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Physical activity and the association of frailty with all-cause and cardiovascular mortality in older adults: a population-based prospective cohort study

Physical activity, frailty and mortality in elderly

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IMPACT STATEMENT: We certify that this work is novel. This research specifically adds to the literature that physical activity might partly compensate for the increased mortality risk associated with frailty status in the old age.

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ABSTRACT

Objective: To examine the separate and joint association of physical activity and frailty with long-term all-cause and cardiovascular (CVD) mortality in older adults.

Design: Population-based prospective cohort study

Setting: Cohort representative of the non-institutionalized Spanish population.

Participants: 3,896 participants aged ≥60 years in Spain 2000-2001.

Measurements: Participants reported their physical activity with a validated instrument and frailty was ascertained with the FRAIL scale (Fatigue, low Resistance, limitation in Ambulation, Illness and weight Loss). Those with 0, 1-2 and ≥3 frailty criteria were considered as robust, pre-frail, and frail, respectively. Cohort participants were followed-up to 2014 to identify deaths from all-cause and CVD. Associations are summarized using hazard ratios (HRs) and Cox regression, after adjustment for main covariates.

Results: During a 14-y median follow-up, 1,801 total deaths occurred, 672 due to CVD. Compared with being robust, the multivariate hazard ratio (95% confidence interval) for all-cause mortality was 1.29 (1.14-1.45) in prefrail individuals, and 2.16 (1.82-2.58) in frail individuals (p-trend <.001). Compared with being physically inactive, being physically active was associated with a statistically significant 18% (1-32%), 28% (16-39%) and 39% (17-55%) lower all-cause mortality among robust, prefrail, and frail individuals, respectively (all p <.001). Compared with participants who were robust and physically active, those who were frail and inactive showed the highest all-cause mortality 2.45 (95%CI: 1.95-3.06); however, the hazard ratio (95% confidence interval) for all-cause mortality in frail individuals who were physically active was comparable to that in pre-frail and inactive participants: 1.70 (1.32-2.19) and 1.56 (1.34-1.82), respectively.

Also, pre-frail active individuals showed a similar mortality to robust inactive counterparts. Results were similar for CVD mortality.

Conclusions: Physical activity might partly compensate for the increased mortality risk associated with frailty status in the old age.

Key words: frailty; physical activity; elderly; mortality

INTRODUCTION

Frailty is a geriatric syndrome resulting from reduced reserve in several physiological systems that is manifested by increased vulnerability to even minor stressors (e.g., mild infection, introduction of a new drug treatment) [1]. As a consequence, frail individuals show an increased risk of falls, hospitalization, disability, institutionalization, and death [1–3]. With the aging of population[4], the prevalence of frailty and its associated adverse health consequences is expected to increase in the next decades. This health condition has a direct cost of the resources of social services and medical attention; therefore, strategies to prevent frailty or morbidity of frailty syndrome may be a key to reduce the cost of these social- and health-care services. Although previous clinical and epidemiologic studies have examined whether pharmacological agents or nutritional interventions may help reduce the prevalence or severity of frailty, physical activity based interventions have been highlighted as the best cost-effective strategies [1,5,6].

Physical activity, defined as any bodily movement by skeletal muscles requiring energy expenditure, is associated with better health status in older adults [7] and, in particular, with lower risk of many chronic diseases (e.g. type 2 diabetes, cardiovascular disease, several cancers, depression), functional impairment, and all-cause and cardiovascular disease (CVD) mortality – the leading cause of deaths in this population [7–10]. Also, intervention studies in frail individuals have found that physical exercise improves physical performance and reduces the risk of frailty-associated outcomes, such as falls [5,11,12]. However, it is still uncertain if physical activity may also reduce mortality among frail older adults.

Therefore, we used data from a nationally representative cohort of older adults in Spain to examine the separate and joint association of physical activity and frailty with long-term all-cause and CVD mortality. Specifically, we aimed to assess whether physical activity could compensate for the excess mortality associated with frailty.

METHODS

Study design and participants

We used data from the UAM (*Universidad Autónoma de Madrid*) cohort, with a total 4,008 individuals, representative of the non-institutionalized population aged 60 years and older in Spain. The cohort methods have been reported in detail elsewhere [13,14]. Study participants were selected in 2000/2001 using probabilistic sampling by multistage clusters. The clusters were stratified according to region of residence and size of municipality. Census sections and households were chosen randomly within each cluster. Finally, study participants were selected according to sex and age (60-69, 70-79, and ≥80 years) strata. Information was collected at the participants' homes through personal interviews and physical examinations were performed by trained and certified personnel. The final study response rate was 71%.

