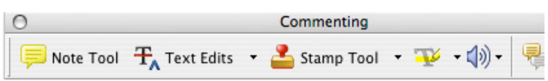
ELSEVIER

INSTRUCTIONS ON THE ANNOTATION OF PDF FILES

To view, print and annotate your content you will need Adobe Reader version 9 (or higher). This program is freely available for a whole series of platforms that include PC, Mac, and UNIX and can be downloaded from http://get.adobe.com/reader/. The exact system requirements are given at the Adobe site: http://www.adobe.com/products/reader/tech-specs.html.

Note: ***Please do NOT make direct edits to the PDF using the editing tools as doing so could lead us to overlook your desired changes.*** *Rather, please request corrections by using the tools in the Comment pane to annotate the PDF and call out the changes you are requesting. If you opt to annotate the file with software other than Adobe Reader then please also highlight the appropriate place in the PDF file.*

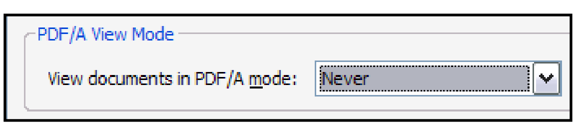
<table>
<tr><th colspan="2">PDF ANNOTATIONS</th></tr>
<tr><th>Adobe Reader version 9</th><th>Adobe Reader version X and XI</th></tr>
<tr><td>
When you open the PDF file using Adobe Reader, the Commenting tool bar should be displayed automatically; if not, click on ‘Tools’, select ‘Comment & Markup’, then click on ‘Show Comment & Markup tool bar’ (or ‘Show Commenting bar’ on the Mac). If these options are not available in your Adobe Reader menus then it is possible that your Adobe Acrobat version is lower than 9 or the PDF has not been prepared properly.



(Mac)

PDF ANNOTATIONS (Adobe Reader version 9)

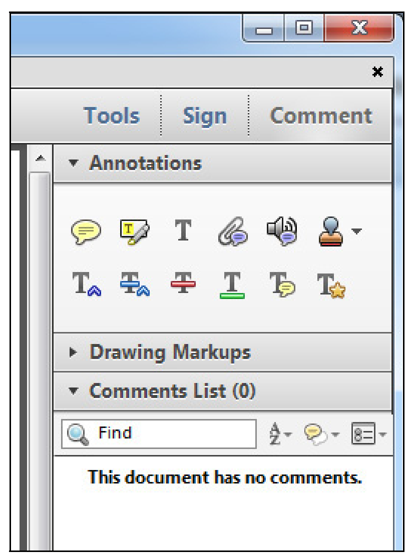
The default for the Commenting tool bar is set to ‘off’ in version 9. To change this setting select ‘Edit | Preferences’, then ‘Documents’ (at left under ‘Categories’), then select the option ‘Never’ for ‘PDF/A View Mode’.



(Changing the default setting, Adobe version 9)
</td><td>
To make annotations in the PDF file, open the PDF file using Adobe Reader XI, click on ‘Comment’.

If this option is not available in your Adobe Reader menus then it is possible that your Adobe Acrobat version is lower than XI or the PDF has not been prepared properly.

This opens a task pane and, below that, a list of all Comments in the text. These comments initially show all the changes made by our copyeditor to your file.



</td></tr>
</table>

HOW TO...		
Action	**Adobe Reader version 9**	**Adobe Reader version X and XI**
Insert text	Click the 'Text Edits' button on the Commenting tool bar. Click to set the cursor location in the text and simply start typing. The text will appear in a commenting box. You may also cut-and-paste text from another file into the commenting box. Close the box by clicking on 'x' in the top right-hand corner.	Click the 'Insert Text' icon on the Comment tool bar. Click to set the cursor location in the text and simply start typing. The text will appear in a commenting box. You may also cut-and-paste text from another file into the commenting box. Close the box by clicking on '_' in the top right-hand corner.
Replace text	Click the 'Text Edits' button on the Commenting tool bar. To highlight the text to be replaced, click and drag the cursor over the text. Then simply type in the replacement text. The replacement text will appear in a commenting box. You may also cut-and-paste text from another file into this box. To replace formatted text (an equation for example) please <u>Attach a file</u> (see below).	Click the 'Replace (Ins)' icon on the Comment tool bar. To highlight the text to be replaced, click and drag the cursor over the text. Then simply type in the replacement text. The replacement text will appear in a commenting box. You may also cut-and-paste text from another file into this box. To replace formatted text (an equation for example) please <u>Attach a file</u> (see below).
Remove text	Click the 'Text Edits' button on the Commenting tool bar. Click and drag over the text to be deleted. Then press the delete button on your keyboard. The text to be deleted will then be struck through.	Click the 'Strikethrough (Del)' icon on the Comment tool bar. Click and drag over the text to be deleted. Then press the delete button on your keyboard. The text to be deleted will then be struck through.
Highlight text/ make a comment	Click on the 'Highlight' button on the Commenting tool bar. Click and drag over the text. To make a comment, double click on the highlighted text and simply start typing.	Click on the 'Highlight Text' icon on the Comment tool bar. Click and drag over the text. To make a comment, double click on the highlighted text and simply start typing.
Attach a file	Click on the 'Attach a File' button on the Commenting tool bar. Click on the figure, table or formatted text to be replaced. A window will automatically open allowing you to attach the file. To make a comment, go to 'General' in the 'Properties' window, and then 'Description'. A graphic will appear in the PDF file indicating the insertion of a file.	Click on the 'Attach File' icon on the Comment tool bar. Click on the figure, table or formatted text to be replaced. A window will automatically open allowing you to attach the file. A graphic will appear indicating the insertion of a file.
Leave a note/ comment	Click on the 'Note Tool' button on the Commenting tool bar. Click to set the location of the note on the document and simply start typing. <u>Do not use this feature to make text edits</u>.	Click on the 'Add Sticky Note' icon on the Comment tool bar. Click to set the location of the note on the document and simply start typing. <u>Do not use this feature to make text edits</u>.

HOW TO...		
Action	**Adobe Reader version 9**	**Adobe Reader version X and XI**
Review	To review your changes, click on the 'Show' button  on the Commenting tool bar. Choose 'Show Comments List'. Navigate by clicking on a correction in the list. Alternatively, double click on any mark-up to open the commenting box.	Your changes will appear automatically in a list below the Comment tool bar. Navigate by clicking on a correction in the list. Alternatively, double click on any mark-up to open the commenting box.
Undo/delete change	To undo any changes made, use the right click button on your mouse (for PCs, Ctrl-Click for the Mac). Alternatively click on 'Edit' in the main Adobe menu and then 'Undo'. You can also delete edits using the right click (Ctrl-click on the Mac) and selecting 'Delete'.	To undo any changes made, use the right click button on your mouse (for PCs, Ctrl-Click for the Mac). Alternatively click on 'Edit' in the main Adobe menu and then 'Undo'. You can also delete edits using the right click (Ctrl-click on the Mac) and selecting 'Delete'.

