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Cardiovascular Events in a Physical Activity Intervention Compared With a Successful Aging Intervention
The LIFE Study Randomized Trial

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IMPORTANCE Whether sustained physical activity prevents cardiovascular disease (CVD) events in older adults is uncertain.

OBJECTIVE To test the hypothesis that cardiovascular morbidity and mortality would be reduced in participants in a long-term physical activity program.

DESIGN, SETTING, AND PARTICIPANTS The Lifestyle Interventions and Independence for Elders (LIFE) study was a multicenter, randomized trial. Participants were recruited at 8 centers in the United States. We randomized 1635 sedentary men and women aged 70 to 89 years with a Short Physical Performance Battery (SPPB) score of 9 or less but able to walk 400 m.

INTERVENTIONS The physcial activity (PA) intervention was a structured moderate-intensity program, predominantly walking 2 times per week on site for 2.6 years on average. The successful aging intervention consisted of weekly health education sessions for 6 months, then monthly.

MAIN OUTCOMES AND MEASURES Total CVD events, including fatal and nonfatal myocardial infarction, angina, stroke, transient ischemic attack, and peripheral artery disease, were adjudicated by committee, and silent myocardial infarction was assessed by serial electrocardiograms. A limited outcome of myocardial infarction, stroke, and CVD death was also studied. Outcome assessors and adjudicators were blinded to intervention assignment.

RESULTS The 1635 LIFE study participants were predominantly women (67%), with a mean (SD) age of 78.7 (5.2) years; 20% were African-American, 6% were Hispanic or other race or ethnic group, and 74% were non-Latino white. New CVD events occurred in 121 of 818 PA participants (14.8%) and 113 of 817 successful aging participants (13.8%) (HR, 1.10; 95% CI, 0.85-1.42). For the more focused combined outcome of myocardial infarction, stroke, or cardiovascular death, rates were 4.6% in PA and 4.5% in the successful aging group (HR, 1.05; 95% CI, 0.67-1.66). Among frailer participants with an SPPB score less than 8, total CVD rates were 14.2% in PA vs 17.7% in successful aging (HR, 0.76; 95% CI, 0.52-1.10), compared with 15.3% vs 10.5% among those with an SPPB score of 8 or 9 (HR, 1.59; 95% CI, 1.09-2.30) (*P* for interaction = .006). With the limited end point, the interaction was not significant (*P* = .59), with an HR of 0.94 (95% CI, 0.50-1.75) for an SPPB score less than 8 and an HR of 1.20 (95% CI, 0.62-2.34) for an SBBP score of 8 or 9.

CONCLUSIONS AND RELEVANCE Among participants in the LIFE Study, an aerobically based, moderately intensive PA program was not associated with reduced cardiovascular events in spite of the intervention's previously documented ability to prevent mobility disability.

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There are few randomized clinical trials testing the ability of physical activity to prevent cardiovascular disease (CVD) events. Many observational studies demonstrate that greater physical activity (PA) is associated with lower rates of incident and recurrent myocardial infarction (MI) across a spectrum of age.[1-3] In clinical trials, physical activity interventions have been shown to slow the progression of coronary artery disease[4,5] and can prolong event-free survival in patients undergoing stent placement.[6,7] Cardiac rehabilitation trials show reduction in cardiovascular events for patients with recent cardiovascular illness, although most trials include risk-factor modification in addition to exercise training, making it difficult to isolate the effect of physical activity. Guidelines[8,9] extend recommendations for 150 minutes of moderate activity per week for middle-aged adults to older adults based on studies to date. However, these trials have not included many frail older adults who are at highest risk for CVD and disability. Thus, many questions remain as to the optimal frequency, intensity, and modality of physical activity for older adults. To our knowledge, whether a physical activity intervention can prevent CVD events in older, functionally limited individuals is unknown.

The Lifestyle Independence and Interventions for Elders (LIFE) Study compared PA with health education and showed that a structured PA program can prevent mobility disability in older adults with functional limitations. In the trial, incident major mobility disability occurred in 30.1% of the PA group and 35.5% of the health education group (hazard ratio [HR], 0.82; 95% CI, 0.69-0.98).[10] As a tertiary outcome, we compared cardiovascular event rates between the 2 study groups. The PA intervention was conducted over an average of 2.5 years and included moderate aerobic activity, mostly walking, of at least 150 minutes per week; thus, the study can be viewed as an evaluation of the benefits of guidelines for prevention of CVD events.[8,9]

Key Points

Question Is cardiovascular morbidity and mortality reduced in participants in a long-term physical activity program?