Written informed consent was obtained from the study participants and an attending family member, and the study protocol was approved by the Clinical Research Ethics Committee of *La Paz* University Hospital in Madrid (Spain) [13,14].

Study variables

Physical activity was assessed using a validated single question taken from the Spanish National Survey, which is habitually used to monitor the prevalence of physical activity in Spain [15]: "which of these choices best describes most of your leisure-time activity?" Participants rated their physical activity as (1) inactive, (2) occasional, (3) several times a month, and (4) several times a week. Because only 2.9% of participants reported engaging in physical activity monthly (2.5%, n=97) or weekly (0.5%, n=19) these two categories and the occasional category were merged into a "physically active" category; these low number of events in the highest categories resulted in unstable estimates and broad 95% CIs [15]. Compared with a validated questionnaire, mean (95% CI) physical activity levels stratified by inactive and increasing physical activity categories from this question were 7.1 (6.2–8.1), 30.0 (28.9–31.0), 43.1 (36.3–50.0), and 56.6 (37.6–75.5) MET-hour/week, respectively (rho=.55, p<.001) in older adults; when the increasingly active categories were merge into the same active category, the average physical activity in MET-hour/week was 30.7 (29.7-31.7) [15].

Frailty was assessed with the FRAIL scale [16,17], which is based on 5 components: Fatigue, Resistance, Ambulation, Illness, and weight Loss [17]. Fatigue, resistance, and ambulation were assessed using 3 questions from the 36-item Short Form Health Survey (SF-36) [18]. Fatigue was measured by asking participants how much time during the past 4 weeks they had feel tired; responses of "all of the time" or "most of the time" scored 1 point. Resistance was assessed by asking participants if their health limited them in walking up 1 flight of stairs, and ambulation by asking if their health limited them in walking several hundred yards; each positive response to these questions was scored 1 point. Weight loss was assigned 1 point if participants reported ≥5% unintentional loss during the preceding year. Finally, the illness domain scored 1 point if participants reported to suffer ≥5 out of the following 11 physician-diagnosed diseases: pneumonia, asthma or chronic bronchitis, hypertension, coronary heart disease, stroke, osteoarthritis or rheumatism, diabetes mellitus, depression under drug treatment, hip fracture, Parkinson's disease, and cancer at any site. The total score ranged from 0 to 5, and those who scored 0 were considered as robust, 1-2 as pre-frail, and ≥3 as frail [17].

Ascertainment of mortality

The outcome variables were all-cause and CVD mortality from study baseline (2000/2001) to follow-up (2014). The date and cause of death during the follow-up period were obtained by a computerized search of the Spanish National Death Index of the Ministry of Health and the vital registry of the Spanish National Institute of Statistics. There is evidence of the complete coverage, accuracy and reliability of vital status information [19]. The underlying cause of death was determined by a nosologist according to the International Classification of Diseases, 10th Edition, with CVD corresponding to codes I00-I99.

Covariates

Age, sex, educational level (no formal and primary, secondary, and university studies) were recorded. Also, tobacco smoking (never, former, and current smoker) and alcohol consumption (never, former, moderate, and heavy drinker) were registered. The cutoff points between moderate and heavy intake were >20 and >30 g of alcohol/day in women and men, respectively. Height and weight were measured using standardized procedures, and body mass index calculated as weight in kg divided by height in square m [20]. Waist circumference was measured using an inelastic belt-type tape at the midpoint between the lowest rib and the iliac crest after breathing out normally. The Mini-Mental State Examination test, which is valid for the Spanish population, was used to assessed cognitive function [21].

Statistical analyses

Of the 4,008 study participants, 112 were excluded because of missing data on the main study variables. Thus, the analyses were conducted with 3,896 individuals. Baseline characteristics of the study participants are presented as mean ± standard deviation or percentages. All-cause and CVD mortality according to frailty status (i.e., robust, pre-frail, and frail) and physical activity (i.e., inactive and active) were summarized using hazard ratios (HRs) and their 95% confidence interval (CI) obtained from Cox regression. Two models with progressive adjustment for potential confounders were fitted. A basic model or model 1 was adjusted for sex and age, and model 2 was additionally adjusted for educational level, smoking status, alcohol consumption, body mass index, waist circumference, and Mini-Mental State Examination score. The confounders have been chosen according to the scientific literature [1,9,12].

Also, we calculated HR (95% CI) for all-cause and CVD mortality according to the 5 components of the FRAIL scale. P-values for trend were estimated from Cox regression models including frailty as a continuous variable with the 0 to 5 score.

