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How to cite

TROMBETTI, Andrea et al. Effect of Physical Activity on Frailty: Secondary Analysis of a Randomized Controlled Trial. In: Annals of Internal Medicine, 2018, vol. 168, n° 5, p. 309–316. doi: 10.7326/M16-2011

This publication URL: https://archive-ouverte.unige.ch/unige:112934

Publication DOI: 10.7326/M16-2011

Annals of Internal Medicine ORIGINAL RESEARCH

Effect of Physical Activity on Frailty

Secondary Analysis of a Randomized Controlled Trial

Andrea Trombetti, MD; Mélany Hars, PhD; Fang-Chi Hsu, PhD; Kieran F. Reid, PhD; Timothy S. Church, MD, PhD; Thomas M. Gill, MD; Abby C. King, PhD; Christine K. Liu, MD; Todd M. Manini, PhD; Mary M. McDermott, MD; Anne B. Newman, MD; W. Jack Rejeski, PhD; Jack M. Guralnik, MD, PhD; Marco Pahor, MD; and Roger A. Fielding, PhD; for the LIFE Study Investigators*

Background: Limited evidence suggests that physical activity may prevent frailty and associated negative outcomes in older adults. Definitive data from large long-term randomized trials are lacking.

Objective: To determine whether a long-term, structured, moderate-intensity physical activity program is associated with a lower risk for frailty and whether frailty status alters the effect of physical activity on the reduction in major mobility disability (MMD) risk.

Design: Multicenter, single-blind, randomized trial.

Setting: 8 centers in the United States.

Participants: 1635 community-dwelling adults, aged 70 to 89 years, with functional limitations.

Intervention: A structured, moderate-intensity physical activity program incorporating aerobic, resistance, and flexibility activities or a health education program consisting of workshops and stretching exercises.

Measurements: Frailty, as defined by the SOF (Study of Osteoporotic Fractures) index, at baseline and 6, 12, and 24 months, and MMD, defined as the inability to walk 400 m, for up to 3.5 years.

Results: Over 24 months of follow-up, the risk for frailty (n = 1623) was not statistically significantly different in the physical activity versus the health education group (adjusted prevalence difference, −0.021 [95% CI, −0.049 to 0.007]). Among the 3 criteria of the SOF index, the physical activity intervention was associated with improvement in the inability to rise from a chair (adjusted prevalence difference, −0.050 [CI, −0.081 to −0.020]). Baseline frailty status did not modify the effect of physical activity on reducing incident MMD (P for interaction = 0.91).

Limitation: Frailty status was neither an entry criterion nor a randomization stratum.

Conclusion: A structured, moderate-intensity physical activity program was not associated with a reduced risk for frailty over 2 years among sedentary, community-dwelling older adults. The beneficial effect of physical activity on the incidence of MMD did not differ between frail and nonfrail participants.

Primary Funding Source: National Institute on Aging, National Institutes of Health.

Ann Intern Med. 2018;168:309-316. doi:10.7326/M16-2011 **Annals.org**

For author affiliations, see end of text.

This article was published at Annals.org on 9 January 2018.

* For members of the LIFE (Lifestyle Interventions and Independence for Elders) Study Investigators, see **Appendix 1** (available at Annals.org).

Frailty, a state of increased vulnerability to stressor events, confers a high risk for surgical complications, morbidity, disability, and mortality in older adults (1–9). Presently, no universally accepted consensus definition of frailty exists (7, 10). However, Ensrud and colleagues (2) proposed a frailty index based on data from the SOF (Study of Osteoporotic Fractures). This widely used index measures frailty on the basis of 2 or more of the following criteria: the inability to rise from a chair 5 times without using the arms, a self-reported reduced energy level, and weight loss.

Emerging evidence suggests that exercise-based interventions may improve physical functioning and prevent disability in frail older persons (11–13). Yet, to date, no large randomized trial has examined whether long-term physical activity reduces the risk for frailty over an extended follow-up or prevents associated mobility disability. The main findings from the LIFE (Lifestyle Interventions and Independence for Elders) trial showed that a structured, moderate-intensity physical activity program reduced major mobility disability (MMD) over 2.7 years among older adults at risk for disability (14). Because frailty status was not examined in the primary LIFE study findings, whether long-term physical activity may also prevent MMD in frail older persons remains unknown.

To address the limitations of previous research, we conducted a secondary analysis of data from the LIFE trial to specifically evaluate the effect of physical activity on frailty and MMD. The objectives of our analyses were to determine whether a long-term, structured, moderate-intensity physical activity program is associated with the risk for frailty, as defined by the SOF frailty index, and whether frailty status at baseline modifies the reduction of MMD observed with physical activity.

Methods

Trial Design

The LIFE study was a multicenter, single-blind, parallel-group randomized trial conducted across the United States between February 2010 and December 2013. It was designed to compare long-term physi-

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Table 1. Baseline Characteristics of Participants, by Randomization Group and Frailty Status*

Characteristic	Physical Activity (*n* = 812)			Health Education (*n* = 811)		
	Frail (*n* = 159)	Not Frail (*n* = 653)	All (*n* = 812)	Frail (*n* = 160)	Not Frail (*n* = 651)	All (*n* = 811)
Mean age (SD), *y*	79.5 (5.7)	78.5 (5.1)	78.7 (5.2)	80.0 (5.3)	78.8 (5.2)	79.1 (5.2)
Female sex, *n (%)*	114 (71.7)	431 (66.0)	545 (67.1)	118 (73.8)	428 (65.7)	546 (67.3)
Race/ethnicity, *n (%)*						
White	110 (69.2)	492 (75.3)	602 (74.1)	128 (80.0)	502 (77.1)	630 (77.7)
African American	37 (23.3)	124 (19.0)	161 (19.8)	25 (15.6)	100 (15.4)	125 (15.4)
Other	12 (7.5)	37 (5.7)	49 (6.0)	7 (4.4)	49 (7.5)	56 (6.9)
Lives alone, *n (%)*	81 (50.9)	306 (46.9)	387 (47.4)	90 (56.3)	326 (50.1)	416 (51.3)
Postgraduate education, *n (%)*	38 (23.9)	153 (23.5)	191 (23.6)	42 (26.6)	165 (25.4)	207 (25.7)
Mean BMI (SD), kg/m^2	30.4 (6.1)	30.0 (5.6)	30.1 (5.7)	29.3 (6.4)	30.6 (6.2)	30.3 (6.2)
Mean 3MSE score (SD)	90.9 (5.6)	91.7 (5.4)	91.6 (5.5)	91.5 (5.7)	91.7 (5.3)	91.6 (5.3)
Mean CES-D score (SD)	14.2 (9.7)	7.0 (6.4)	8.4 (7.7)	14.0 (9.2)	7.6 (7.0)	8.8 (7.9)
Mean quality-of-life score (SD)	0.6 (0.1)	0.6 (0.1)	0.6 (0.1)	0.6 (0.1)	0.6 (0.1)	0.6 (0.1)
Mean albumin level (SD), *g/L*	41 (3)	42 (3)	41 (3)	41 (3)	42 (2)	41 (2)
Mean creatinine clearance (SD), $mL/min/1.73\ m^2$	70.1 (29.0)	69.6 (24.6)	69.7 (25.5)	67.1 (25.8)	72.4 (26.4)	71.3 (26.4)
Mean chronic conditions (SD), *n*	1.8 (1.1)	1.8 (1.2)	1.8 (1.1)	2.0 (1.2)	1.8 (1.1)	1.8 (1.2)
Mean accelerometry of moderate physical activity (SD), *min/wk*†	149.9 (117.1)	201.3 (159.4)	191.7 (153.7)	165.7 (166.6)	210.4 (188.9)	201.8 (185.6)
Mean SPPB score (SD)	6.5 (1.9)	7.7 (1.4)	7.4 (1.6)	6.3 (1.8)	7.6 (1.4)	7.3 (1.6)
SPPB score ≥8, *n (%)*	60 (37.7)	403 (61.7)	463 (57.0)	53 (33.1)	384 (59.0)	437 (53.9)
Inability to rise from a chair 1 time without using the arms, *n (%)*	43 (27.0)	33 (5.1)	76 (9.4)	63 (39.4)	36 (5.5)	99 (12.2)
Mean chair stand time (SD), *s*	16.4 (5.9)	16.8 (4.8)	16.7 (5.0)	18.8 (12.5)	16.8 (5.0)	17.0 (6.3)
Mean handgrip strength (SD), *kg*	21.9 (8.0)	25.5 (10.5)	24.8 (10.2)	22.4 (9.0)	24.9 (9.8)	24.5(9.7)
Mean 400-m gait speed (SD), *m/s*	0.8 (0.2)	0.8 (0.2)	0.8 (0.2)	0.8 (0.2)	0.8 (0.2)	0.8 (0.2)
Criteria for the SOF frailty index, *n (%)*						
Inability to rise from a chair 5 times without using the arms	67 (42.1)	48 (7.4)	115 (14.2)	87 (54.4)	51 (7.8)	138 (17.0)
Weight loss‡	111 (69.8)	38 (5.8)	149 (18.3)	112 (70.0)	37 (5.7)	149 (18.4)
Reduced energy level§	152 (95.6)	263 (40.3)	415 (51.1)	150 (93.8)	277 (42.5)	427 (52.7)
Frail according to the SOF frailty index, *n (%)*	159 (100)	0 (0)	159 (19.6)	160 (100)	0 (0)	160 (19.7)
Mean SOF frailty index criteria (SD), *n*	2.1 (0.3)	0.5 (0.5)	0.8 (0.8)	2.2 (0.4)	0.6 (0.5)	0.9 (0.8)
Number of SOF frailty index criteria, *n (%)*						
0	0 (0)	304 (46.6)	304 (37.4)	0 (0)	286 (43.9)	286 (35.3)
1	0 (0)	349 (53.4)	349 (43.0)	0 (0)	365 (56.1)	365 (45.0)
2	147 (92.5)	0 (0)	147 (18.1)	131 (81.9)	0 (0)	131 (16.2)
3	12 (7.6)	0 (0)	12 (1.5)	29 (18.1)	0 (0)	29 (3.6)