SEND YOUR ANNOTATED PDF FILE BACK TO ELSEVIER

Save the annotations to your file and return as instructed by Elsevier. Before returning, please ensure you have answered any questions raised on the Query Form and that you have inserted all corrections: later inclusion of any subsequent corrections cannot be guaranteed.

FURTHER POINTS

- Any (grey) halftones (photographs, micrographs, etc.) are best viewed on screen, for which they are optimized, and your local printer may not be able to output the greys correctly.
- If the PDF files contain colour images, and if you do have a local colour printer available, then it will be likely that you will not be able to correctly reproduce the colours on it, as local variations can occur.
- If you print the PDF file attached, and notice some 'non-standard' output, please check if the problem is also present on screen. If the correct printer driver for your printer is not installed on your PC, the printed output will be distorted.

AUTHOR QUERY FORM

ELSEVIER	**Journal:** JMCP **Article Number:** 2271	**Please e-mail your responses and any corrections to:** **E-mail:** **k.genovario@elsevier.com**

Dear Author,

Please check your proof carefully and mark all corrections at the appropriate place in the proof (e.g., by using on-screen annotation in the PDF file) or compile them in a separate list. **It is crucial that you NOT make direct edits to the PDF using the editing tools as doing so could lead us to overlook your desired changes.** Note: if you opt to annotate the file with software other than Adobe Reader then please also highlight the appropriate place in the PDF file. To ensure fast publication of your paper please return your corrections within 48 hours.

For correction or revision of any artwork, please consult http://www.elsevier.com/artworkinstructions.

Any queries or remarks that have arisen during the processing of your manuscript are listed below and highlighted by flags in the proof.

Location in article	Query / Remark: Click on the Q link to find the query's location in text Please insert your reply or correction at the corresponding line in the proof
	If there are any drug dosages in your article, please verify them and indicate that you have done so by initialing this query
Q1	Sara Higueras-Fresnillo—changed degree from McS to MSc (master of science). Is this correct?
Q2	Grant Support—please ensure that the information presented is correct as shown. Can/should the numerous abbreviations be written out?
Q3	Is this statement correct? If there are any potential competing interests, please provide them.
Q4	Is it OK to publish your e-mail address?
Q5	The sentence beginning "Interestingly" was deleted because the "Objective" section of the Abstract is only one sentence per MCP style.
Q6	Per MCP style, information presented in the Abstract should also appear in the text. The statement "a mortality reduction of 36%…" appears in the Discussion section but not in the Results section. Please insert where appropriate in the Results section of the text.
Q7	In the sentence beginning "Alcohol drinking status," is citation of ref 12 (a study of older Chinese people) correct?
Q8	MCP requires inclusion of absolute numbers corresponding to percentages. In the sentence beginning "Overall," and throughout the text, please provide absolute numbers.
Q9	MCP requires inclusion of a *P* value with use of the term *significant*. We inserted *P* values from Table 2 in the sentence beginning "Table 2 shows." Please ensure accuracy.

(*continued on next page*)

Q10	In the sentence beginning "In addition," please provide *P* value(s) to support use of the term *significantly* or change to another term (eg, substantially, considerably, markedly). If all *P* values are the same, insert at the end of the sentence "(all *P*=.XX)"
Q11	The sentence beginning "The rate advancement" was unclear ("analysis showed that the lower mortality cognitive frailty inactive individuals…was equivalent to being 6.8 years older"). Does edited sentence retain your intended meaning?
Q12	Unable to verify ref 29. Please ensure that the author, title, and website URL are correct.
Q13	Please verify that all figures, figure labels, and figure legends are correct.
Q14	Figure 2—labels for the 4 groups were changed in part B to match those in part A and text, and 95% CI was deleted from labels on y-axis and defined in legend. OK? We also repeated the very helpful labels from the x-axis on part B on part A. OK?
Q15	Table 1—MCP requires inclusion of absolute numbers corresponding to percentages. Please provide numerators for all percentage entries and carry percentages out to one decimal place (see first entry, "Women", for format).
Q16	Have we correctly interpreted the following funding source(s) and country names you cited in your article: MINECO, Spain; Instituto de Salud Carlos III, Spain; Alicia Koplowitz Foundation, Spain?
Q17	Please confirm that given names and surnames have been identified correctly and are presented in the desired order and please carefully verify the spelling of all authors' names.
	Please check this box or indicate your approval if you have no corrections to make to the PDF file ☑

Thank you for your assistance.

MAYO CLINIC

ORIGINAL ARTICLE

Cognitive Frailty and Mortality in a National Cohort of Older Adults: the Role of Physical Activity

Irene Esteban-Cornejo, PhD; Verónica Cabanas-Sánchez, PhD; Sara Higueras-Fresnillo, MSc; Francisco B. Ortega, PhD; Arthur F. Kramer, PhD; Fernando Rodriguez-Artalejo, MD, PhD; and David Martinez-Gomez, PhD

Abstract

Objective: To examine the association between cognitive frailty and long-term all-cause mortality and the stratified and combined associations of physical activity and cognitive frailty with long-term all-cause mortality in a population-based cohort of older adults from Spain.

Patients and Methods: A representative cohort of 3677 noninstitutionalized individuals from Spain aged 60 years or older was recruited between April 17, 2000, and April 28, 2001, with follow-up through December 28, 2014. Information on self-reported physical activity and cognitive frailty status were collected at baseline. Analyses were performed with Cox regression after adjustment for confounders.

Results: The median follow-up was 14 years (range, 0.03-14.25 years), corresponding to 40,447 person-years, with a total of 1634 deaths. The hazard ratio (HR) for all-cause mortality among participants with cognitive frailty compared to robust participants was 1.69 (95% CI, 1.43-2.01). Being active was associated with a mortality reduction of 36% (95% CI, 21%-47%) in cognitively frail individuals. Compared to those who were robust and active, participants with cognitive frailty who were inactive had the highest mortality risk (HR, 2.13; 95% CI, 1.73-2.61), which was equivalent to being 6.8 (95% CI, 5.33-7.99) years older.

Conclusion: Cognitive frailty was more markedly associated with increased mortality in the inactive older adults, and being active reduced the mortality risk among cognitively frail individuals by 36%. These novel results highlight that engaging in physical activity could improve survival among cognitively frail older adults.