To examine the separate association of physical activity or frailty with all-cause and CVD mortality, we conducted stratified analyses by level of frailty or physical activity, as appropriate. We checked the potential modifier effect of physical activity on the associations between frailty and mortality by including an interaction term in Cox models; multicollinearity detection was examined in this analysis but variance inflation factors were in the normal range since both variables were not strongly related (Spearman r=-.35 with frailty and physical activity as continuous variables). To assess the combined association of physical activity (i.e., inactive and active) and each level of frailty (i.e., robust, pre-frail and frail) with mortality outcomes, we modeled six categories of exposure, and run Cox models with robust and physical active participants as the reference category.

We assessed the assumption of proportionality of hazards both graphically and by testing the interaction between frailty status or physical activity and time of follow-up. There was no evidence of departure in any of this assumption (all P>.1). Statistical significance was set at p<.05 and all tests were 2-sided. Analyses were performed with STATA v.14.1.

RESULTS

The prevalence of the 5 components of the FRAIL scale was 12% for fatigue, 36.7% for low resistance, 34.4% for limitation in ambulation, 2% for weight loss, and 2% for illness. As a result, 52% of study participants were robust, 39.4% pre-frail, and 8.6% frail. Compared with robust individuals, those with frailty were older, had higher waist circumference, and lower Mini-State Examination score, and there was higher proportion to be women, had lower education, never smokers, never drinkers and physically inactive (all p<.05) (Table 1). Descriptive information across groups of frailty and physical activity are shown in supplementary table 1 (Table S1).

Over a median follow-up of 14 years, a total of 1,801 deaths occurred, 672 due to CVD. Age- and sex-adjusted HRs (95%CI) for all-cause mortality in participants with pre-frail and frail status compared with those who were robust were 1.29 (1.14-1.45) and 2.16 (1.82-2.58), respectively (HR per one-category increase = 1.26 (1.20-1.33), p for trend <.001 for all-cause mortality and 1.34 (1.23-1.46), p for trend <.001 for CVD mortality). In full-adjusted analyses, the results did not substantially change, so that the HR (95%CI) for all-cause mortality was 1.26 (1.12-1.42) for pre-frail participants and 2.05 (1.71-2.45) for frail participants (p for trend <.001). Compared with robust participants, pre-frail and frail showed a higher CVD mortality risk; in full-adjusted analyses, for CVD mortality risk, the HR (95%CI) was 1.40 (1.14-1-72) for pre-frailty, and 2.32 (1.74-3.10) for frailty (p for trend <.001) (Figure 1). Each of the 5 components of the FRAIL scale was linked to higher all-cause and CVD mortality, except for the association between illness criteria and all-cause mortality which did not achieve statistical significance (Table S2).

The association between physical activity and mortality stratified by frailty status is shown in Table 2. In full-adjusted analyses (model 2), being physically active was associated with 18% (95%CI: 1-32%), 28% (95%CI: 16-39%) and 39% (95%CI: 17-55%) lower all-cause mortality in robust, pre-frail, and frail individuals, respectively (Table 2). The corresponding reductions in CVD mortality were 38% (14-56%) for robust, 29% (6-46%) for pre-frail and 48% (6-71%) for frail participants (Table 2).

When examining the association of frailty with all-cause mortality by physical activity group, clear dose-response associations were found in both groups (HR per one-category increase was 1.26 (1.18-1.35), p for trend <.001 in the inactive group, and 1.15 (1.05-1.26), p for trend =.002 in the active group; the corresponding risk estimates for CVD mortality were 1.26 (1.12-1.41) and 1.29 (1.12-1.49), both p for trend ≤.001). Therefore, the main effect of frailty was not modified by physical activity (p for interaction =.685 and =.333 for all-cause and CVD mortality, respectively). All-cause and CVD mortality risks across physical activity and frailty categories are shown in Figure 2. Compared with participants who were robust and physically active at baseline, those who were frail and inactive showed the highest all-cause 2.45 (95%CI: 1.95-3.06) and CVD 3.27 (95%CI: 2.32-4.60) mortality. In addition, HRs for all-cause and CVD mortality in frail individuals who were physically active were comparable to those in pre-frail and inactive participants and pre-frail active individuals showed similar mortality rates than their robust inactive counterparts (Figure 2).

DISCUSSION

In this nationally representative cohort of older adults in Spain, pre-frailty and frailty were associated with increased all-cause and CVD mortality. However, being physically active was linked to lower mortality among pre-frail and frail individuals; moreover, all-cause and CVD mortality in physically active individuals with frailty were similar to that in pre-frail and inactive subjects. Taken together, these findings suggest that physical activity might partly reduce the increased mortality risk associated with frailty in the old age.