3MSE = modified Mini-Mental State Examination; BMI = body mass index; CES-D = Center for Epidemiologic Studies Depression Scale; SOF = Study of Osteoporotic Fractures; SPPB = Short Physical Performance Battery.
* Frailty was defined according to the SOF frailty index. Percentages may not sum to 100 due to rounding.
† Defined based on the 760 counts/min cut point.
‡ Based on weight measurements except at the baseline visit. This criterion was considered present at baseline if the participant reported a loss of appetite on the health-related quality-of-life questionnaire.
§ Defined by using the following statement from the health-related quality-of-life questionnaire: "During the past week, how often have you felt full of energy?"

cal activity with a health education program with regard to the incidence of MMD (ClinicalTrials.gov: NCT01072500). This article presents the results of a secondary analysis that was not prespecified in the study protocol. The rationale, design, and methods of the LIFE study were presented in detail elsewhere

Table 2. Cumulative Incidence of First Frailty Among Nonfrail Participants at Baseline, by Randomization Group*

Assessment Time	Physical Activity (*n* = 653)		Health Education (*n* = 651)	
	Participants, *n*	Count/Person-Year (95% CI)	Participants, *n*	Count/Person-Year (95% CI)
6 mo	69	0.25 (0.20 to 0.30)	99	0.34 (0.30 to 0.39)
12 mo	120	0.23 (0.20 to 0.26)	133	0.25 (0.22 to 0.28)
24 mo	168	0.18 (0.16 to 0.20)	186	0.19 (0.17 to 0.21)

IPW = inverse probability weighting; ITT = intention-to-treat.
* Frailty was defined according to the Study of Osteoporotic Fractures frailty index.
† Test based on Poisson regression after adjusting for sex and clinical sites. Logarithm of follow-up time was used as an offset.
‡ Weighted for the inverse probability of randomization to the intervention group among nonfrail participants to account for the potential imbalance in the number of frail participants by group at baseline caused by the secondary analysis design.
§ Weighted for the inverse probability of incomplete follow-up to account for loss to follow-up and adjusted for the probability of randomization to the intervention group among nonfrail participants (treated as a propensity score) to account for baseline imbalance.

(14–16). The study protocol was approved by the institutional review boards at all participating sites. Written informed consent was obtained from all participants.

Participants

Participants were described previously (14, 16). Briefly, persons were eligible for the study if they were between the ages of 70 and 89 years, had a high risk for mobility disability (that is, a Short Physical Performance Battery [SPPB] score ≤9 points) (17), could walk 400 m in 15 minutes or less unassisted, and were sedentary.

Randomization and Interventions

Participants were randomly assigned in a 1:1 allocation to the physical activity or health education program, with stratification by sex and field center. Each participant was followed until the last person randomly assigned completed the 24-month visit. The intervention period ranged from approximately 2 to 3.5 years.

The physical activity intervention involved a combination of walking (up to 150 min/wk) and strength, balance, and flexibility exercises, as previously described (15). The health education program included workshops emphasizing topics relevant to older adults (15).

Outcome Measures

Participants were assessed every 6 months, and assessment staff (nurses or project coordinators) were blinded to the intervention assignment.

Frailty

Frailty status was determined at baseline and 6, 12, and 24 months by using the SOF frailty index (2). The inability to rise from a chair 5 times without using the arms was obtained from the chair-rise test component of the SPPB (17). Self-reported reduced energy level was defined by asking the following question on the health-related quality-of-life questionnaire: "During the past week, how often have you felt full of energy?" The criterion was considered to be present if the participant answered "Some of the time," "A little bit of the time," or "None of the time." Weight loss was based on weight measurements and was met if the participant had a body weight loss of 4.55 kg or more (or ≥5%) during the preceding 12 months or 2.275 kg or more (or ≥2.5%) during the preceding 6 months, with the exception of the baseline visit. Because no objective information was available at baseline regarding weight loss, the criterion was met at that point if the participant reported a loss of appetite on the health-related quality-of-life questionnaire. Subjects were considered "frail" if at least 2 of the 3 criteria were fulfilled.

MMD

Major mobility disability was defined as the inability to complete a 400-m walk, and persistent mobility disability (PMD) was defined as having 2 consecutive MMD assessments or MMD followed by death (14, 15).

Statistical Analysis

Baseline characteristics were summarized by randomization group and frailty status by using mean and SD, or percentages. The intention-to-treat (ITT) approach was used as the primary analysis, in which participants were grouped according to their assignment. All eligible randomly assigned participants were included in the analyses, except for the incidence analysis, which excluded those who had frailty at baseline.

The difference in cumulative incidence of first frailty between the 2 intervention groups at each visit among nonfrail participants at baseline was analyzed by using Poisson regression (*poisson* in Stata [StataCorp]), adjusting for sex and center, with logarithm of time as an offset. No competing risk analysis was considered. The marginal standardization approach (*margins* in Stata) (18) was used to calculate the 95% CI of the difference in cumulative incidence. Sensitivity analyses also were performed. To correct for the potential imbalance in the number of frail participants by group at baseline due to the secondary analysis design, we weighted by the probability of randomization calculated from a logistic regression using the inverse probability weighting (IPW) approach (19). In addition, we explored the impact of incomplete follow-up by using the same approach (Appendix 2, available at Annals.org).

The differences in prevalence between the 2 intervention groups for frailty and each criterion of frailty among the whole population were analyzed by using generalized estimating equation models with the logit link function, binomial distribution, and exchangeable working correlation (*xtgee* in Stata). The marginal stan-

Table–Continued

Difference Between Physical Activity and Health Education (95% CI)					
ITT Model	***P* Value†**	**IPW Model 1‡**	***P* Value†**	**IPW Model 2§**	***P* Value†**
−0.05 (−0.09 to −0.01)	0.013	−0.04 (−0.08 to −0.005)	0.029	−0.04 (−0.08 to −0.002)	0.041
−0.02 (−0.08 to 0.03)	0.38	−0.01 (−0.07 to 0.04)	0.59	−0.02 (−0.07 to 0.04)	0.54
−0.06 (−0.13 to −0.001)	0.048	−0.05 (−0.11 to 0.01)	0.099	−0.05 (−0.12 to 0.01)	0.110

Table 3. Risk for Frailty Over 24 Months Among all Study Participants, by Randomization Group*