Findings In a randomized trial cardiovascular disease events occurred in 14.8% of the physical activity group and 13.8% of the successful aging group. This difference was not significant.

Meaning Among participants in the LIFE Study, an aerobically based, moderately intensive physical activity program was not associated with reduced cardiovascular events in spite of the intervention's previously documented ability to prevent mobility disability.

Methods

The LIFE study was a multicenter, single-blinded, randomized trial of PA compared with health education conducted at 8 field centers across the United States (University of Florida, Gainesville and Jacksonville; 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, Gainesville, and the Data Management, Analysis, and Quality Control Center was at Wake Forest School of Medicine. The field centers included rural, suburban, and urban communities.

Details of the trial design, recruitment, and primary outcome have been published previously (eFigure 1 in the Supplement).[10-12] Men and women aged 70 to 89 years were eligible if they were sedentary, defined as reporting less than 20 minutes/week in the past month performing regular PA and reporting less than 125 minutes/week of moderate PA; were at high risk for mobility disability based on objective lower extremity functional limitations as measured by the Short Physical Performance Battery (SPPB)[13] score of 9 or lower of a total of 12 (45% of participants were targeted to have an SPPB score <8); could walk 400 m in 15 minutes or less without sitting, leaning, or the help of another person or walker; had no major cognitive impairment (Modified Mini-Mental State Examination[14] 1.5 SDs below education- and race/ethnicity–specific norms); and could safely participate in the intervention as determined by medical history, a practitioner-administered physical examination, and resting electro-cardiogram (ECG) reading. 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.[10,11] 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 safety monitoring board appointed by the National Institute on Aging.

Randomization

Participants were randomized to a PA or to a successful aging (SA) program via a secure, internet-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 PA intervention involved walking (with a goal of 150 minutes/week), strength training, flexibility training, and balance training.[11] 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 PA for medical reasons. The PA 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's Scale of Self-perceived Exertion[15] (score range, 6-20), was used to measure intensity of activity. Participants were asked to walk at an intensity of 13 ("somewhat hard"), and lower extremity strengthening exercises were performed at an intensity of 15 to 16. The SA group attended weekly workshops of health education during the first 26 weeks and then monthly sessions thereafter.

Cardiovascular Disease Assessment

At baseline, prevalent CVD was defined as self-report of MI, congestive heart failure, stroke, or MI pattern on ECG. At each 6-month contact, all participants (or a proxy informant if the participant was unavailable) were questioned about all hospitalizations since the last visit. Proxy reports accounted for less than 0.1% of the follow-up contacts. Hospital records were obtained to abstract information for study criteria for the primary and secondary outcomes, masked to group assignment. Cardiovascular disease events were a predefined tertiary outcome and consisted of a composite of MI, hospitalized angina, hospitalized congestive heart failure, revascularization with bypass surgery or percutaneous angioplasty, ruptured abdominal aortic aneurysm, hospitalization for carotid artery disease, hospitalization for peripheral artery disease or outpatient revascularization for peripheral artery disease, any stroke, transient ischemic attack requiring hospitalization, and death from CVD. Records and abstraction forms were sent to the administrative coordinating center for central review by 2 physician investigators who were also masked to group assignment, with adjudication as definite or probable by 2 reviewers. If there were differences between these reviewers, cases were discussed by the full committee. Only definite events were included in this report.

Reports of death were tracked through regular surveillance, and death certificates were obtained to supplement the hospital record review. Silent MI was assessed by ECGs obtained at baseline, 18 months, and 36 months and read using standard algorithms at a central reading center.[16] The time from randomization date to the first cardiovascular event, fatal or nonfatal, was used to define incidence during the trial. Total CVD events and a limited outcome of MI (excluding silent MI on ECG), stroke, or CVD death were examined. Analyses were conducted for the overall sample and by baseline history vs no history of cardiovascular disease.