 ■ Mayo Clin Proc. 2019;■■(■):1-10

Cognitive impairment and physical frailty are independently associated with a higher risk of adverse health outcomes, including hospitalization, disability, and mortality.[1] Cognitive impairment ranges in severity from mild to severe because of the deterioration in several domains (eg, memory, learning, and/or executive function), and physical frailty represents a state of increased vulnerability to stressor events resulting from reduced capacity in multiple physiologic systems. Both aging indicators also share some pathogenic mechanisms such as brain alterations, hormonal dysregulation, chronic inflammation, and oxidative stress.[2,3] In fact, physical frailty has consistently been linked to cognitive impairment, dementia, and Alzheimer disease.[4-6] On this basis, an international consensus group has developed the concept of cognitive frailty as a heterogeneous clinical manifestation characterized by the simultaneous presence of both physical frailty and cognitive impairment, in the absence of dementia.[7]

Cognitive frailty seems to entail a greater death risk than physical frailty or cognitive impairment separately, as reported in both community-based[8-12] and population-based[13,14] studies. Interestingly, despite the

From the Center for Cognitive and Brain Health, Department of Psychology, Northeastern University, Boston, MA (I.E.-C., A.F.K.); PROFITH "PROmoting FITness and Health through physical activity" Research Group, Department of Physical Education and Sports, Faculty of Sport Sciences, University of Granada, Granada, Spain (I.E.-C., F.B.O.); Research Centre in Physical Activity, Health and Leisure (CIAFEL), Faculty of Sport, University

Affiliations continued at the end of this article.

potential effect of regular physical activity to slow cognitive decline[15,16] and its association with lower mortality in nonfrail individuals,[17,18] no previous studies have investigated whether and to what extent physical activity could attenuate the effect of cognitive frailty on mortality. Accordingly, this study examined (1) the association between cognitive frailty and long-term all-cause mortality over 14 years and (2) the stratified and combined associations of physical activity and cognitive frailty with long-term all-cause mortality in a population-based cohort of older adults from Spain.

PATIENTS AND METHODS

Study Design and Participants

Data were obtained from the Universidad Autonoma de Madrid cohort, a representative cohort of the noninstitutionalized population aged 60 years and older in Spain. Detailed information about the study methods have been reported elsewhere.[19,20] In brief, study participants were selected between April 17, 2000, and April 28, 2001, with follow-up through December 28, 2014, using probabilistic sampling by multistage clusters. The clusters were stratified according to region of residence and size of municipality. Next, census sections and households were randomly selected within each cluster. Finally, study participants were selected in the households according to age and sex strata. Baseline information was collected at the participants' homes through personal interviews and physical examination by trained and certified personnel. The study response rate was 71%, with a total of 4008 individuals (2269 women) recruited.[19,20] After missing data were excluded, the present analysis included 3677 individuals (92% of the original sample).

Written informed consent was obtained from study participants and from one family member. The study was approved by the Clinical Research Ethics Committee of La Paz University Hospital in Madrid, Spain.

Cognitive Frailty Phenotype

The International Academy of Nutrition and Aging and the International Association of Gerontology and Geriatrics established a first definition for cognitive frailty in older adults in 2013.[7] The proposed diagnostic criteria for this novel and heterogeneous clinical age-related condition included the simultaneous presence of physical frailty and mild cognitive impairment (MCI) without a concurrent diagnosis of Alzheimer or other dementias. Since that time, several criteria have been proposed to determine both physical frailty and MCI.[8-14] In the present study, we used the FRAIL scale (fatigue, resistance, ambulation, illness, and loss of weight) to assess physical frailty[21] and the Mini-Mental Status Examination (MMSE) to assess MCI,[22] excluding those who were diagnosed with Alzheimer or other dementias at baseline or died in the subsequent 2 years from Alzheimer or other dementias.

Physical Frailty

Physical frailty was assessed with the FRAIL scale.[21,23] Fatigue, resistance, and ambulation were identified with the following questions from the 36-Item Short-Form Health Survey questionnaire.[24]

Fatigue: "During the last 4 weeks, did you feel tired?" Possible responses were (1) all of the time, (2) most of the time, (3) a good bit of the time, (4) some of the time, (5) a little bit of the time, and (6) none of the time. Participants were deemed to be fatigued when they responded "all of the time" or "most of the time."

Resistance: "In a typical day, does your health now limit you in climbing one flight of stairs?" Response options were (1) yes, limited a lot, (2) yes, limited a little, and (3) no, not limited at all. Resistance was defined as either of the first 2 responses.

Ambulation: "In a typical day, does your health now limit you in walking several blocks?" Response options were (1) yes, limited a lot, (2) yes, limited a little, and (3) no, not limited at all. Ambulation was considered to be affected when either of the first 2 responses was provided.

FLA 5.5.0 DTD ■ JMCP2271_proof ■ 25 January 2019 ■ 3:06 pm

Illness and weight loss were self-reported. Illness was defined as having 5 or more of the following self-reported physician-diagnosed conditions: (1) asthma or chronic bronchitis, (2) hypertension, (3) coronary heart disease, (4) stroke, (5) osteoarthritis or rheumatism, (6) pneumonia, (7) diabetes mellitus, (8) depression with drug treatment, (9) hip fracture, (10) Parkinson disease, and (11) cancer at any site. Weight loss was defined as unintentional loss of 5% or more of body weight within the preceding 12 months.

The physical frailty score ranges from 0 to 5.[23] Individuals with zero criteria were considered physically robust, those with scores of 1 to 2 were categorized as prefrail, and those with 3 or more criteria were considered frail. For analytic proposes, we merged prefrail and frail individuals into a single category, as has been performed in other recent studies.[1,25]

Mild Cognitive Impairment

Cognitive function was assessed with the MMSE,[26] which has been adapted and validated for use in the Spanish population.[22] The MMSE includes 7 domains (orientation to time, orientation to place, registration, attention and calculation, recall, language, and visual construction), and its score ranges from 0 to 30. Higher scores indicate better cognitive functioning. For this analysis and similar to previous studies, a score of 25 or less was considered MCI.[1,26,27]

Operationalizing Cognitive Frailty

As in previous studies,[1,13,25] participants were classified into 4 groups according to physical frailty and cognitive function: (1) robust: those without physical frailty (ie, nonprefrail/frail) and without MCI, (2) physical prefrailty: physically frail individuals (ie, prefrail/frail) without MCI, (3) cognitive prefrailty: individuals without physical frailty (ie, nonprefrail/frail) but with MCI, and (4) cognitive frailty: those with physical frailty (ie, prefrail/frail) and MCI.