Model	Average Prevalence Over 24 Months, %†		Prevalence Difference (95% CI)‡			
	Physical Activity	Health Education (Reference)	Unadjusted	*P* Value	Adjusted	*P* Value
ITT§	19.1	20.8	−0.021 (−0.049 to 0.008)	0.156	−0.021 (−0.049 to 0.007)	0.148
IPW§‖	-	-	−0.015 (−0.045 to 0.014)	0.30	−0.016 (−0.045 to 0.014)	0.30

IPW = inverse probability weighting; ITT = intention-to-treat.
* Frailty was defined according to the Study of Osteoporotic Fractures frailty index.
† Calculated as the sum of prevalence from each visit, including baseline, in the raw data divided by 4.
‡ Marginal standardization was used to obtain these values.
§ Sex and field center (both used to stratify randomization), intervention, time, time^2, and time^3 were included in the generalized estimating equation models (logit link function, binomial distribution [Stata]). Baseline outcome was retained in the outcome vector.
‖ Weighted for the inverse probability of remaining in the study.

dardization approach was used to calculate the CI of the prevalence difference. In these models, baseline outcome measure was retained in the outcome vector, and time was treated as continuous. Unadjusted and adjusted models were fitted. Centered time (time minus mean of time), time^2, and time^3 were entered into the model as covariates in addition to sex, field center, and intervention. Sensitivity analyses were performed by using IPW analysis (weight equivalent to the probability of remaining in the study calculated by using logistic regression). In addition, transition models (20) were used and complier-average causal effect (CACE) analysis was performed (**Appendix 2**) (21, 22).

The ordinal logistic regression with clustered sandwich estimator was used to assess the effect of the intervention on the number of frailty criteria with the same covariates specified in the models (*ologit* in Stata), with the interactions between time variables and intervention also entered into the models. The sensitivity analyses detailed earlier also were performed (**Appendix 2**).

The cumulative incidence curves for the first postrandomization occurrence of MMD and PMD when death was considered as a competing risk were plotted by intervention and baseline frailty groups (*proc lifetest* in SAS). Event time was defined as the time from randomization to the initial end point or death and censoring time as the time from randomization to the last assessment. The effects of the intervention and baseline frailty status on the first postrandomization occurrence of MMD and PMD were analyzed by using Cox proportional hazards models considering death as a competing risk (*proc phreg* in SAS [SAS Institute]). Sex and field center were treated as stratifying variables for the baseline hazard. Intervention and frailty status and their interaction were included in the model.

A 2-sided *P* value of 0.05 or less was considered statistically significant. Statistical analyses were performed in SAS, version 9.4 (TS1M3), and Stata/IC, version 12.1.

The LIFE trial was overseen by ethics committees at all 8 participating institutions, by the coordinating center, and by a data and safety monitoring board. Each institution obtained human subjects committee approval, and informed consent was given by all participants.

Role of the Funding Source

The National Institutes of Health (NIH) sponsor was a voting member of the 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.

RESULTS

Of the 14 831 persons screened, 1635 were randomly assigned (**Appendix Figure**, available at Annals.org). Overall, the mean age of participants was 78.9 years (SD, 5.2) and 67.2% were women. Baseline characteristics were similar in the 2 randomization groups (14, 16). At baseline, 12 participants had no frailty data and 19.7% (319 of 1623) were frail (**Table 1**). The mean number of frailty criteria was 0.9 (SD, 0.8) (**Appendix Table 1**, available at Annals.org). Intervention adherence over 24 months in the physical activity group did not differ between participants classified as frail and those not frail at enrollment (**Appendix Tables 2** and **3**, available at Annals.org). By month 24, 97 participants (5.9%) had dropped out of the study, including 53 who died.

Among nonfrail participants at baseline, the cumulative incidence of first frailty was lower in the physical activity than the health education group at 6 months (adjusted difference, −0.05 [CI, −0.09 to −0.01]; *P* = 0.013) and 24 months (−0.06 [CI, −0.13 to −0.001]; *P* = 0.048) (**Table 2**). The difference at 6 months remained statistically significant in IPW analyses.

The adjusted prevalence difference for the risk for frailty was not statistically significant in either the ITT or IPW analysis (−0.021 [CI, −0.049 to 0.007]; *P* = 0.148 in ITT analysis) (**Table 3** and **Appendix Table 1**). Conditional on the frailty status at the previous visit in transition models, the prevalence of frailty was lower in the physical activity than the health education group (ITT unadjusted prevalence difference, −0.021 [CI, −0.042 to −0.0003]; *P* = 0.047), although the adjusted estimate and IPW transition models were not statistically significant (**Appendix Table 4**, available at Annals.org).

When adherence to the interventions was taken into account, the CACE estimates of the reduction in frailty with physical activity compared with health education were statistically significant in all models (**Appendix Table 5**, available at Annals.org).

The inability to rise from a chair 5 times was the only frailty criterion affected by the intervention over the 24-month follow-up in both ITT and IPW analyses (adjusted prevalence difference in the ITT analysis, −0.050 [CI, −0.081 to −0.020]; $P = 0.001$) (**Appendix Table 6**, available at Annals.org). The prevalence of inability to rise from a chair was 2.8% to 5.8% lower in the physical activity than the health education group across assessment visits (**Appendix Table 1**).

The mean number of frailty criteria was generally lower in the physical activity than the health education group over time (**Appendix Table 1**). The risk for getting SOF frailty criteria in the physical activity group decreased over time compared with the health education group (P for the interaction between time and randomization group, 0.033 in the ITT analysis) (**Table 4**). The results for the transition models showed that participants in the physical activity group had lower odds of having a greater number of frailty criteria compared with the health education group in both the ITT and IPW analyses after adjustment for criteria at the previous visit (odds ratio, 0.88 [CI, 0.78 to 0.98]; $P = 0.019$ in the ITT analysis) (**Appendix Table 7**, available at Annals.org). The CACE result was not stable (data not shown).

Among the subgroup of frail participants, 67 of 159 physical activity participants (42%) and 78 of 160 health education participants (49%) had MMD, whereas 37 of 159 (23%) and 45 of 160 (28%), respectively, had PMD. Overall, baseline frailty status did not modify the effect of physical activity on reducing incident MMD (P for interaction = 0.91) and PMD (P for interaction = 0.64) (**Figure**).

DISCUSSION

This study demonstrated that 24 months of a structured, moderate-intensity physical activity program was not associated with a reduction in the overall risk for frailty in older adults, but it was associated with improvement in the SOF index criterion of inability to rise from a chair. The beneficial effects of the physical intervention on the incidence and persistence of MMD were not influenced by frailty status.

Data from the LIFE-P (LIFE Pilot) study suggested that physical activity was associated with a reduction in frailty prevalence, as measured by the Fried frailty index (9, 23). This measure includes the level of physical activity as a frailty criterion, and this study's findings were the result of increased physical activity behavior while the other criteria of frailty were not modified, suggesting that physical activity may not influence frailty status (23). In addition, the small number of frail participants may have limited the study's statistical power. Another randomized trial examining whether a multifactorial intervention including physical exercise could reduce frailty in participants who met the Fried criteria showed that the 12-month intervention reduced frailty by 14.7% (24). Because physical exercise was only one component of the intervention, isolating its specific effect from the other components was not possible. In the current study, our analysis used the SOF frailty index, which does not include physical activity as a criterion. We showed that the physical activity program was not associated with a reduced risk for frailty but did have a beneficial effect on the chair-rise criterion of the SOF index, by reducing the proportion of participants unable to get up from a chair 5 times without using their arms. Although we observed a robust reduction in the incidence of frailty at 6 months and the number of frailty criteria, the effect of the intervention on frailty prevalence was not consistent across different analytic approaches.