To our knowledge, this is the first study to examine the impact of physical activity on all-cause and CVD mortality in pre-frail and frail older adults. However, our results are in line with those from previous research studies on the role of physical activity in modulating the excess mortality associated with frailty-related criteria, such as fatigue, muscle weakness, gait speed, functional disability or multimorbidity [22–26]. In an earlier work with our cohort, we showed that being physically active was associated with a lower risk of all-cause and CVD mortality among disabled elders [22]. Also in the same cohort, physical activity was linked to a mortality reduction of 47% in participants with three or more chronic diseases [23]. Moreover, in a recent work with 498,135 participants in the UK Biobank, the highest death risk was found among participants with the lowest levels of both muscle strength and physical activity, and the risk of mortality increased with each decreased quintile of physical activity [24]. Another work in the Health, Aging and Body Composition Study reported that older adults with low physical activity had a faster decline in gait speed; therefore, physical activity may protect older adults from the impact of slowness on mortality [25]. Finally, in community-dwelling older adults from the Jerusalem Longitudinal Study, a higher level of physical activity weakened the association between fatigue and mortality [26]. These and our results suggest that physical activity increases survival among older people with physical impairments. However, taken into account the "potentially reversible" nature of the frailty concept, the present study has not only clinical but also public health relevance.

Several mechanisms may contribute to the beneficial effect of physical activity on mortality in the frail elderly. Physical activity reduces the incidence of chronic diseases and disability, which in turn, may decrease mortality [7,8,11]. Also, in frail older adults, physical activity improves strength, balance, agility, gait speed, and sarcopenia [12,27–30], which are components of the 'frailty cycle' [2]. In a recent systematic review of exercise interventions in frail older adults, 70% of the studies showed a reduction in falls, 54% an enhancement of gait ability, 80% an improvement in balance, and 70% an increase in muscle strength [12]. Moreover, a recent meta-analysis of 15 studies including 1,350 frail older adults found beneficial effects of exercise-based interventions on maximum strength, gait speed, and static and dynamic balance assessed by the

Timed-Up-and-Go test [27]. Another review of 8 randomized trials with 1,068 frail older adults reported that, compared with the control group, the exercise group increased gait speed by 0.07 m/s (95% CI 0.02-0.11), balance by 1.69 (95% CI 0.56-2.82), and Activities of Daily Living performance score by 5.33 (95% CI 1.01-9.64) [28].

Older adults are the most physically inactive population group, and it seems that older adults with frailty are even less physically active than those without frailty [31,32]. In our study, for example, those with frailty were less physically active (22%) than their pre-frail (44%) and robust peers (70%); this could support that some criteria to define frailty include 'low physical activity' as a component. Our results suggest that there is variability in the levels of physical activity among frail older adults and that the effect of such levels of activity may be important for their future health. For this reason, public health physical activity guidelines suggest that, when older adults cannot do the recommended amount of physical activity owing to their health status or physical limitations, they should be as physically active as their abilities and conditions allow them [7,33]. According to compelling evidence on the health benefits of physical activity, public health organizations must develop new strategies to increase levels of physical activity among older adults with frailty.

This study has several strengths. This cohort includes a representative, which allows for generalization of results among community-dwelling older adults in Spain. Also, the long-term follow-up allowed us identify a large number of death events. Moreover, the study data were obtained by certified staff after performing several training sessions and under standardized procedures, and analyses were adjusted for a good number of potential confounders. However, some limitations should be acknowledged. Although we examined a relatively large and representative sample, the sample size for some stratified analyses (i.e. frail elders) could be small to obtain robust estimates. The observational design precludes causal inference, but the strength and dose-response of the associations between physical activity and reduced mortality, as well as the consistency across frailty status, lends confidence on our results. Another limitation is that there is no a universal approach to diagnose frailty, and therefore, it is unclear whether operationalizing frailty with other criteria these results would be confirmed. Lastly, physical activity was self-reported, which may have led to recall bias and misclassification. Also, owing to the characteristics of the sample and the physical activity tool, the answers had to be grouped in two categories (i.e. inactive vs. active). Hence, more studies are required using objective measurements such as accelerometry-based and heart rate monitors.

In conclusion, physical activity was associated with lower mortality among pre-frail and frail individuals, and mortality outcomes in physically active older adults with frailty appeared similar enough to those without frailty to suggest that physical activity may attenuate the increased risk of mortality associated with frailty. Future intervention studies should be conducted to assess the effectiveness of mobility programs to reduce mortality in frail older adults.