Physical Activity

Physical activity was assessed with a single question taken from the Spanish National Health Survey, which is used to monitor the prevalence of physical activity in Spain.[20,28] Participants self-reported their leisure time physical activity level as (1) inactive, (2) occasional, (3) several times a month, and (4) several times a week. Responses correlate well with results from the well-validated questionnaire used in the Nurses' Health Study and the Health Professionals' Follow-up Study for assessing physical activity in older adults (Spearman correlation coefficient, ρ=0.55; the mean physical activity level in metabolic equivalent task h/wk was 7.1 (95% CI, 6.2-8.1) for the inactive category, and 30.0 (95% CI, 28.9-31.0), 43.1 (95% CI, 36.3-50.0), and 56.6 (95% CI, 37.6-75.5) for the occasional, several times a month, and several times a week categories, respectively).[28] Participants were classified as physically inactive (ie, inactive category) and physically active (ie occasionally, monthly, and weekly categories).[20]

Ascertainment of Mortality

The outcome variable for the present study was all-cause mortality from study baseline to the end of follow-up on December 31, 2014. Mortality data were obtained from the National Death Index, which contains information on the vital status of all residents in Spain. The vital status was ascertained for 99.9% of the Universidad Autonoma de Madrid cohort.[29]

Covariates

Sex, age, and the highest educational level attained (no formal education, primary, and secondary or higher) were recorded. Tobacco consumption was reported as never, former, or current smoking. Alcohol consumption status was obtained with the scale used in the Spanish National Health Survey,[12] which collects the frequency and quantity of beer, wine, and spirits consumed during the past year to calculate total alcohol intake; the cutoff point between moderate and excessive consumption was alcohol intake of 30 g/d or less in men and 20 g/d or less in women.[30] Participants were classified as abstainers, former drinkers, moderate drinkers, and excessive drinkers. Body height and weight were measured using standardized procedures, and body mass index was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured with an nonelastic belt-type tape at the midpoint between the lowest rib and the iliac crest after breathing out normally.[19]

Statistical Analyses

Baseline characteristics of the study participants by cognitive frailty status are presented as mean ± SD or percentages, as appropriate. Mortality risk according to cognitive frailty status was summarized with hazard ratios (HRs) and their 95% CIs, obtained using the Cox proportional hazards regression model. Robust individuals were used as reference in the analyses. Regression models were adjusted for sex, age, educational attainment, smoking, alcohol consumption, body mass index, and waist circumference.

We used similar Cox models to examine the stratified association of physical activity (ie, active vs inactive as a reference category) and mortality by cognitive frailty status. Preliminary analysis revealed no significant interaction between physical activity and cognitive frailty status in relationship to mortality risk (P=.110 for interaction). Then, we examined the combined association of physical activity (ie, active vs inactive) and cognitive frailty status (robust, physical prefrailty, cognitive prefrailty, and cognitive frailty) with mortality by building 8 categories of exposure (ie, 2 physical activity categories × 4 cognitive frailty categories) and taking those who were robust and physically active as the reference category.

We calculated rate advancement periods to estimate the difference in survival in cognitively frail inactive individuals vs robust active individuals that is equivalent to increasing chronological age; as such, we divided the β coefficient for mortality in those cognitively frail inactive individuals vs robust active individuals by the β coefficient for mortality associated with each yearly increase in age.

We checked the assumption of proportionality of hazards both visually and by testing the statistical significance of the interaction of cognitive frailty status and physical activity with time of follow-up. No evidence was found of departure from the proportional hazards assumption (all P>.1). Statistical significance was set at 2-sided P<.05. Analyses were performed with Stata statistical software, version 14 for Windows (StataCorp).

RESULTS

Descriptive Characteristics

Table 1 shows the baseline characteristics of the study sample. Overall, XXX of the 3677 study participants (22.6%) had cognitive frailty. Compared to robust individuals, age, percentage of women, lower education, never smokers, and alcohol abstainers increased across categories of cognitive frailty. However, the MMSE score decreased across categories (all P<.05).

Association Between Cognitive Frailty and All-Cause Mortality

The median follow-up was 14 years (range, 0.03-14.25 years), corresponding to 40,447 person-years, with a total of 1634 deaths. Figure 1 shows the cumulative survival according to cognitive frailty status. The multivariate HRs (95% CIs) for all-cause mortality among participants with physical prefrailty, cognitive prefrailty, and cognitive frailty compared to robust participants were 1.42 (1.21-1.66), 1.34 (1.11-1.61), and 1.69 (1.43-2.01), respectively.

Stratified Association Between Physical Activity and All-Cause Mortality by Cognitive Frailty Status

Table 2 shows the association between physical activity and mortality risk stratified by cognitive frailty status. In cognitively frail individuals, those who were physically active vs inactive had significantly lower mortality (HR, 0.64; 95% CI, 0.53-0.79; P<.001), but

TABLE 1. Characteristics of the Study Sample, Stratified by Cognitive Frailty Status[a,b]

Variable	All (N=3677)	Robust (n=1370)	Physical prefrailty (n=897)	Cognitive prefrailty (n=578)	Cognitive frailty (n=832)
Women	XXX (56.X)	45	58	56	72
Age (y)	71.50±7.78	68.81±6.23	71.41±7.70	72.10±7.41	75.61±8.54
Education level					
No education	51	33	48	66	73
Primary	36	45	37	28	24
Secondary or higher	13	22	14	6	3
Body mass index (kg/m^2)	28.92±4.50	28.52±4.00	29.41±4.60	28.57±4.39	29.30±5.12
Waist circumference (cm)	98.88±12.03	98.29±11.19	99.70±12.60	98.21±11.52	99.42±13.01
Smoking					
Never	66	57	67	67	78
Former	24	30	24	22	16
Current	10	13	9	11	6
Alcohol consumption					
Abstainer	49	39	54	49	62
Former	12	9	13	13	13
Moderate	29	39	24	27	20
Excessive	10	13	9	11	5
Physical frailty criteria					
Fatigue	12	0	23	0	28
Resistance	36	0	68	0	84
Ambulation	33	0	67	0	75
Illness	2	0	3	0	4
Weight loss	2	0	4	0	4
Physical frailty score	0.84±1.03	0	1.65±0.71	0	1.95±0.76
MMSE score	25.30±4.77	28.36±1.36	28.02±1.33	21.73±3.55	19.80±4.92
MMSE score ≤25	38	0	0	64	41
Physically active	57	73	48	66	35

[a]MMSE = Mini-Mental State Examination.
[b]Data are presented as mean ± SD or No. (percentage) of participants.

this association did not achieve statistical significance for the rest of cognitive frailty categories (robust, P=.163; physical prefracilty, P=.057; cognitive prefrailty, P=.083).