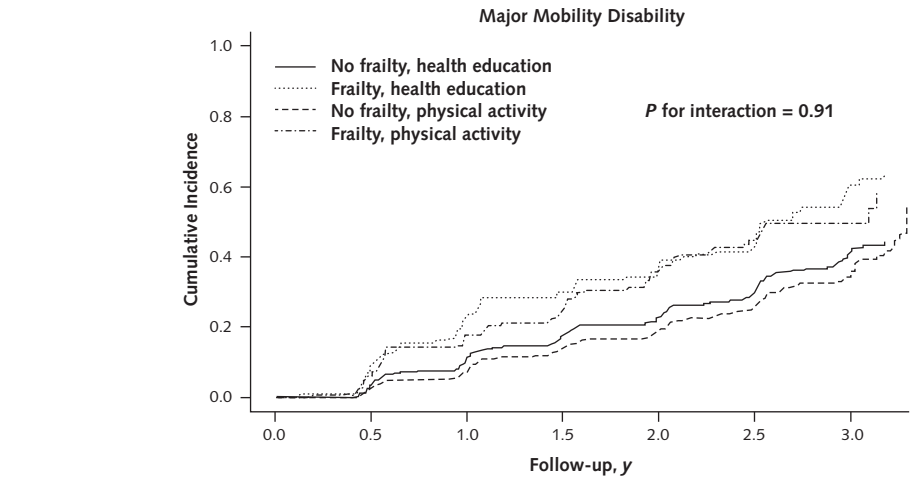
The interactions between frailty status and randomization group were not statistically significant for MMD outcome, suggesting that the effect of intervention did not differ according to frailty status. The results suggest the potential value of engaging frail persons in such structured physical activity programs, given the important benefit they might gain. The effect of exercise on disability among frail persons was examined by Daniels and colleagues (12) in a systematic review including studies in which participants had at least 1 physical

Table 4. Association Between the Number of Frailty Criteria and Randomization Group Over 24 Months in All Study Participants*

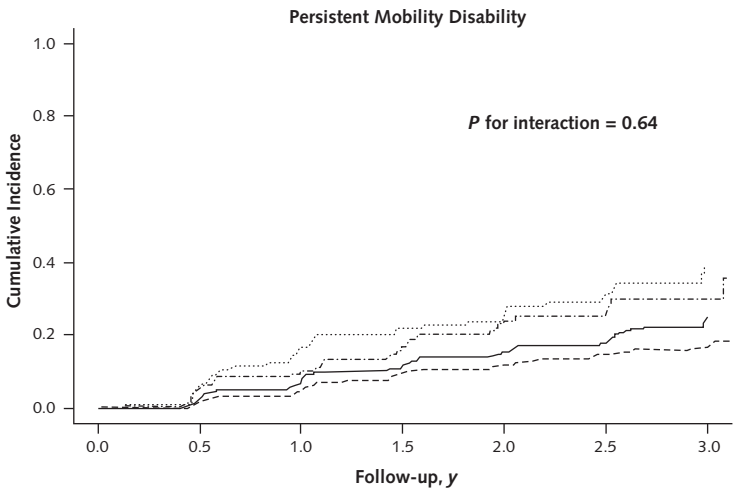
Model	Average Mean Frailty Criteria Over 24 Months (SD), n†		Odds Ratio (95% CI)				*P* Value for Interaction Time × Randomization Group‡
	Physical Activity	Health Education (Reference)	Unadjusted	*P* Value	Adjusted	*P* Value	
ITT§	0.86 (0.76)	0.92 (0.78)	0.88 (0.76–1.01)	0.075	0.87 (0.75–1.01)	0.072	0.033
IPW§‖	-	-	0.89 (0.77–1.03)	0.130	0.89 (0.77–1.03)	0.127	0.042

IPW = inverse probability weighting; ITT = intention-to-treat.
* Frailty was defined according to the Study of Osteoporotic Fractures frailty index.
† Calculated as the sum of the mean number from each visit, including baseline, in the raw data divided by 4.
‡ With the interaction time × randomization group entered into the models.
§ Sex and field center (both used to stratify randomization), intervention, time, time^2, and time^3 were included in the ordinal logistic regression models. Baseline outcome was retained in the outcome vector. The odds ratios from ordinal logistic regression models with clustered sandwich estimators were presented.
‖ Weighted for the inverse probability of remaining in the study.

Figure. Cumulative incidences of major mobility disability (*top*) and persistent mobility disability (*bottom*), by baseline frailty and intervention groups.



Participants at risk, *n*					
No frailty, health education	651	618	567	449	133
Frailty, health education	160	147	120	90	30
No frailty, physical activity	653	613	580	467	153
Frailty, physical activity	159	142	126	92	26



Participants at risk, *n*					
No frailty, health education	651	618	568	450	133
Frailty, health education	160	147	121	90	31
No frailty, physical activity	653	614	580	468	153
Frailty, physical activity	159	142	127	93	26

Frailty was defined according to the SOF index. SOF = Study of Osteoporotic Fractures.

frailty indicator, although frailty was not based on a validated definition (25). Their results suggest that physical activity may reduce disability but were not confirmed by another meta-analysis using a more stringent definition of frailty (11). The main problem inherent in previous studies in the field was the heterogeneity of the frailty definition applied, which often was not based on validated criteria.

This study has important strengths, including a large sample of participants with well-defined frailty status, who typically have been excluded from randomized trials of physical activity; extended intervention and follow-up periods; and a high retention rate. However, our findings should be interpreted in light of several limitations. First, the inclusion criteria of the LIFE study may limit the generalizability of the findings. Second, even if each frailty criterion was evaluated, no information was available for weight loss at baseline, and this item was replaced by loss of appetite. Third, the study was a secondary analysis not prespecified in the protocol, and frailty status was neither an entry criterion nor a randomization stratum. Thus, findings should be

confirmed in other studies. Finally, we could not determine which of the components of the physical activity intervention were instrumental to the reduction in frailty status.

In conclusion, a structured, moderate-intensity physical activity program was not associated with a reduction in overall frailty status compared with a health education program over 2 years among sedentary, community-dwelling older adults. However, the beneficial effect on incidence and persistence of MMD was not altered by frailty status. These findings highlight the feasibility and importance of effective long-term, community-based physical activity programs for frail and nonfrail older adults.

From Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland, and Tufts University, Boston, Massachusetts; Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland; Wake Forest School of Medicine, Winston-Salem, North Carolina; Tufts University, Boston, Massachusetts; Pennington Biomedical Research Center, Baton Rouge, Louisiana; Yale School of Medicine, New Haven, Connecticut; Stanford University, School of Medicine, Stanford, California; Tufts University and Boston University School of Medicine, Boston, Massachusetts; University of Florida, Gainesville, Florida; Northwestern University, Feinberg School of Medicine, Chicago, Illinois; University of Pittsburgh, Pittsburgh, Pennsylvania; Wake Forest University and School of Medicine, Winston-Salem, North Carolina; and University of Florida, Gainesville, Florida, and University of Maryland School of Medicine, Baltimore, Maryland.

Note: The authors had full access to all the study data, take responsibility for the accuracy or integrity of the analysis, and had authority over manuscript preparation and the decision to submit the manuscript for publication. All authors approved the manuscript and agree to adhere to all terms outlined in *Annals of Internal Medicine* information for authors including terms for copyright.

Disclaimer: The content of this article is solely the responsibility of the authors and does not necessarily represent the official view of the U.S. Department of Agriculture.

Grant Support: The LIFE study was funded by cooperative agreement UO1AG22376 from the NIH and National Institute on Aging (NIA) and supplement 3U01AG022376-05A2S from the National Heart, Lung, and Blood Institute (NHLBI), 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 is supported by the NIH/National Center for Research Resources Clinical and Translational Science Award program at Stanford University (UL1 RR025744), University of Florida (U54RR025208), and Yale University (UL1 TR000142). Tufts University is also supported by the Boston Rehabilitation Outcomes Center (1R24HD065688-01A1). The following LIFE investigators also are partially supported: Dr. Gill (Yale University) is the recipient of an Academic Leadership Award (K07AG3587) from the NIA. Dr. Fielding (Tufts University) is partially supported by the U.S. Department of Agriculture under agreement 58-1950-4-003.

Disclosures: Dr. McDermott reports grants from the NHLBI during the conduct of the study, and donations of study medication from ReserveAge, grants from Novartis and the Patient-Centered Outcomes Research Institute, and donations of study intervention from Hershey's, outside the submitted work. Dr. Fielding reports grants from the NIH (NIA) during the conduct of the study and grants, personal fees, and equity stock options from Axcella Health; equity stock options from InsideTracker; grants and personal fees from Biophytis, Astellas, and Nestlé; and personal fees from Cytokinetics, Amazentis, and GlaxoSmithKline, outside the submitted work. Authors not named here have disclosed no conflicts of interest. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M16-2011.

Reproducible Research Statement: *Study protocol:* Available at www.thelifestudy.org/public/index.cfm. *Statistical code and data set:* Available to approved persons through agreement with the LIFE study steering committee (e-mail, Roger.Fielding@tufts.edu).