Measurements

Participants were assessed at baseline and every 6 months at clinic visits by assessors who were also masked to intervention group assignment. The baseline assessments included self-reported demographic and contact information, medical and hospitalization history, medication inventory, ECG, physical examination, health care use, physical activity assessed with the Community Healthy Activities Model Program for Seniors questionnaire[17] and with accelerometry over 7-day periods (Actigraph Inc), cognitive testing, 400 m walk test,[18] the SPPB, body weight, blood pressure, and pulse rate. These measures were repeated during follow-up at varied intervals.[11] The SPPB consisted of a 4-m walk at usual pace, a timed repeated chair stand, and 3 increasingly difficult standing balance tests.[13,19] 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. Home, telephone, and proxy assessments were attempted if the participants could not come to the clinic.

Statistical Considerations

The collection of cardiovascular events was added as a tertiary outcome after the sample size was fixed for the primary outcome. As such, the power for the combined cardiovascular events outcome was lower than desired. Assuming 8%/year loss to follow-up, a 4%/year event rate in the SA group, and a 30% effect (HR of 0.7), we had only 51% power using a 2-sided test at the 5% level. With 80% power, we could detect a minimum effect size of 42% and with 90% power, a 47% effect. Baseline characteristics were summarized by intervention group using mean (SD) or percentages. The effect of the intervention on CVD (ie, time until the initial ascertainment) 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 intervention arms, we used a likelihood ratio test from a Cox regression model, stratified by field center and sex. Interaction terms were entered into these Cox models to assess the consistency of the intervention effect across levels of prespecified baseline subgroups (ethnicity/race, sex, CVD, diabetes, walking speed, and SPPB score). No explicit assessment for multiplicity was made.

Results

The 1635 LIFE study participants were predominantly women (67%), with a mean (SD) age of 78.7 (5.2) years; 288 (20%) were African American, 108 (6%) were Hispanic or other race/ethnic group, and 1239 (74%) were non-Latino white. The overall prevalence of CVD at baseline was 129 (8%) for MI, 104 (6.5%) for stroke, and 71 (4.2%) for heart failure with an overall baseline prevalence of 30%. Hypertension and diabetes were common (1151 [69%] and 415 [26%], respectively), while only 50 (3%) currently smoked cigarettes. Mean (SD) body mass index (calculated as weight in kilograms divided by height in meters squared) was 30 (5.5). Lipid levels, blood pressure, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol varied. Reflecting a high risk of disability, the mean SBBP was 7.4. These characteristics were balanced between the intervention groups (**Table 1**).

Total incident CVD occurred in 14.3% overall, with 121 of 818 PA participants (14.8%) and 113 of 817 SA participants (13.8%) or 6.2 vs 5.6 events per 100 person-years (HR, 1.10; 95% CI, 0.85-1.42). For the more limited combined outcome of MI, stroke, or cardiovascular death, rates were 38 (4.6%) in the PA group and 37 (4.5%) in the SA group or 1.8 vs 1.7 events per 100 person-years (HR, 1.05; 95% CI, 0.67-1.66). There was no

difference in the rate of individual events between intervention groups (**Table 2** and **Figure 1**).

In prespecified subgroup analyses, there were no differences in rates of incident vs recurrent CVD (**Figure 2**). Among participants with an SPPB score less than 8, CVD rates were 14.2% in PA vs 17.7% in SA (HR, 0.76; 95% CI, 0.52-1.10), compared with 15.3% vs 10.5% (HR, 1.59; 95% CI, 1.09-2.30) among those with an SPPB score of 8 or 9 (*P* for interaction = .006). The interaction was not significantly different for the more limited composite end point of MI, stroke, or CVD death. For the limited outcome, among participants with an SPPB score less than 8, CVD rates were 5.4% in PA vs 5.6% in SA (HR, 0.94; 95% CI, 0.50-1.75), compared with 4.1% vs 3.6% (HR, 1.20; 95% CI, 0.62-2.34) among those with an SPPB score of 8 or 9 (*P* for interaction = .59) (eFigures 2 and 3 in the Supplement).