Combined Association of Physical Activity and Cognitive Frailty With All-Cause Mortality

Figure 2 presents the combined association of physical activity and cognitive frailty status with mortality risk. Compared to those who were robust and active, participants with cognitive frailty who were inactive had the highest mortality risk (HR, 2.13; 95% CI, 1.73-2.61). In addition, excess mortality in active participants with cognitive frailty (HR, 1.34; 95% CI, 1.06-1.70) was significantly smaller than in inactive participants with cognitive prefrailty (HR, 1.72; 95% CI, 1.33-2.23) or with physical prefrailty (HR, 1.63; 95% CI, 1.33-2.01). By contrast, cognitively prefrail active participants (HR, 1.29; 95% CI, 1.02-1.64) and physically prefrail active participants (HR,1.38; 95% CI, 1.12-1.69) had excess mortality fairly similar to their robust inactive counterparts (HR, 1.17; 95% CI, 0.92-1.70). Lastly, we found a more marked dose-response relationship between cognitive frailty categories and mortality risk for the inactive participants, namely, the mortality risk increased with advancing cognitive frailty categories (Figure 2A). The rate advancement period analysis revealed that

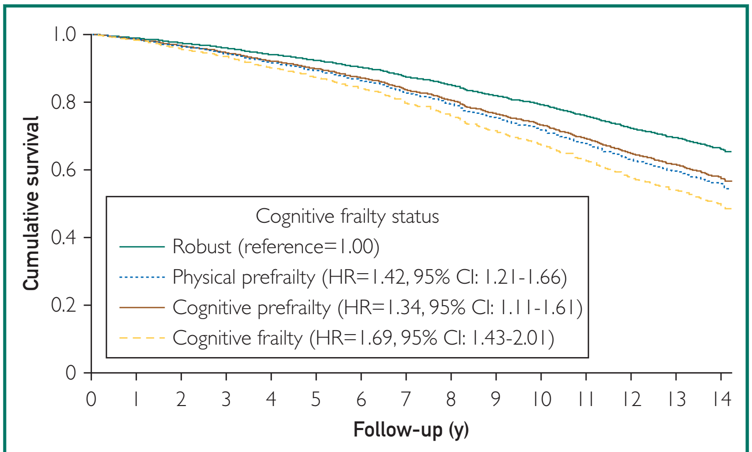


FIGURE 1. Cumulative survival according to cognitive frailty status in 3677 older adults. Analyses were adjusted for sex, age, educational level (no education/primary/secondary or higher), smoking (never/former/current), alcohol consumption (abstainer/former/moderate/excessive), body mass index, and waist circumference. HR = hazard ratio; Ref. = reference group (robust and physically active individuals). Error bars indicate 95% CI.

compared with robust active individuals, the mortality risk of those with cognitive frailty who were inactive was equivalent to being 6.8 years older (95% CI, 5.33-7.99) in chronological age (Figure 2B). All individual and combined analyses were repeated after excluding participants with depression, and the strength of the associations did not materially change (data not shown).

DISCUSSION

The main findings of this study were that (1) cognitive frailty was associated with increased mortality more markedly in the inactive older adults and (2) being physically active may reduce the mortality risk among cognitively frail individuals by 36%. These novel results highlight that engaging in physical activity could improve vital prognosis among cognitively frail older adults.

Most studies investigating the effect of cognitive frailty on mortality were conducted in community-based settings.[8-12,31] These studies found that those who were both physically frail and cognitively impaired had the highest risk of mortality,[8-12] except the study by Jacobs et al,[31] in which the effect of physical frailty was more marked than the effect of cognitive impairment in models including both factors. Only 3 studies were population based.[13,14,32] Cano et al[32] reported that physical frailty was a stronger predictor of mortality than cognitive impairment (ie, MMSE score ≤21), and no additional mortality risk was found for cognitive frailty. The other 2 studies found that cognitive frailty was associated with increased mortality independent of the cognitive criteria used (ie, positive response to item 14 of the 30-item Geriatric Depression Scale or MMSE score <26).[13,14] Solfrizzi et al[14] found that cognitive frailty was associated with a 75% increased risk of mortality over a period of 3.5 years and a 40% increased risk over a period of 7 years. Feng et al[13] reported that cognitive frailty conferred additional greater risk for mortality than either physical frailty or isolated cognitive impairment; specifically, the risk of mortality related to cognitive frailty (ie, ≥1 Fried criteria and MMSE score <26) was approximately 90% higher over a period of 10 years. Importantly, despite the differences in measures of cognitive frailty used, the operationalization of its 2 components (ie, physical frailty and cognitive impairment), the setting of the studies, or the sociodemographic characteristics of the study population, cognitive frailty seems to increase the risk of mortality in older adults.

Our study results are consistent with previous findings in that cognitively frail individuals were at the highest risk of mortality (around 70%) over a period of 14 years. In addition, those with cognitive frailty had about a 30% higher death risk than those with only cognitive prefrailty or physical prefrailty, highlighting the cumulative effect of cognitive frailty on mortality. This finding suggests that cognitively frail individuals, characterized as prefrail/frail individuals (ie, ≥1 FRAIL criteria) with MCI (MMSE score ≤25), were the most vulnerable to risk of mortality, which provides strong support for the prognostic validity of cognitive frailty. The prevalence of cognitive frailty operationalized as aforementioned was 22.6%, higher than in previous studies with ranges from 1.0% in population-based studies to 22.0% in clinical-based studies.[1]

TABLE 2. Stratified Association Between Physical Activity and Mortality Risk in 3677 Study Participants, Stratified by Cognitive Frailty Status[a]

	All-cause mortality			
Cognitive frailty status	All	Deaths	Hazard ratio (95% CI)	*P* value
Robust				
Inactive	368	131	1 (reference)	...
Active	1003	300	0.83 (0.64-1.08)	.163
Physical prefrailty				
Inactive	465	228	1 (reference)	...
Active	432	194	0.81 (0.65-1.01)	.057
Cognitive prefrailty				
Inactive	194	98	1 (reference)	...
Active	384	180	0.76 (0.56-1.04)	.083
Cognitive frailty				
Inactive	544	358	1 (reference)	...
Active	287	144	**0.64 (0.53-0.79)**	**<.001**

[a]Analyses were adjusted for sex, age, educational level (no education/primary/secondary or higher), smoking (never/former/current), alcohol consumption (abstainer/former/moderate/excessive), body mass index, and waist circumference. Statistically significant values are shown in bold.

However, further research is needed to standardize the operationalization of cognitive frailty and determine its subsequent effect on mortality.