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Author contributions: SHF, FRA and DMG: study concept and design. SHF and DMG: statistical analyses. SHF: drafting the manuscript. All authors: data analysis and interpretation, revision of manuscript for important intellectual content, approval of final version.

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Table 1. Characteristics of study participants by frailty status.

	Frailty status			
	Robust	**Pre-frail**	**Frail**	***p***
n	2026	1536	334	
Women (%)	48.28	63.29	72.39	<.001
Age (years)	70.00±6.94	73.62±8.46	74.90±8.52	<.001
Education level (%)				<.001
No education	43.39	59.72	64.51	
Primary	39.97	31.04	29.14	
Secondary or higher	16.64	9.23	6.35	
Body mass index (kg/m^2)	28.50±4.12	29.22±4.61	29.65±5.63	<.001
Waist circumference (cm)	98.22±11.24	99.19±12.46	100.24±13.39	.001
Smoking (%)				<.001
Never	59.74	71.48	76.06	
Former	28.12	20.47	18.09	
Currently	12.15	8.05	5.86	
Alcohol drinking (%)				<.001
Never	41.77	57.27	61.00	
Former	10.73	12.41	16.87	
Moderate	35.07	22.98	18.10	
Heavy	12.44	7.34	4.03	
MMSE (0-30 score)	26.40±3.65	24.76±4.72	22.39±5.95	<.001
Physically active (%)	70.49	44.28	22.05	<.001

Values are means ±SD or percentages. MMSE: Mini Mental State Examination

Table 2. Hazard ratios (95% confidence interval) for all-cause and cardiovascular disease (CVD) mortality according to physical activity stratified by frailty status.

	All-cause mortality		**CVD mortality**	
	Inactive	Active	Inactive	Active
Robust				
n/deaths	598/254	1428/508	598/102	1428/148
Model 1	1 (Ref.)	**0.79 (0.66-0.95)**	1 (Ref.)	**0.59 (0.43-0.82)**
Model 2	1 (Ref.)	**0.82 (0.68-0.99)**	1 (Ref.)	**0.62 (0.44-0.86)**
Pre-frail				
n/deaths	856/500	680/314	856/207	680/121
Model 1	1 (Ref.)	**0.72 (0.62-0.84)**	1 (Ref.)	**0.70 (0.54-0.92)**
Model 2	1 (Ref.)	**0.72 (0.61-0.84)**	1 (Ref.)	**0.71 (0.54-0.94)**
Frail				
n/deaths	260/179	74/46	260/78	74/16
Model 1	1 (Ref.)	**0.70 (0.54-0.91)**	1 (Ref.)	0.59 (0.34-1.02)
Model 2	1 (Ref.)	**0.61 (0.45-0.83)**	1 (Ref.)	**0.52 (0.29-0.94)**

Model 1 adjusted for age and sex. Model 2 adjusted as in model 1 plus educational level, smoking status, alcohol consumption, body mass index, waist circumference, and Mini-Mental State Examination. Values in bold indicate $p<.05$.