Requests for Single Reprints: Andrea Trombetti, MD, Division of Bone Diseases, Department of Internal Medicine Specialties, Geneva University Hospitals and Faculty of Medicine, Rue Gabrielle-Perret-Gentil 4, CH-1211 Geneva 14, Switzerland; e-mail, Andrea.Trombetti@hcuge.ch.

Current author addresses and author contributions are available at Annals.org.

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Current Author Addresses: Drs. Trombetti and Hars: Division of Bone Diseases, Department of Internal Medicine Specialties, Geneva University Hospitals and Faculty of Medicine, Rue Gabrielle-Perret-Gentil 4, CH-1211 Geneva 14, Switzerland.
Dr. Hsu: Department of Biostatistical Sciences, Wake Forest School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157.
Drs. Reid and Fielding: Nutrition, Exercise Physiology, and Sarcopenia Laboratory, Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, 711 Washington Street, Boston, MA 02111.
Dr. Church: 6400 Perkins Road, Baton Rouge, LA 75080.
Dr. Gill: Yale School of Medicine, Adler Geriatric Center, 874 Howard Avenue, New Haven, CT 06510.
Dr. King: Stanford University School of Medicine, 259 Campus Drive, HRP Redwood Building, Room T221, Stanford, CA 94305.
Dr. Liu: Boston University School of Medicine, 88 East Newton Street, Robinson 2, Boston, MA 02118.
Dr. Manini: Institute on Aging, Department of Aging and Geriatric Research, P.O. Box 112610, Gainesville, FL 32611.
Dr. McDermott: Department of Medicine and Preventive Medicine, Northwestern University, Feinberg School of Medicine, Galter Room 18-200, 675 North Saint Clair, Chicago, IL 60611.
Dr. Newman: Graduate School of Public Health, University of Pittsburgh, A527 Crabtree Hall, 130 DeSoto Street, Pittsburgh, PA 15261.
Dr. Rejeski: Department of Health and Exercise Science, Box 7868, Wake Forest University, Winston-Salem, NC 27109.
Dr. Guralnik: University of Maryland School of Medicine, Department of Epidemiology and Public Health, Division of Gerontology, 660 West Redwood Street, Room 204, Baltimore, MD 21201.
Dr. Pahor: Department of Aging and Geriatric Research, College of Medicine, University of Florida, 2004 Mowry Road, Gainesville, FL 32611.

Author Contributions: Conception and design: A. Trombetti, M. Hars, F.-C. Hsu, K.F. Reid, T.S. Church, T.M. Gill, A.C. King, C.K. Liu, T.M. Manini, M.M. McDermott, A.B. Newman, W.J. Rejeski, J.M. Guralnik, M. Pahor, R.A. Fielding.
Analysis and interpretation of the data: A. Trombetti, M. Hars, F.-C. Hsu, K.F. Reid, T.S. Church, T.M. Gill, A.C. King, C.K. Liu, T.M. Manini, M.M. McDermott, A.B. Newman, W.J. Rejeski, J.M. Guralnik, M. Pahor, R.A. Fielding.
Drafting of the article: A. Trombetti, M. Hars, K.F. Reid, R.A. Fielding.
Critical revision of the article for important intellectual content: A. Trombetti, M. Hars, F.-C. Hsu, K.F. Reid, T.S. Church, T.M. Gill, A.C. King, C.K. Liu, T.M. Manini, M.M. McDermott, A.B. Newman, W.J. Rejeski, J.M. Guralnik, M. Pahor, R.A. Fielding.
Final approval of the article: A. Trombetti, M. Hars, F.-C. Hsu, K.F. Reid, T.S. Church, T.M. Gill, A.C. King, C.K. Liu, T.M. Manini, M.M. McDermott, A.B. Newman, W.J. Rejeski, J.M. Guralnik, M. Pahor, R.A. Fielding.
Provision of study materials or patients: K.F. Reid, T.S. Church, T.M. Gill, A.C. King, C.K. Liu, T.M. Manini, M.M. McDermott, A.B. Newman, W.J. Rejeski, J.M. Guralnik, M. Pahor, R.A. Fielding.
Statistical expertise: F.-C. Hsu.
Administrative, technical, or logistic support: K.F. Reid, T.S. Church, T.M. Gill, A.C. King, C.K. Liu, T.M. Manini, M.M. McDermott, A.B. Newman, W.J. Rejeski, J.M. Guralnik, M. Pahor, R.A. Fielding.
Collection and assembly of data: A. Trombetti, M. Hars, F.-C. Hsu, K.F. Reid, R.A. Fielding.

Appendix 1: Research Investigators for the LIFE Study

The LIFE Investigators who authored this work are Fang-Chi Hsu, PhD (Wake Forest School of Medicine, Winston-Salem, North Carolina); Kieran F. Reid, PhD, MPH (Tufts University, Boston Massachusetts); Timothy S. Church, MD, PhD, Field Center Principal Investigator (Pennington Biomedical Research Center, Baton Rouge, Louisiana); Thomas M. Gill, MD, Field Center Principal Investigator (Yale School of Medicine, New Haven, Connecticut); Abby C. King, PhD, Field Center Principal Investigator (Stanford University, School of Medicine, Stanford, California); Christine K. Liu, MD (Tufts University and Boston University School of Medicine, Boston, Massachusetts); Todd M. Manini, PhD, Field Center Principal Investigator (University of Florida, Gainesville, Florida); Mary M. McDermott, MD, Field Center Principal Investigator (Northwestern University, Feinberg School of Medicine, Chicago, Illinois); Anne B. Newman, MD, Field Center Principal Investigator (University of Pittsburgh, Pittsburgh, Pennsylvania); W. Jack Rejeski, PhD (Wake Forest University and School of Medicine, Winston-Salem, North Carolina); Jack M. Guralnik, MD, PhD, Co-investigator (University of Maryland School of Medicine, Baltimore, MD); Marco Pahor, MD, Principal Investigator (University of Florida, Gainesville, Florida); and Roger A. Fielding, PhD, Field Center Principal Investigator (Tufts University, Boston, Massachusetts).

The LIFE Investigators who contributed to this work but did not author it are as follows:

Administrative Coordinating Center, University of Florida, Gainesville, Florida: Christiaan Leeuwenburgh, PhD; Connie Caudle; Lauren Crump, MPH; Latonia Holmes; Jocelyn Lee, PhD; and Ching-ju Lu, MPH.

Data Management, Analysis, and Quality Control Center (DMAQC), Wake Forest University, Winston-Salem, North Carolina: Michael E. Miller, PhD (DMAQC Principal Investigator); Mark A. Espeland, PhD (DMAQC Co-investigator); Walter T. Ambrosius, PhD; William Applegate, MD; Daniel P. Beavers, PhD, MS; Robert P. Byington, PhD, MPH; Delilah Cook, CCRP; Curt D. Furberg, MD, PhD; Lea N. Harvin, BS; Leora Henkin, MPH, Med; John Hepler, MA; Laura Lovato, MS; Wesley Roberson, BSBA; Julia Rushing, BSPH, MStat; Scott Rushing, BS; Cynthia L. Stowe, MPM; Michael P. Walkup, MS; Don Hire, BS; Jeffrey A. Katula, PhD, MA; Peter H. Brubaker, PhD; Shannon L. Mihalko, PhD; and Janine M. Jennings, PhD.

NIA, Bethesda, Maryland: Evan C. Hadley, MD; Sergei Romashkan, MD, PhD; and Kushang V. Patel, PhD.

NHLBI, Bethesda, Maryland: Denise Bonds, MD, MPH.

Northwestern University, Chicago, Illinois: Bonnie Spring, PhD (Field Center Co-investigator); Joshua Hauser, MD (Field Center Co-investigator); Diana Kerwin, MD (Field Center Co-investigator); Kathryn Domanchuk, BS; Rex Graff, MS; and Alvito Rego, MA.

Pennington Biomedical Research Center, Baton Rouge, Louisiana: 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; Heidi K. Millet, MPA; Catrine Tudor-Locke, PhD; Ben P. Butitta, BS; Sheletta G. Donatto, MS, RD, LDN, CDE; and Shannon H. Cocreham, BS.

Stanford University, Palo Alto, California: Cynthia M. Castro, PhD; William L. Haskell, PhD; Randall S. Stafford, MD, PhD; Leslie A. Pruitt, PhD; Kathy Berra, MSN, NP-C; and Veronica Yank, MD.

