and Human Services; 2008.

33. Szanton SL, Allen JK, Seplaki CL, Bandeen-Roche K, Fried LP. Allostatic load and frailty in the Women's Health and Aging studies. *Biol Res Nurs*. 2009;10(3):248-256.

Copyright 2014 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 10/01/2014