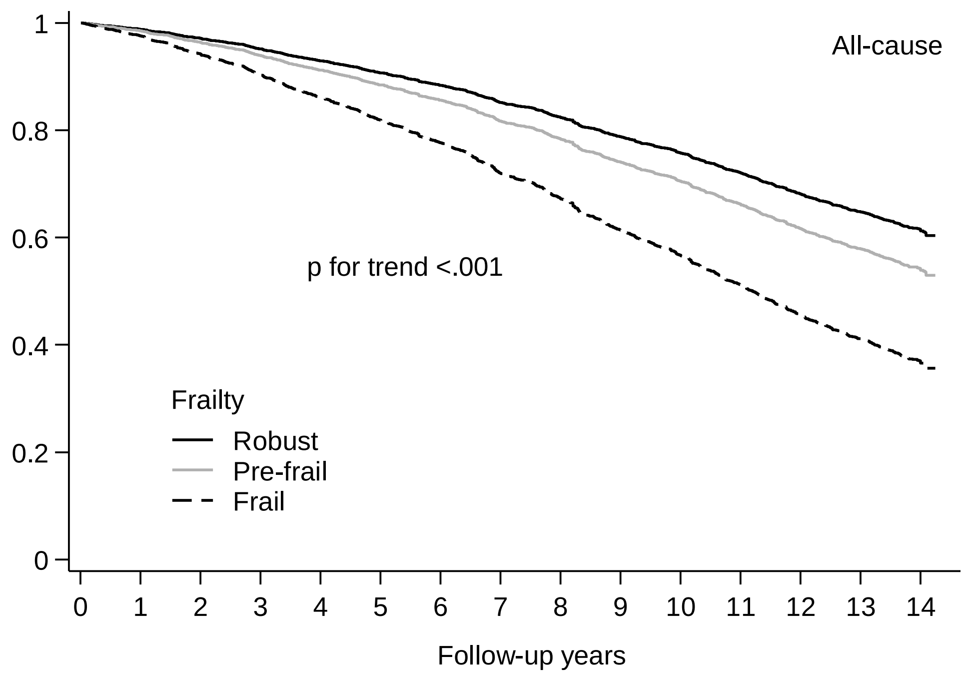
LEGENDS

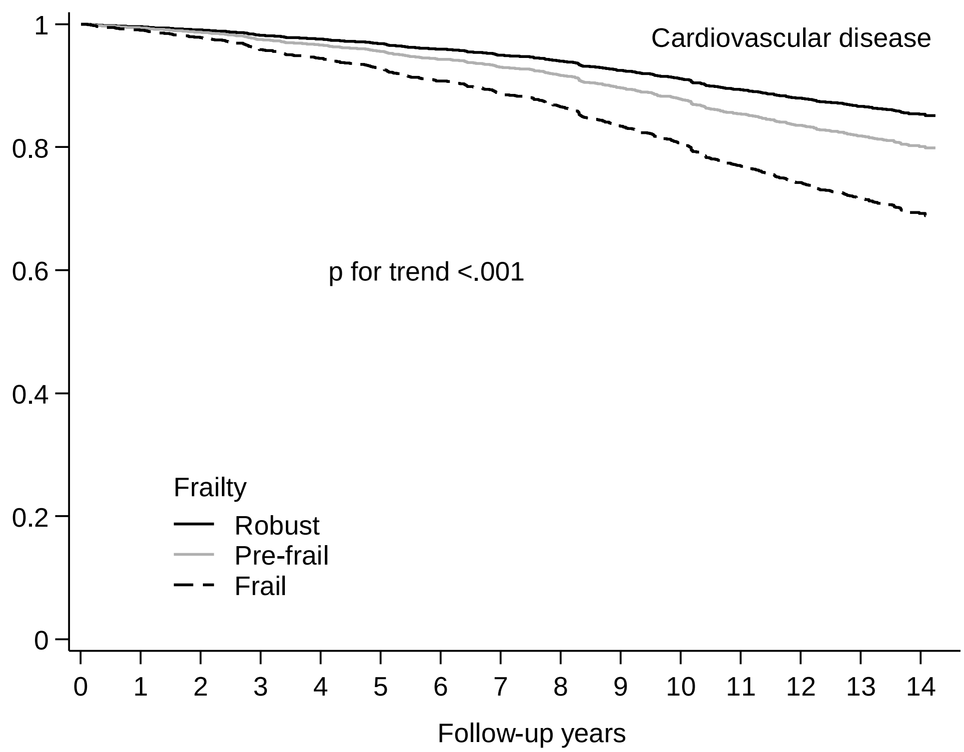
Figure 1. All-cause and cardiovascular disease (CVD) cumulative survival according to frailty status in older adults (n= 3,896). Analyses were adjusted for age, sex, educational level, smoking status, alcohol consumption, body mass index, waist circumference, and the Mini-Mental State Examination scores.