Because the observed effect of the intervention on CVD outcomes was marginally significant in lower vs higher SPPB subgroup, we examined the demographic, health characteristics, and types of CVD events by SPPB subgroup. We also examined the level of PA and level of exertion with PA during the trial by intervention group as well as SPPB subgroup (eTable in the Supplement). There were no differences in baseline characteristics by SPPB subgroup such as prevalent CVD, CVD risk factors, physical activity, or perceived level of exertion at baseline. There were more silent MIs by ECG in the higher SPPB subgroup but not more cardiovascular procedures, and this did not explain the relatively higher risk in the higher SPPB subgroup. Over the course of the study, higher SPPB subgroups had higher measured activity and lower perceived exertion than the lower SBBP subgroups in both the PA group and the SA group (eFigure 4 in the Supplement).

Table 1. Baseline Characteristics of Participants by Intervention Group

Description	Physical Activity (n = 818)	Successful Aging (n = 817)
Age at randomization, mean (SD), y	78.7 (5.2)	79.1 (5.2)
Women, No. (%)	547 (66.9)	551 (67.4)
Race/ethnicity, white, No. (%)	604 (73.8)	635 (77.7)
Education: college or higher, No. (%)	515 (63.0)	529 (65.1)
Lower extremity Short Physical Performance Battery score <8, No. (%)	353 (43.2)	378 (46.3)
3MSE: total score (max = 100), mean (SD)	91.5 (5.5)	91.6 (5.3)
Cardiovascular disease, No. (%)	236 (28.9)	254 (31.1)
Myocardial infarction, No. (%)	60 (7.4)	69 (8.5)
Stroke, No. (%)	57 (7.0)	52 (6.4)
Heart failure, No. (%)	26 (3.2)	45 (5.6)
Other self-report CVD, No. (%)	157 (19.2)	163 (20.0)
Framingham Risk score, mean (SD)	10.1 (7.3)	10.1 (7.3)
Hypertension, No. (%)	573 (70.5)	578 (71.5)
Diabetes, No. (%)	199 (24.4)	216 (26.6)
Smoker, No. (%)		
Past	381 (47.2)	341 (42.7)
Current	26 (3.2)	24 (3.0)
Cholesterol level, mean (SD), mg/dL		
Total	179.3 (39.6)	178.5 (39.9)
LDL	93.6 (32.2)	93.1 (33.1)
HDL	61.1 (18.0)	61.1 (17.6)

Abbreviations: 3MSE, Modified Mini-Mental State Examination; CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; max, maximum.

SI conversion: To convert high-density lipoprotein cholesterol to micromoles per liter, multiply by 0.0259; to convert to low-density lipoprotein cholesterol to micromoles per liter, multiply by 0.0259.

Table 2. Type of CVD Outcome by Intervention Group

Outcome	Physical Activity (n = 818)		Successful Aging (n = 817)			
	Annualized Incidence Rate per 100 py, (95% CI)[a]	No. (%)	Annualized Incidence Rate per 100 py, (95% CI)[a]	No. (%)	HR (95% CI)[b]	*P* Value
Total fatal or nonfatal cardiovascular disease[c]	6.2 (5.2-7.4)	121 (14.8)	5.6 (4.7-6.8)	113 (13.8)	1.10 (0.85-1.42)	.49
Fatal or nonfatal myocardial infarction, stroke or cardiovascular death	1.8 (1.3-2.5)	38 (4.6)	1.7 (1.3-2.4)	37 (4.5)	1.05 (0.67-1.66)	.83
Cardiovascular death	0.5 (0.3-0.9)	10 (1.2)	0.7 (0.4-1.1)	14 (1.7)	0.71 (0.32-1.60)	.41
Myocardial infarction	0.6 (0.3-1.0)	12 (1.5)	0.5 (0.3-0.9)	10 (1.2)	1.22 (0.53-2.83)	.64
Silent myocardial infarction	1.7 (1.2-2.4)	35 (4.3)	1.8 (1.3-2.5)	38 (4.7)	0.92 (0.58-1.45)	.71
Angina/symptomatic coronary artery disease	0.8 (0.5-1.2)	16 (2.0)	0.5 (0.3-0.9)	10 (1.2)	1.64 (0.74-3.61)	.22
Stroke	0.9 (0.6-1.4)	19 (2.3)	1.0 (0.6-1.5)	21 (2.6)	0.94 (0.51-1.76)	.85
Coronary revascularization	1.0 (0.6-1.5)	20 (2.4)	0.5 (0.3-0.9)	10 (1.2)	2.08 (0.97-4.45)	.05
CHF	1.3 (0.9-1.9)	28 (3.4)	1.3 (0.9-1.9)	27 (3.3)	1.06 (0.62-1.79)	.84
Abdominal aortic aneurysm	0.1 (0.0-0.4)	3 (0.4)	0.0 (0.0-0.3)	1 (0.1)	2.99 (0.31-28.76)	.31
Peripheral artery disease	0.2 (0.1-0.6)	5 (0.6)	0.3 (0.1-0.6)	6 (0.7)	0.85 (0.26-2.78)	.78
Carotid revascularization	0.0 (0.0-0.0)	0	0.1 (0.0-0.4)	2 (0.2)	0.00 (0.00-0.0)	.10
Transient ischemic attack	0.3 (0.1-0.6)	6 (0.7)	0.2 (0.1-0.6)	5 (0.6)	1.24 (0.38-4.07)	.72