There are several pathways that may lead from cognitive frailty to death, including hormonal, inflammatory, and vascular mechanisms influencing both physical frailty and cognitive impairment.[33,34] First, decreased levels of sex steroids (eg, testosterone) and growth hormones (eg, brain-derived neurotrophic factor [BDNF]). Testosterone and BDNF produce cognitive protection by increasing synapse plasticity at the hippocampus; importantly, both testosterone and BDNF tend to decrease in physically frail individuals.[35,36] Conversely, increased cortisol is associated with reduced hippocampal volume and defective response to stressors by dysregulation of the hypothalamic-pituitary-adrenal axis in frail elderly people.[37] Second, increased levels of inflammatory markers such as C-reactive protein or interleukins are implicated in motor dysfunction, cognitive impairment, and dementia, which may strengthen the diagnosis of cognitive frailty.[38,39] Last, atherosclerotic disease reduces blood flow to the brain and skeletal muscle. Particularly, white matter hyperintensities (ie, leukoaraiosis) reflect chronic blood flow reduction linked to cognitive deficits, gait disorders, and impaired balance leading to cognitive impairment and physical frailty and in turn to higher mortality.[40] Taken together, the determination of the aforementioned factors may be useful for early detention of cognitive frailty, although further research is necessary to better understand the neurobiological basis of cognitive frailty and ultimately increase survival.

Interestingly, we found a dose-response relationship between cognitive frailty categories and mortality risk for the inactive participants (ie, the mortality risk increased with advancing cognitive frailty categories) and that physical activity could reduce long-term mortality among cognitively frail older adults. Rate advancement periods highlight the clinical implications of the data by showing that, compared with a robust active individual, a cognitively frail inactive individual had on average a mortality rate equivalent to being almost 7 years older. These findings are extremely important because they provide the first empirical evidence about the impact of physical activity on mortality in cognitively frail individuals. However, in our study the prevalence of physical inactivity in cognitively frail individuals was around 65%. Therefore, promoting physical activity among cognitively frail

FLA 5.5.0 DTD ■ JMCP2271_proof ■ 25 January 2019 ■ 3:06 pm

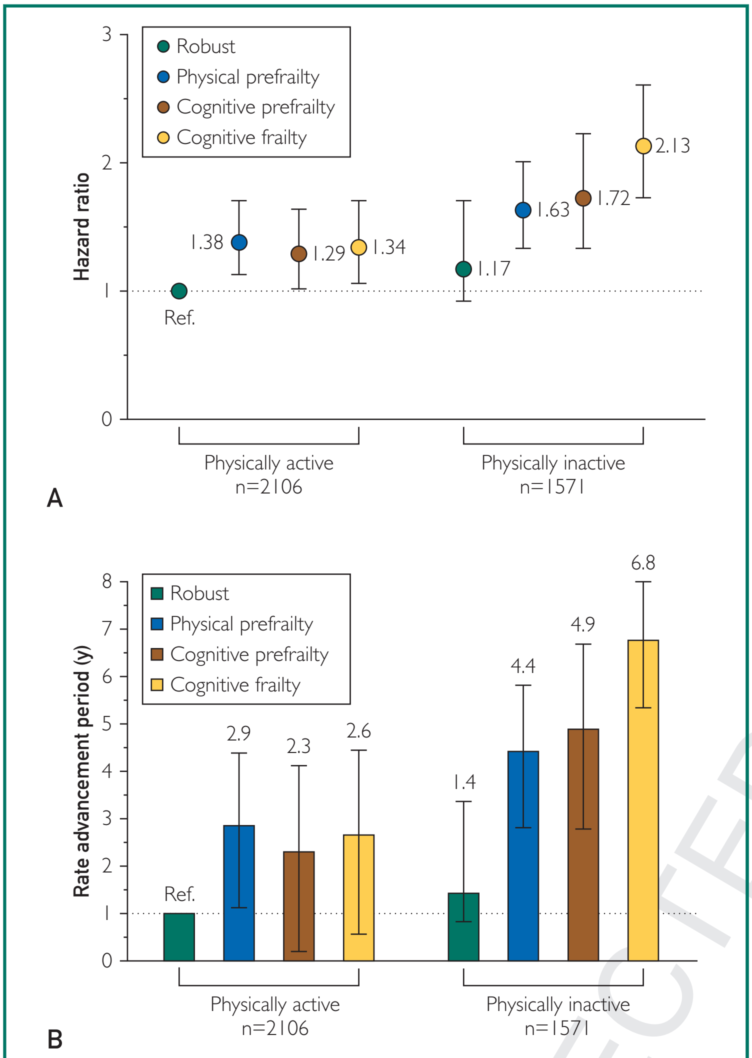


FIGURE 2. Combined association of physical activity and cognitive frailty status with mortality risk in 3677 older adults using hazard ratio (A) and rate advancement period (B). Analyses were adjusted for sex, age, educational level (no education/primary/secondary or higher), smoking (never/former/current), alcohol consumption (abstainer/former/moderate/excessive), body mass index, and waist circumference. The reference group (Ref.) was robust and physically active individuals. Error bars indicate 95% CI.

elderly persons is crucial because they have room for improvement and it may increase their survival.

Evidence on physical activity interventions among cognitively frail individuals is very scarce, but a small number of studies point to the cognitive benefits of physical activity.[1] In particular, in randomized control trials, physical exercise in combination with other strategies (eg, diet or cognitive training)[41,42] or alone[43] improved cognitive outcomes in physically frail and prefrail states, opening new routes for the prevention and management of cognitive and functional decline in these individuals. Of note, in our study, active individuals with cognitive frailty had lower mortality than inactive counterparts with physical prefrailty, highlighting that physical activity was particularly relevant in the cognitively frail elderly. Exercise-based randomized trials should assess the most effective type of exercise program with the optimal intensity, volume, and frequency that would improve functional and cognitive capacity and reduce mortality in the cognitively frail elder.[44]

Our study has some limitations. First, the observational design limits a causal interpretation of the study associations, particularly for physical activity and cognitive frailty that were assessed at the same time point. Physical activity was self-reported and is thus prone to measurement error. Future research should consider using objective measures of physical activity, such as accelerometry. Lastly, although the international consensus group separated prefrailty from frailty,[7] we merged both categories into a single entity as has been performed in other recent studies[1,25] and to obtain a higher power in the analyses. Indeed, inclusion of the prefrail state may allow for reversing cognitive frailty through appropriate interventions, which is supported by a home-based program that prevents functional decline in older adults with moderate frailty but not in those with severe frailty.[44] In addition, a previous study found that the risk of dementia among older adults with MCI was similar in prefrail and frail individuals.[8]

Strengths of our study include a relatively large and representative sample, the long follow-up, and the population-based setting, which minimizes selection bias. Also, study data were collected by trained staff using standardized methods. Moreover, analyses were adjusted for a good number of covariates, which reduces residual confounding.