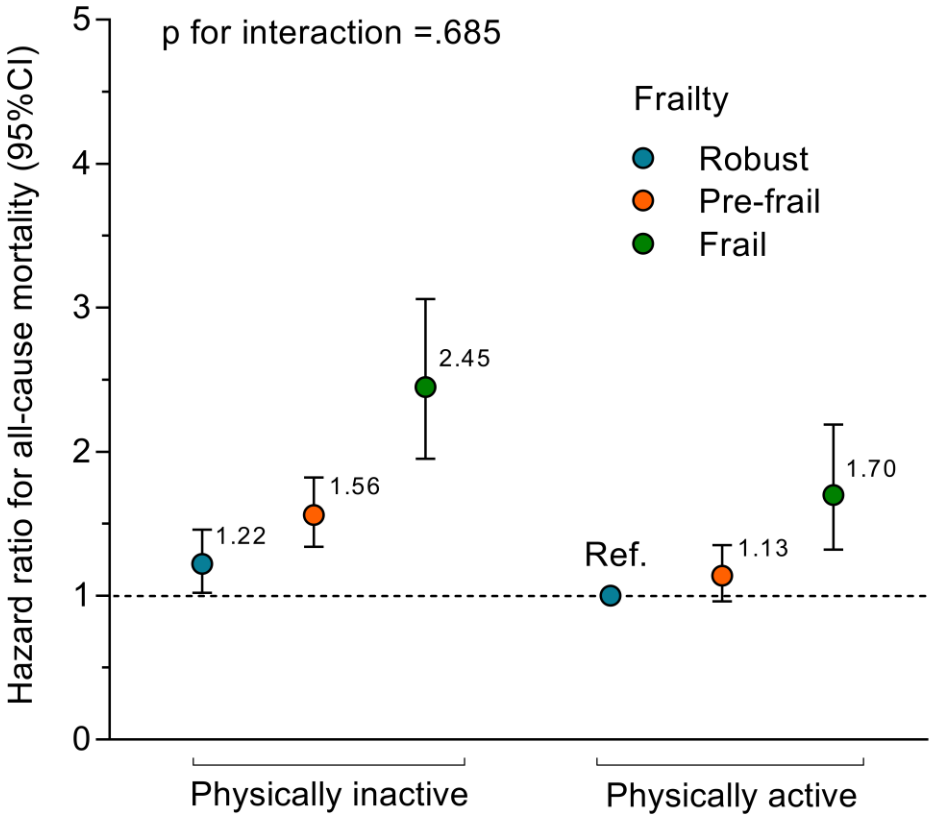
Figure 2. Hazard ratios and 95% confidence interval (CI) for all-cause and cardiovascular disease (CVD) mortality according to physical activity and frailty status in older adults (n= 3,896). Analyses were adjusted for age, sex, educational level, smoking status, alcohol consumption, body mass index, waist circumference, and the Mini-Mental State Examination scores. Number of participants in each increasing category from the X-axis segment was as follows: 598, 856, 260, 1428 (Ref.), 680, and 74.

Table S1. Characteristics of the study participants across groups of frailty and physical activity.

Table S2. Hazard ratios (95% confidence interval) for all-cause and cardiovascular disease (CVD) mortality according to individual frailty criteria.


All-cause
p for trend <.001
Frailty
Robust
Pre-frail
Frail
1
0.8
0.6
0.4
0.2
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Follow-up years


Cardiovascular disease
p for trend <.001
Frailty
Robust
Pre-frail
Frail
1
0.8
0.6
0.4
0.2
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Follow-up years


p for interaction =.685
Frailty
Robust
Pre-frail
Frail
Hazard ratio for all-cause mortality (95%CI)
5
4
3
2
1
0
2.45
1.56
1.22
1.70
1.13
Ref.
Physically inactive
Physically active