Abbreviations: CHF, congestive heart failure; CVD, cardiovascular disease; HR, hazard ratio; py, person-years.

[a] Incident event rates estimated from an exponential survival model.

[b] Hazard ratios from a proportional hazards model stratified by clinical site and sex.

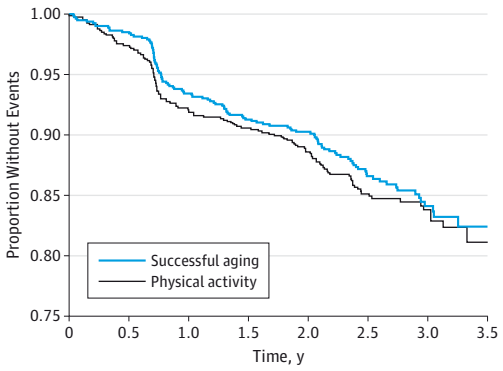
[c] Fatal or nonfatal myocardial infarction, stroke, cardiovascular death, silent myocardial infarction, angina/symptomatic coronary artery disease, peripheral artery disease, and abdominal aortic aneurysm (our predefined primary CVD end point). The total incidence is the number of participants who developed any of these conditions during the trial and thus will differ from the sum of the disease-specific totals.

Discussion

Among participants in the LIFE Study, an aerobically based, moderately intensive PA program was not associated with reduced cardiovascular events. Participants in the LIFE study had a substantial baseline burden of prevalent CVD and cardiovascular risk factors and had a high rate of cardiovascular events (14.3%) during the 2.6 years of follow-up in the LIFE Study. In what is, to our knowledge, the only randomized trial of sustained PA in functionally limited older adults, the benefits of activity appear to be primarily reduced mobility disability[10] and perhaps improved cognition.[20]

The lack of benefit for CVS was similar in most subgroups including the one-third of the cohort with prevalent CVD at baseline. Individuals with poorer physical performance at baseline, defined as an SPPB score less than 8, had a more favorable benefit from PA for the outcome of CVD than those with a more moderate level of SPPB, as indicated by the statistically significant interaction term. In the LIFE study, a pattern of relatively more favorable benefit for older and more poorly functioning individuals was observed for the primary outcome of major mobility disability[10]and for other secondary outcomes.[10,21,22] In the case of the CVD outcome, the subgroup with less severe impairment had a higher rate of events in the PA group when compared with the SA/health education group. Further evaluation of the characteristics and activity of the SPPB 8 to 9 subgroup did not provide an obvious explanation for the higher event rate with PA in the high SPPB subgroup (8-9) vs the low SPPB subgroup (≤7). Participants with a higher baseline SPPB score reported a lower level of exertion

Figure 1. Total Cardiovascular Disease Event Rates by Intervention Group



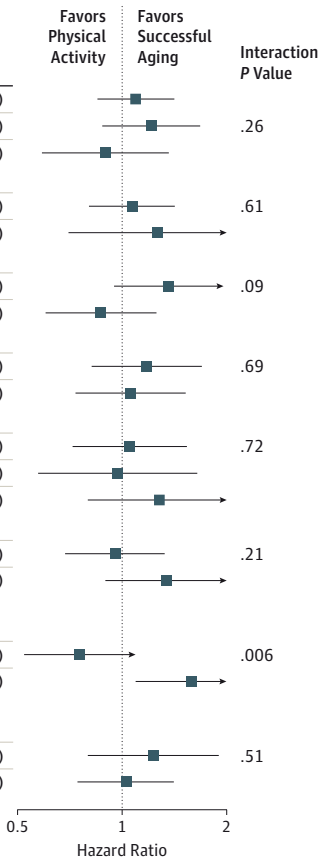
No. at risk

Successful aging	817	797	745	715	654	447	217	17
Physical activity	818	780	728	701	633	426	207	11

Cumulative hazards plot.