Tufts University, Boston, Massachusetts: Miriam E. Nelson, PhD (Field Center Co-investigator); Sara C. Folta, PhD (Field Center Co-investigator); Edward M. Phillips, MD; Erica C. McDavitt, MS; Won S. Kim, BS; Vince E. Beard, BS.

University of Florida, Gainesville, Florida: 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; and Irina Korytov, MD.

Brooks Rehabilitation Clinical Research Center, Jacksonville, Florida: Holly L. Morris, MSN, RN, CCRC; Margo Fitch, PT; Floris F. Singletary, MS, CCC-SLP; Jackie Causer, BSH, RN; and Katie A. Radcliff, MA.

University of Pittsburgh, Pittsburgh, Pennsylvania: Stephanie A. Studenski, MD, MPH (Field Center Co-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); and Diane G. Ives, MPH.

Wake Forest University, Winston-Salem, North Carolina: Stephen B. Kritchevsky, PhD (Field Center Principal Investigator); Anthony P. Marsh, PhD (Field Center Co-investigator); Tina E. Brinkley, PhD; Jamehl S. Demons, MD; Kaycee M. Sink, MD, MAS; Kimberly Kennedy, BA, CCRC; Rachel Shertzer-Skinner, MA, CCRC; Abbie Wrights, MS; Rose Fries, RN, CCRC; and Deborah Barr, MA, RHEd, CHES.

Yale University, New Haven, Connecticut: Robert S. Axtell, PhD (Field Center Co-investigator, 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; and Bridget M. Mignosa, AS.

Cognition Coordinating Center, Wake Forest University, Winston-Salem, North Carolina: Jeff Williamson, MD, MHS (Center Principal Investigator); Kaycee M. Sink, MD, MAS (Center Co-investigator); 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; and Janine Jennings, PhD.

Electrocardiogram Reading Center, University of Florida, Gainesville, Florida: Carl J. Pepine, MD; Mario Ariet, PhD; Eileen Handberg, PhD, ARNP; Daniel Deluca, BS; James Hill, MD, MS; and Anita Szady, MD.

Spirometry Reading Center, Yale University, New Haven, Connecticut: Geoffrey L. Chupp, MD; Gail M. Flynn, RCP, CRFT; John L. Hankinson, PhD (Hankinson Consulting); and Carlos A. Vaz Fragoso, MD*.

Cost-Effectiveness Analysis Center: Erik J. Groessl, PhD (University of California, San Diego, and VA San Diego Healthcare System); and Robert M. Kaplan, PhD (Office of Behavioral and Social Sciences Research, NIH).

* Dr. Vaz Fragoso is the recipient of a Career Development Award from the Department of Veterans Affairs.

Appendix 2: Supplementary Details of Sensitivity Analyses

Sensitivity analyses were performed by using IPW analysis, transition models, and CACE analysis.

First, to investigate the effect of loss to follow-up, we used the IPW approach. A weight equivalent to the probability of remaining in the study at 24 months was assigned to each participant on the basis of age, sex, race, education, number of chronic diseases, living alone, field center, baseline SPPB, and baseline 400-m gait speed and was calculated by using logistic regression. For the analysis in Table 2, when probabilities of both randomization (defined as the probability of randomization to the intervention group among nonfrail participants and calculated using logistic regression) and remaining in the study were considered, we could not include both probabilities as weights in the model. Therefore, the probability of randomization was treated as a propensity score and adjusted for as a covariate in the model, and the probability of remaining in the study was treated as a weight in the model. Propensity score is defined as the probability of treatment assignment conditional on observed baseline covariates (26).

Four propensity score methods are usually used for removing the confounding effects when estimating the treatment effect on outcomes: propensity score matching, stratification on the propensity score, IPW using the propensity score, and covariate adjustment using the propensity score (27). The IPW approach and covariate adjustment were used in this study. The covariates we used to calculate the probability of randomization were the same as those we used to calculate the probability of remaining in the study.

Second, in transition models, we modeled the conditional distribution of the outcome measure at any follow-up visit given the outcome measure at the previous visit, assuming the first-order Markov chain model. Transition models using the generalized estimating equation models were used (20) to study the association between SOF frailty and intervention over 24 months. Sex and field center (both used to stratify randomization), intervention, time, time^2, time^3, and outcome at the previous visit were included in the models. For this regression setting, we modeled the transition probability as a function of covariates under the special case in which no interactions occur between the previous outcome measure and the covariates. The interpretation of the intervention effect is slightly different from the effect estimated from the other models we presented. It is the intervention effect after adjusting for covariates and the previous outcome measure. We did not adjust for the previous outcome measure in the other models. Note that conditioning on the history of previous outcome measure may lead to attenuation of the intervention effect. For number of SOF frailty criteria, ordinal logistic regression with a clustered sandwich estimator was used. The same covariates were adjusted in the models.

Third, the CACE analysis was used to account for the intervention adherence by using an instrumental variable approach (21, 22). Assuming that the randomization effect on the outcome was mediated by the adherence to the intervention and the same proportion of participants in the groups would not have adhered to the intervention if they had been offered it, randomization was treated as an instrumental variable. The CACE analysis was performed as a longitudinal data analysis. Baseline outcome was retained in the outcome vector. For SOF frailty index, a binary outcome, an instrumental variable probit model (*ivprobit* command in Stata) was used. Sex; field centers; and continuous time, including time, time^2, and time^3, were adjusted for in the models. A Wald test of the exogeneity of the instrumental variables was provided. Exogeneity is defined as no correlation between covariate (for example, adherence) and error term. For the instrumental variable model to be valid, the covariate must be exogenous. Because the covariate may be endogenous (correlated with the error term), we would like to replace the covariate with a "proxy" variable, known as an instrumental variable (for example, randomization groups), which is independent of the error term. To be valid, an instrument must meet 2 conditions. The first is instrument relevance; that is, the correlation between the instrumental variable and the covariate does not equal 0. The second condition is instrument exogeneity. This test is provided in Stata. If the test is statistically significant, we reject the null hypothesis of no endogeneity. If the test is not statistically significant, we do not reject the null hypothesis, so it may not be necessary to use an instrumental variable analysis. For number of SOF frailty criteria, the analysis was explored in its continuous form with estimation using instrumental variable regression (*ivregress* command with 2-stage least squares in Stata). The same covariates listed for the binary outcome analysis were included in the model, except that time^2 and time^3 were not adjusted.

To provide a more detailed description of the adherence measure used in the CACE analysis, the mean number of intervention sessions attended and due by randomization groups are presented in **Appendix Table 2**. The median for the attendance percentage after excluding medical leaves throughout the whole follow-up was 0.71 (average, 0.63) in the physical activity group, and the median for the attendance percentage was 0.82 (average, 0.72) in the health education group. In CACE analysis, adherence was treated as a binary variable by using the median as a cutoff point (≥median vs. <median).