CONCLUSION

In this study, the cognitive fragility phenotype, namely the coexistence of both physical frailty and cognitive impairment, was associated with increased mortality, more marked in the inactive older adults. However, physical activity may attenuate 36% of the increased risk of mortality among cognitively frail individuals. This research may have important implications because the levels of physical activity are dramatically reduced in the elderly while cognitive and physical functioning decline is naturally occurring. From a public health perspective, promoting a physically active lifestyle could be one of the main strategies against cognitive frailty−related mortality. However, further longitudinal and experimental studies are needed to shed light on the importance of physical activity to decrease mortality in cognitively frail individuals.

ACKNOWLEDGMENTS

We thank the study participants who made this study possible.

Abbreviations and Acronyms: **BDNF** = brain-derived neurotrophic factor; **FRAIL** = fatigue; **resistance** = ambulation; **illness** = and loss of weight; **HR** = hazard ratio; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental Status Examination

Affiliations (Continued from the first page of this article.): of Porto, Porto, Portugal (V.C.-S.); Department of Physical Education, Sport and Human Movement, Autonomous University of Madrid, Madrid, Spain (S.H.-F., D.M.-G.); Beckman Institute, University of Illinois at Urbana-Champaign, Urbana, IL (A.F.K.); Department of Preventive Medicine and Public Health, School of Medicine, Universidad Autónoma de Madrid/IdiPAZ and CIBER in Epidemiology and Public Health (CIBERESP), Madrid, Spain (F.R.-A.); and IMDEA Food Institute, CEI UAM + CSIC, Madrid, Spain (F.R.-A., D.M.-G.).

Grant Support: This work was supported in part by the Instituto de Salud Carlos III, State Secretary of R+D+I and FEDER/FSE (FIS grants 12/1166 and 16/609), MINECO R+D+I grant DEP2013-47786-R, the FRAILOMIC Initiative (European Union FP7-HEALTH-2012-Proposal No. 305483-2), the ATHLOS project (European project H2020-Project ID: 635316), a grant from the Alicia Koplowitz Foundation (I.E.-C.), an FPI grant from Autonomous University of Madrid (S.H.-F.), and a 'Ramon y Cajal' contract (RYC-2016-20546) (D.M.-G.).

Potential Competing Interests: The authors report no competing interests.

Correspondence: Address to Irene Esteban-Cornejo, PhD, Department of Physical Education and Sport, Faculty of Sport Sciences, University of Granada, Camino de Alfacar s/n 18071, Granada, Spain (ireneesteban@ugr.es).

REFERENCES

1. Panza F, Lozupone M, Solfrizzi V, et al. Different cognitive frailty models and health- and cognitive-related outcomes in older age: from epidemiology to prevention. *J Alzheimers Dis*. 2018; 62(3):993-1012.
2. Robertson DA, Savva GM, Kenny RA. Frailty and cognitive impairment—a review of the evidence and causal mechanisms. *Ageing Res Rev*. 2013;12(4):840-851.
3. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people [published correction appears in *Lancet*. 2013; 382(9901):1328]. *Lancet*. 2013;381(9868):752-762.
4. Kojima G, Taniguchi Y, Iliffe S, Walters K. Frailty as a predictor of Alzheimer disease, vascular dementia, and all dementia among community-dwelling older people: a systematic review and meta-analysis. *J Am Med Dir Assoc*. 2016;17(10):881-888.
5. Boyle PA, Buchman AS, Wilson RS, Leurgans SE, Bennett DA. Physical frailty is associated with incident mild cognitive impairment in community-based older persons. *J Am Geriatr Soc*. 2010;58(2):248-255.
6. Rosado-Artalejo C, Carnicero JA, Losa-Reyna J, et al. Cognitive performance across 3 frailty phenotypes: Toledo Study for Healthy Aging. *J Am Med Dir Assoc*. 2017;18(9):785-790.
7. Kelaiditi E, Cesari M, Canevelli M, et al; IANA/IAGG. Cognitive frailty: rational and definition from an (I.A.N.A./I.A.G.G.) international consensus group. *J Nutr Health Aging*. 2013;17(9): 726-734.
8. Avila-Funes JA, Amieva H, Barberger-Gateau P, et al. Cognitive impairment improves the predictive validity of the phenotype of frailty for adverse health outcomes: the Three-City Study. *J Am Geriatr Soc*. 2009;57(3):453-461.
9. Matusik P, Tomaszewski K, Chmielowska K, et al. Severe frailty and cognitive impairment are related to higher mortality in 12-month follow-up of nursing home residents. *Arch Gerontol Geriatr*. 2012;55(1):22-24.
10. St John PD, Tyas SL, Griffith LE, Menec V. The cumulative effect of frailty and cognition on mortality—results of a prospective cohort study. *Int Psychogeriatr*. 2017;29(4):535-543.
11. Liu L-K, Chen C-H, Lee W-J, et al. Cognitive frailty and its association with all-cause mortality among community-dwelling older adults in Taiwan: results from I-Lan Longitudinal Aging Study. *Rejuvenation Res*. 2018;21(6):510-517.
12. Yu R, Morley JE, Kwok T, Leung J, Cheung O, Woo J. The effects of combinations of cognitive impairment and pre-frailty on adverse outcomes from a prospective community-based cohort study of older Chinese people. *Front Med (Lausanne)*. 2018;5:50.
13. Feng L, Zin Nyunt MS, Gao Q, Feng L, Yap KB, Ng TP. Cognitive frailty and adverse health outcomes: findings from the Singapore Longitudinal Ageing Studies (SLAS). *J Am Med Dir Assoc*. 2017;18(3):252-258.
14. Solfrizzi V, Scafato E, Seripa D, et al; Italian Longitudinal Study on Aging Working Group. Reversible cognitive frailty, dementia, and all-cause mortality: the Italian Longitudinal Study on Aging. *J Am Med Dir Assoc*. 2017;18(1):89.e1-89.e8.
15. Kramer AF, Erickson KI. Effects of physical activity on cognition, well-being, and brain: human interventions. *Alzheimers Dement*. 2007;3(2, suppl):S45-S51.
16. Kramer AF, Erickson KI, Colcombe SJ. Exercise, cognition, and the aging brain. *J Appl Physiol (1985)*. 2006;101(4):1237-1242.