Figure 2. Total Cardiovascular Disease Event Rates

Subgroup	Physical Activity: No. of Events/ No. of Participants	Successful Aging: No. of Events/ No. of Participants	Hazard Ratio (95% CI)	Interaction *P* Value
Overall sex	121/818	113/817	1.10 (0.85-1.42)	
Female	79/547	68/551	1.21 (0.88-1.68)	.26
Male	42/271	45/266	0.90 (0.59-1.36)	
Ethnicity/race				
Non-Hispanic white	93/604	94/635	1.07 (0.80-1.42)	.61
Other	28/211	19/180	1.26 (0.70-2.28)	
Age				
70-79 y	67/477	52/455	1.36 (0.95-1.96)	.09
≥80 y	54/341	61/362	0.87 (0.60-1.26)	
History of cardiovascular disease				
No cardiovascular disease	62/582	53/563	1.18 (0.81-1.70)	.69
Cardiovascular disease	59/236	60/254	1.06 (0.73-1.53)	
History of diabetes				
None	54/406	53/414	1.05 (0.72-1.54)	.72
Impaired FG	28/192	28/165	0.97 (0.57-1.65)	
Diabetes	39/220	32/238	1.28 (0.80-2.06)	
Gait speed				
<0.8 m/s	67/485	72/508	0.96 (0.68-1.33)	.21
≥0.8 m/s	54/333	41/309	1.34 (0.89-2.02)	
Short physical performance battery score				
<8	50/353	67/378	0.76 (0.52-1.10)	.006
8 or 9	71/465	46/439	1.59 (1.09-2.30)	
Modified Mini-Mental State Examination				
<90	56/261	38/261	1.23 (0.80-1.90)	.51
≥90	75/557	75/556	1.03 (0.75-1.42)	



Hazard ratios and interaction *P* values by intervention group and subgroups. FG indicates fasting glucose.

with activity and had a similar relative increase in activity compared with the control group, as did the low SPPB subgroup. Of note, this interaction was not significant when CVD events were restricted to MI, stroke, and CVD death. While prespecified, these subgroup comparisons were meant to be hypothesis-generating rather than designed to test specific hypotheses.

There are several potential explanations for a lack of CVD reduction in the LIFE study. It is possible that the dose of activity was of suboptimal duration or intensity. Given the high burden of CVD, it is also possible that it was too late for this high-risk group to benefit. We also noted that both the SA and PA groups became more physically active by self-report, although only the PA group by actigraphy.[10] Potentially the contrast between the PA and SA groups was less than if a completely sedentary comparator had been used. It is also possible that the more frequent contact biased the PA group to report more events to the masked assessors or that PA could have precipitated some events in this vulnerable population. In the analysis stratified by SPPB score, when we excluded the symptomatic outcomes in the limited outcome, the difference by SPPB score was not statistically significant.

There are several important limitations to this study. Follow-up was only 2.6 years on average. Statistical power was limited to detect small differences in rates or in subgroups.

Previous trials of activity in older adults have focused on intermediate outcomes such as lowering of blood pressure, weight, and improving function.[23,24] In adults with type 2 diabetes, the Look AHEAD (Action for Health for Diabetes) study tested whether a lifestyle intervention that included sustained PA with weight loss could reduce CVD events. While findings were negative for the primary CVD outcome,[25] rates of disability were reduced.[24] Together, these studies suggest that physical activity should be recommended for improving quality of the remaining years of life.

Conclusions

Guidelines for PA for older adults include at least 150 minutes/week of moderate-intensity aerobic activity with weight training.[23] The LIFE intervention meets these guidelines and proved to be safe and efficacious for the prevention of major mobility disability. The lack of association between increased PA and reduced CVD found here should not detract from efforts to promote a program of sustained walking and weight training in frail older adults.

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Author Contributions: Dr Ambrosius 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.
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