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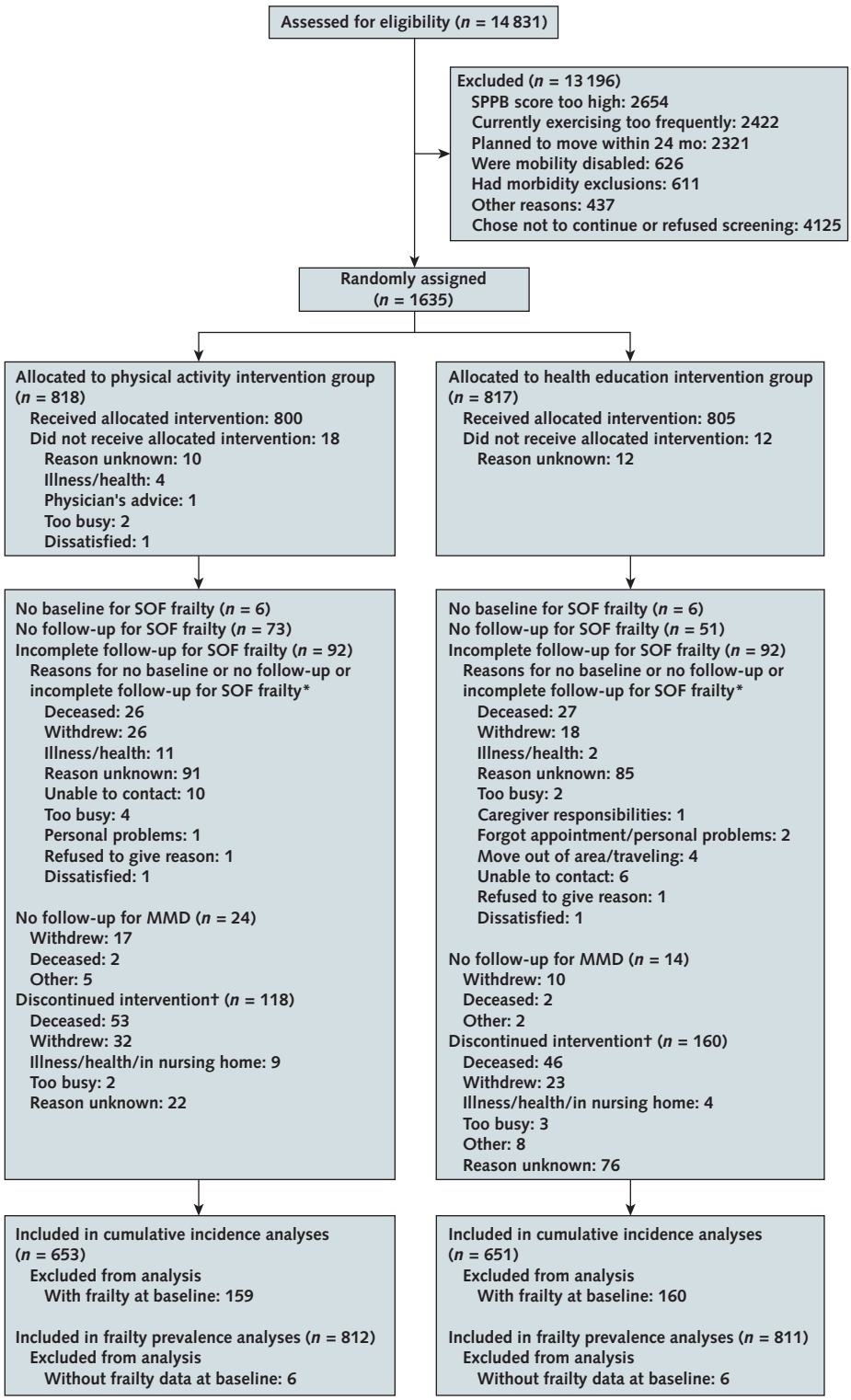
Appendix Figure. Flow of participants through the trial.



MMD = major mobility disability; SOF = Study of Osteoporotic Fractures; SPPB = Short Physical Performance Battery.
* SOF frailty was assessed over 24 months.
† 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 before the last planned follow-up visit date. Deaths and intervention withdrawals are included in these numbers.

Appendix Table 1. SOF Frailty Index and Its Individual Components, by Randomization Group and Baseline Frailty Status*

Variable	Physical Activity (*n* = 812)			Health Education (*n* = 811)		
	Frail (*n* = 159)	Not Frail (*n* = 653)	All	Frail (*n* = 160)	Not Frail (*n* = 651)	All
Prevalence of SOF frailty index						
Baseline	159 (100)	0 (0)	159 (19.6)	160 (100)	0 (0)	160 (19.7)
6 months	66 (48.2)	69 (11.5)	135 (18.3)	76 (53.2)	99 (16.1)	175 (23.0)
12 months	50 (40.0)	95 (17.2)	145 (21.5)	59 (44.4)	84 (14.6)	143 (20.2)
24 months	40 (35.1)	71 (13.2)	111 (17.0)	50 (40.7)	88 (15.9)	138 (20.4)
Inability to rise from a chair 5 times without using the arms						
Baseline	67 (42.1)	48 (7.4)	115 (14.2)	87 (54.4)	51 (7.8)	138 (17.0)
6 months	47 (32.6)	45 (7.3)	92 (12.0)	57 (38.0)	82 (13.0)	139 (17.8)
12 months	48 (34.0)	57 (9.5)	105 (14.2)	67 (45.9)	79 (12.9)	146 (19.2)
24 months	44 (35.5)	76 (13.3)	120 (17.3)	64 (48.5)	99 (17.2)	163 (23.1)
Weight loss†						
Baseline	111 (69.8)	38 (5.8)	149 (18.3)	112 (70.0)	37 (5.7)	149 (18.4)
6 months	44 (31.2)	172 (28.0)	216 (28.6)	46 (31.1)	150 (23.9)	196 (25.3)
12 months	38 (30.2)	158 (28.2)	196 (28.6)	38 (28.1)	133 (22.9)	171 (23.8)
24 months	21 (16.7)	67 (12.0)	88 (12.8)	23 (17.0)	88 (15.1)	111 (15.5)
Reduced energy level‡						
Baseline	152 (95.6)	263 (40.3)	415 (51.1)	150 (93.8)	277 (42.5)	427 (52.7)
6 months	139 (95.2)	243 (39.5)	382 (50.2)	139 (93.3)	268 (42.7)	407 (52.4)
12 months	101 (70.6)	273 (44.9)	374 (49.8)	99 (67.8)	279 (44.8)	378 (49.2)
24 months	99 (73.9)	275 (47.1)	374 (52.1)	100 (72.5)	310 (52.0)	410 (55.9)
Mean SOF frailty index criteria (SD), *n*						
Baseline	2.08 (0.26)	0.53 (0.50)	0.84 (0.77)	2.18 (0.39)	0.56 (0.50)	0.88 (0.80)
6 months	1.57 (0.67)	0.74 (0.66)	0.89 (0.74)	1.61 (0.69)	0.79 (0.73)	0.95 (0.79)
12 months	1.32 (0.78)	0.81 (0.71)	0.90 (0.75)	1.42 (0.77)	0.80 (0.71)	0.92 (0.77)
24 months	1.28 (0.72)	0.71 (0.73)	0.81 (0.76)	1.37 (0.77)	0.84 (0.72)	0.94 (0.76)
Number of SOF frailty index criteria						
Baseline						
0	0 (0)	304 (46.6)	304 (37.4)	0 (0)	286 (43.9)	286 (35.3)
1	0 (0)	349 (53.4)	349 (43.0)	0 (0)	365 (56.1)	365 (45.0)
2	147 (92.5)	0 (0)	147 (18.1)	131 (81.9)	0 (0)	131 (16.2)
3	12 (7.5)	0 (0)	12 (1.5)	29 (18.1)	0 (0)	29 (3.6)
6 months						
0	1 (0.7)	228 (37.9)	229 (31.0)	3 (2.1)	235 (38.1)	238 (31.3)
1	70 (51.1)	305 (50.7)	375 (50.7)	64 (44.8)	283 (45.9)	347 (45.7)
2	53 (38.7)	66 (11.0)	119 (16.1)	62 (43.4)	91 (14.7)	153 (20.1)
3	13 (9.5)	3 (0.5)	16 (2.2)	14 (9.8)	8 (1.3)	22 (2.9)
12 months						
0	17 (13.6)	199 (36.1)	216 (32.0)	13 (9.8)	208 (36.2)	221 (31.3)
1	58 (46.4)	257 (46.6)	315 (46.6)	61 (45.9)	282 (49.1)	343 (48.5)
2	43 (34.4)	94 (17.1)	137 (20.3)	49 (36.8)	76 (13.2)	125 (17.7)
3	7 (5.6)	1 (0.2)	8 (1.2)	10 (7.5)	8 (1.4)	18 (2.5)
24 months						
0	13 (11.4)	234 (43.4)	247 (37.8)	13 (10.6)	184 (33.3)	197 (29.2)
1	61 (53.5)	234 (43.4)	295 (45.2)	60 (48.8)	280 (50.7)	340 (50.4)
2	35 (30.7)	63 (11.7)	98 (15.0)	41 (33.3)	79 (14.3)	120 (17.8)
3	5 (4.4)	8 (1.5)	13 (2.0)	9 (7.3)	9 (1.6)	18 (2.7)

SOF = Study of Osteoporotic Fractures.
* Values are numbers (percentages) unless otherwise indicated.
† Based on weight measurements except at the baseline visit. This criterion was considered present at baseline if the participant reported a loss of appetite on the health-related quality-of-life questionnaire.
‡ Defined by using the following statement from the health-related quality-of-life questionnaire: "During the past week, how often have you felt full of energy?"