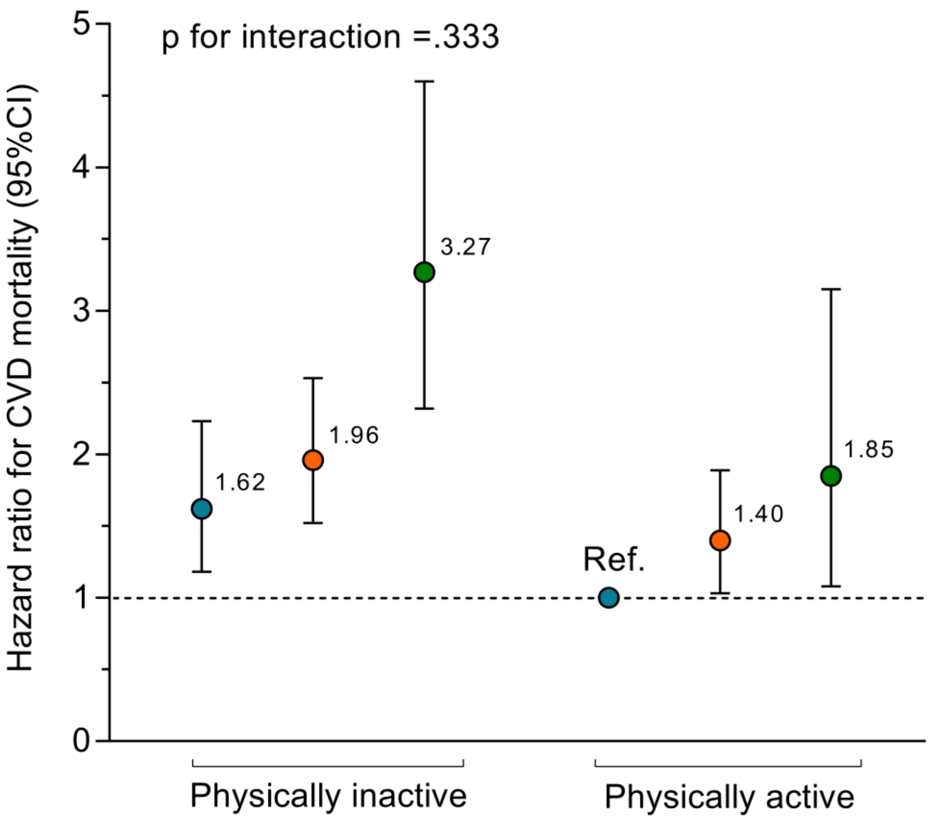

p for interaction =.333
Hazard ratio for CVD mortality (95%CI)
5
4
3
2
1
0
3.27
1.96
1.62
1.85
1.40
Ref.
Physically inactive
Physically active

Table S1. Characteristics of the study participants across groups of frailty and physical activity.

	Robust		**Pre-frail**		**Frail**	
	Inactive	Active	Inactive	Active	Inactive	Active
n	598	1428	856	680	260	74
Women (%)	55.76	45.15	67.50	58	75.09	62.84
Age (years)	70.50±17.26	69.79±6.79	74.65±8.68	72.32±7.98	75.32±8.63	73.43±8.00
Education level (%)						
No education	55.29	38.41	65	53.09	68.22	51.43
Primary	32.51	43.09	27.42	35.61	26.28	39.25
Secondary or higher	12.20	18.50	7.59	11.30	5.51	9.32
Body mass index (kg/m^2)	28.71±4.24	28.41±4.07	29.31±4.70	29.10±4.50	29.78±5.68	29.20±5.46
Waist circumference (cm)	98.53±11.60	98.10±11.09	99.43±13.40	98.89±11.17	100.42±13.66	99.60±12.50
Smoking (%)						
Never	63.26	58.26	74.50	67.69	79.52	63.84
Former	26.46	28.81	18.41	23.05	14.69	30.09
Currently	10.28	12.93	7.09	9.26	5.79	6.07
Alcohol drinking (%)						
Never	48.06	39.13	59.75	54.15	63.78	51.18
Former	12.05	10.17	14.22	10.14	15.53	21.60
Moderate	28.85	37.67	20.02	26.70	17.80	19.14
Heavy	11.03	13.02	6.02	9.01	2.88	8.09
MMSE (0-30 score)	25.83±4.21	26.64±3.36	24.24±5.02	25.41±4.23	21.95±6.05	23.93±5.34

Values are mean±SD or percentage. MMSE: Mini Mental State Examination

Table S2. Hazard ratios (95% confidence interval) for all-cause and cardiovascular disease (CVD) mortality according to individual frailty criteria.

	All-cause mortality			**CVD mortality**		
	n/deaths	Model 1	Model 2	n/deaths	Model 1	Model 2
Fatigue						
No	3429/1538	Ref.	Ref.	3429/570	Ref.	Ref.
Yes	467/263	**1.61 (1.39-1.87)**	**1.52 (1.30-1.77)**	467/102	**1.61 (1.27-2.03)**	**1.50 (1.18-1.92)**
Resistance						
Without difficulty	2465/947	Ref.	Ref.	2465/320	Ref.	Ref.
With difficulty	1432/854	**1.48 (1.32-1.65)**	**1.43 (1.28-1.61)**	1432/352	**1.64 (1.36-1.97)**	**1.57 (1.30-1.91)**
Ambulation						
Without difficulty	2555/1002	Ref.	Ref.	2555/337	Ref.	Ref.
With difficulty	1341/799	**1.44 (1.29-1.61)**	**1.39 (1.24-1.56)**	1341/335	**1.65 (1.37-1.98)**	**1.57 (1.30-1.91)**
Weight loss						
≤5%	3820/1754	Ref.	Ref.	3820/653	Ref.	Ref.
>5%	76/47	**1.85 (1.32-2.59)**	**1.75 (1.25-2.45)**	76/19	**2.00 (1.20-3.33)**	**1.82 (1.09-3.04)**
Illnesses						
0-4 comorbidities	3819/1759	Ref.	Ref.	3819/649	Ref.	Ref.
5+ comorbidities	78/42	1.14 (0.81-1.61)	1.14 (0.82-1.59)	78/23	**1.61 (1.05-2.47)**	**1.59 (1.04-2.43)**

Model 1 adjusted for age and sex. Model 2 adjusted as in model 1 plus educational level, smoking status, alcohol consumption, body mass index, waist circumference, and the Mini-Mental State Examination scores.