17. Martinez-Gomez D, Guallar-Castillon P, Garcia-Esquinas E, Bandinelli S, Rodríguez-Artalejo F. Physical activity and the effect of multimorbidity on all-cause mortality in older adults. *Mayo Clin Proc*. 2017;92(3):376-382.
18. Martínez-Gómez D, Guallar-Castillón P, León-Muñoz LM, Rodríguez-Artalejo F. Household physical activity and mortality in older adults: a national cohort study in Spain. *Prev Med*. 2014;61:14-19.
19. Gutiérrez-Fisac JL, López E, Banegas JR, Graciani A, Rodríguez-Artalejo F. Prevalence of overweight and obesity in elderly people in Spain. *Obes Res*. 2004;12(4):710-715.
20. Martinez-Gomez D, Guallar-Castillón P, Hallal PC, Lopez-Garcia E, Rodríguez-Artalejo F. Nonexercise cardiorespiratory fitness and mortality in older adults. *Med Sci Sports Exerc*. 2015;47(3):568-574.
21. Ministerio de Sanidad Igualdad y Servicios sociales. Documento de consenso sobre prevención de fragilidad y caídas en la persona mayor: Estrategia de Promoción de la Salud y Prevención en el SNS. *Inf Estud e Investig*. 2013:1-85.
22. Lobo A, Saz P, Marcos G, et al. Revalidation and standardization of the cognition mini-exam (first Spanish version of the Mini-Mental Status Examination) in the general geriatric population [in Spanish] [published correction appears in *Med Clin (Barc)*. 1999;113(5):197]. *Med Clin (Barc)*. 1999;112(20):767-774.
23. Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. *J Nutr Health Aging*. 2012;16(7):601-608.
24. López-García E, Banegas JR, Graciani Pérez-Regadera A, Gutiérrez-Fisac JL, Alonso J, Rodríguez-Artalejo F. Population-based reference values for the Spanish version of the SF-36 Health Survey in the elderly [in Spanish]. *Med Clin (Barc)*. 2003;120(15):568-573.
25. Panza F, Lozupone M, Solfrizzi V, et al. Cognitive frailty: a potential target for secondary prevention of dementia. *Expert Opin Drug Metab Toxicol*. 2017;13(10):1023-1027.
26. Perneczky R, Wagenpfeil S, Komossa K, Grimmer T, Diehl J, Kurz A. Mapping scores onto stages: Mini-Mental State Examination and Clinical Dementia Rating. *Am J Geriatr Psychiatry*. 2006;14(2):139-144.
27. Roppolo M, Mulasso A, Rabaglietti E. Cognitive frailty in Italian community-dwelling older adults: prevalence rate and its association with disability. *J Nutr Health Aging*. 2017;21(6):631-636.
28. Martínez-Gómez D, Guallar-Castillón P, Higueras-Fresnillo S, Rodríguez-Artalejo F. Concurrent validity of the Historical Leisure-time Physical Activity Question of the Spanish National Health Survey in Older Adults [in Spanish]. *Rev Esp Cardiol (Engl Ed)*. 2017;70(8):669-670.
29. Instituto Nacional de Estadística S. Informes metodológicos estandarizados. Estadística de Defunciones según la Causa de Muerte, http://wwwinees/dynt3/metadatos/es/RespuestaPrint html?oper=23 2017http://wwwinees/dyngs/INEbase/es/opera cionhtm?c=Estadistica_C&cid=1254736176780&menu=ulti Datos&idp=1254735573175. Accessed November 29, 2017.
30. Guallar-Castillón P, Rodríguez-Artalejo F, Díez Gañán LD, Banegas Banegas JR, Lafuente Urdinguio PL, Herruzo Cabrera RH. Consumption of alcoholic beverages and subjective health in Spain. *J Epidemiol Community Health*. 2001;55(9):648-652.
31. Jacobs JM, Cohen A, Ein-Mor E, Maaravi Y, Stessman J. Frailty, cognitive impairment and mortality among the oldest old. *J Nutr Health Aging*. 2011;15(8):678-682.
32. Cano C, Samper-Ternent R, Al Snih S, Markides K, Ottenbacher KJ. Frailty and cognitive impairment as predictors of mortality in older Mexican Americans. *J Nutr Health Aging*. 2012;16(2):142-147.
33. Halil M, Cemal Kizilarslanoglu M, Emin Kuyumcu M, Yesil Y, Cruz Jentoft AJ. Cognitive aspects of frailty: mechanisms behind the link between frailty and cognitive impairment. *J Nutr Health Aging*. 2015;19(3):276-283.
34. Vella Azzopardi R, Beyer I, Vermeiren S, et al. Increasing use of cognitive measures in the operational definition of frailty—a systematic review. *Ageing Res Rev*. 2018;43:10-16.
35. Muller M, Grobbee DE, Thijssen JH, van den Beld AW, van der Schouw YT. Sex hormones and male health: effects on components of the frailty syndrome. *Trends Endocrinol Metab*. 2003;14(6):289-296.
36. Inglés M, Gambini J, Mas-Bargues C, García-García FJ, Viña J, Borrás C. Brain-derived neurotrophic factor as a marker of cognitive frailty. *J Gerontol A Biol Sci Med Sci*. 2017;72(3):450-451.
37. Lee BK, Glass TA, McAtee MJ, et al. Associations of salivary cortisol with cognitive function in the Baltimore memory study. *Arch Gen Psychiatry*. 2007;64(7):810-818.
38. Baune BT, Ponath G, Golledge J, et al. Association between IL-8 cytokine and cognitive performance in an elderly general population—the MEMO-Study. *Neurobiol Aging*. 2008;29(6):937-944.
39. Puts MT, Visser M, Twisk JW, Deeg DJ, Lips P. Endocrine and inflammatory markers as predictors of frailty. *Clin Endocrinol (Oxf)*. 2005;63(4):403-411.
40. Morley JE. White matter lesions (leukoaraiosis): a major cause of falls [editorial]. *J Am Med Dir Assoc*. 2015;16(6):441-443.
41. Romera-Liebana L, Orfila F, Segura JM, et al. Effects of a primary care-based multifactorial intervention on physical and cognitive function in frail, elderly individuals: a randomized controlled trial. *J Gerontol A Biol Sci Med Sci*. 2018;73(12). 1688-1674.
42. van de Rest O, van der Zwaluw NL, Tieland M, et al. Effect of resistance-type exercise training with or without protein supplementation on cognitive functioning in frail and pre-frail elderly: secondary analysis of a randomized, double-blind, placebo-controlled trial. *Mech Ageing Dev*. 2014;136-137:85-93.
43. Langlois F, Vu TT, Chassé K, Dupuis G, Kergoat MJ, Bherer L. Benefits of physical exercise training on cognition and quality of life in frail older adults. *J Gerontol B Psychol Sci Soc Sci*. 2013;68(3):400-404.
44. Gill TM, Baker DI, Gottschalk M, Peduzzi PN, Allore H, Byers A. A program to prevent functional decline in physically frail, elderly persons who live at home. *N Engl J Med*. 2002;347(14):1068-1074.