Appendix Table 2. Intervention Sessions Attended

Variable	Physical Activity (n = 806)				Health Education (n = 807)†	
	Excluding Sessions Not Attended Due to Medical Leaves*		Including All Scheduled Sessions†			
	Mean Sessions Attended/Mean Sessions Due, *n/N*	Mean ± SD (Median, 75th percentile), %	Mean Sessions Attended/Mean Sessions Due, *n/N*	Mean ± SD (Median, 75th percentile), %	Mean Sessions Attended/Mean Sessions Due, *n/N*	Mean ± SD (Median, 75th Percentile), %
6 months	31.6/41.1	0.76 ± 0.22 (0.82, 0.91)	31.6/43.9	0.72 ± 0.25 (0.81, 0.91)	17.2/22.3	0.77 ± 0.23 (0.84, 0.92)
12 months	61.0/83.6	0.72 ± 0.23 (0.79, 0.88)	60.9/92.0	0.66 ± 0.27 (0.75, 0.87)	23.4/30.2	0.77 ± 0.23 (0.85, 0.93)
24 months	110.6/163.0	0.66 ± 0.25 (0.74, 0.85)	110.5/185.1	0.59 ± 0.28 (0.68, 0.82)	32.4/42.9	0.75 ± 0.24 (0.84, 0.91)
All	140.4/219.7	0.63 ± 0.27 (0.71, 0.83)	140.3/254.6	0.55 ± 0.29 (0.65, 0.79)	39.0/53.9	0.72 ± 0.25 (0.82, 0.90)

* The calculation excluded medical leaves. Only the physical activity group had a count of medical leaves. Note that the mean number of sessions attended when medical leaves were excluded is not exactly the same as that when all scheduled sessions were included. When the extended leave sessions were excluded, participants who did not contribute any data were excluded. Thus, the denominators in the calculations differ.
† The calculation used all scheduled sessions.

Appendix Table 3. Intervention Sessions Attended, by Baseline SOF Frailty Status

Variable	Physical Activity (n = 806)						Health Education (n = 807)		
	Mean Sessions Attended (Median), Excluding Sessions Not Attended Due to Medical Leaves, %*		*P* Value	Mean Sessions Attended (Median), Including All Scheduled Sessions, %†		*P* Value	Mean Sessions Attended (Median), %†		*P* Value
	Frail (n = 158)	Not Frail (n = 648)		Frail (n = 158)	Not Frail (n = 648)		Frail (n = 159)	Not Frail (n = 648)	
6 months	0.74 (0.79)	0.76 (0.83)	0.23	0.69 (0.78)	0.73 (0.82)	0.22	0.73 (0.81)	0.79 (0.85)	0.005
12 months	0.70 (0.75)	0.72 (0.79)	0.21	0.63 (0.72)	0.67 (0.75)	0.142	0.73 (0.81)	0.79 (0.86)	0.002
24 months	0.64 (0.72)	0.67 (0.74)	0.28	0.56 (0.64)	0.60 (0.69)	0.133	0.70 (0.80)	0.77 (0.85)	<0.001
All	0.62 (0.70)	0.64 (0.72)	0.59	0.52 (0.59)	0.56 (0.65)	0.27	0.66 (0.73)	0.74 (0.83)	<0.001

SOF = Study of Osteoporotic Fractures.
* The calculation excluded medical leaves. Only the physical activity group had a count of medical leaves.
† The calculation used all scheduled sessions.

Appendix Table 4. Association Between SOF Frailty and Randomization Group Over 24 Months in All Study Participants, Using Transition Models

Physical Activity Versus Health Education	Average Prevalence Over 24 Months, %*		Prevalence Difference (95% CI)			
	Physical Activity	Health Education (Reference)	Unadjusted	*P* Value	Adjusted	*P* Value
ITT†	19.1	20.8	−0.021 (−0.042 to −0.0003)	0.047	−0.020 (−0.041 to 0.0005)	0.055
IPW†‡	-	-	−0.018 (−0.039 to 0.003)	0.099	−0.017 (−0.038 to 0.004)	0.119

IPW = inverse probability weighting; ITT = intention-to-treat; SOF = Study of Osteoporotic Fractures.
* Calculated as the sum of prevalence from each visit, including baseline, in the raw data divided by 4.
† Sex and field center (both used to stratify randomization), intervention, time, time^2, time^3, and outcome at the previous visit included in the transition models. The prevalence differences from the generalized estimating equation models (logit link, binomial distribution [Stata]) were presented.
‡ Weighted for the inverse probability of remaining in the study.

Appendix Table 5. Association Between SOF Frailty and Randomization Group Over 24 Months in All Study Participants, Taking Adherence to Intervention Into Account*

Physical Activity Versus Health Education	Average Marginal Effect (95% CI)†	*P* Value	*P* Value for Test of Exogeneity
Excluding sessions not attended due to medical leaves‡			
CACE§	−0.60 (−0.70 to −0.51)	<0.001	0.411
CACE + IPW§‖	−0.59 (−0.78 to −0.39)	<0.001	0.416
Including all scheduled sessions¶			
CACE§	−0.57 (−0.75 to −0.38)	<0.001	0.229
CACE + IPW§‖	−0.54 (−0.89 to −0.19)	0.028	0.352

CACE = complier-average causal effect; IPW = inverse probability weighting; SOF = Study of Osteoporotic Fractures.
* Adherence to intervention is defined as the attendance percentage larger or equal to median (0.71 in physical activity after excluding medical leaves, 0.65 in physical activity while including all sessions, and 0.82 in health education). Nonadherence to intervention is defined as the attendance percentage smaller than median.
† Average marginal effect of the difference of probability of SOF frailty.
‡ Adherence percentage calculated on the basis of scheduled sessions excluding medical leaves.
§ Sex and field center (both used to stratify randomization), intervention, time, time^2, and time^3 included in the models. Baseline outcome was retained in the outcome vector.
‖ Weighted for the inverse probability of remaining in the study.
¶ Adherence percentage calculated based on all scheduled sessions without excluding medical leaves.

Appendix Table 6. Association Between Each SOF Frailty Criterion and Randomization Group Over 24 Months in All Study Participants

Physical Activity Versus Health Education	Prevalence Difference (95% CI)*			
	Unadjusted	*P* Value	Adjusted	*P* Value
Reduced energy level				
ITT model†	−0.018 (−0.058 to 0.021)	0.37	−0.018 (−0.057 to 0.021)	0.36
IPW model†‡	−0.012 (−0.052 to 0.028)	0.56	−0.012 (−0.051 to 0.028)	0.56
Weight loss				
ITT model†	0.011 (−0.016 to 0.037)	0.43	0.013 (−0.012 to 0.039)	0.30
IPW model†‡	0.010 (−0.016 to 0.037)	0.45	0.013 (−0.014 to 0.040)	0.35
Inability to rise from a chair 5 times without using the arms				
ITT model†	−0.050 (−0.081 to −0.020)	0.001	−0.050 (−0.081 to −0.020)	0.001
IPW model†‡	−0.047 (−0.080 to −0.015)	0.004	−0.048 (−0.079 to −0.016)	0.003

IPW = inverse probability weighting; ITT = intention-to-treat; SOF = Study of Osteoporotic Fractures.
* Marginal standardization was used to obtain the prevalence difference and its 95% CI.
† Sex and field center (both used to stratify randomization), intervention, time, time^2, and time^3 included in the generalized estimating equation models (logit link, binomial distribution). Baseline outcome was retained in the outcome vector.
‡ Weighted for the inverse probability of remaining in the study.

Appendix Table 7. Association Between the Number of SOF Frailty Criteria and Randomization Group Over 24 Months in All Study Participants, Using Transition Models

Physical Activity Versus Health Education	Odds Ratio (95% CI)			
	Unadjusted	*P* Value	Adjusted	*P* Value
ITT model*	0.88 (0.78 to 0.98)	0.021	0.88 (0.78 to 0.98)	0.019
IPW model*†	0.89 (0.79 to 0.99)	0.038	0.89 (0.79 to 0.99)	0.038

IPW = inverse probability weighting; ITT = intention-to-treat; SOF = Study of Osteoporotic Fractures.
* Sex and field center (both used to stratify randomization), intervention, time, time^2, time^3, and outcome at the previous visit included in the transition models. The odds ratios from ordinal logistic regression models with clustered sandwich estimators were presented.
† Weighted for the inverse probability of remaining in the study.