PHYSICAL FRAILTY IS ASSOCIATED WITH LONGITUDINAL DECLINE IN GLOBAL COGNITIVE FUNCTION IN NON-DEMENTED OLDER ADULTS: A PROSPECTIVE STUDY

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Abstract: *Objectives:* To assess the relationship between physical frailty and subsequent decline in global cognitive function in the non-demented elderly. *Design and setting:* A prospective population-based study in a west Japanese suburban town, with two-year follow-up. *Participants:* Community-dwellers aged 65 and older without placement in long-term care, and not having a history of dementia, Parkinson's disease and depression at baseline, who participated in the cohort of the Sasaguri Genkimon Study and underwent follow-up assessments two years later (N = 1,045). *Measurements:* Global cognitive function was assessed using the Montreal Cognitive Assessment (MoCA). Physical frailty was identified according to the following five components: weight loss, low grip strength, exhaustion, slow gait speed and low physical activities. Linear regression models were used to examine associations between baseline frailty status and the MoCA scores at follow-up. Logistic regression models were used to estimate the risk of cognitive decline (defined as at least two points decrease of MoCA score) according to baseline frailty status. *Results:* Seven hundred and eight non-demented older adults were included in the final analyses (mean age: 72.6 ± 5.5 years, male 40.3%); 5.8% were frail, and 40.8% were prefrail at baseline. One hundred and fifty nine (22.5%) participants experienced cognitive decline over two years. After adjustment for baseline MoCA scores and all confounders, being frail at baseline was significantly associated with a decline of 1.48 points (95% confidence interval [CI], -2.37 to -0.59) in MoCA scores, as compared with non-frailty. Frail persons were over two times more likely to experience cognitive decline (adjusted odds ratio 2.28; 95% CI, 1.02 to 5.08), compared to non-frail persons. *Conclusion:* Physical frailty is associated with longitudinal decline in global cognitive function in the non-demented older adults over a period of two years. Physically frail older community-dwellers should be closely monitored for cognitive decline that can be sensitively captured by using the MoCA.

Key words: Cognitive decline, community-dweller, elderly, frailty, prospective study.

Introduction

The co-occurrence of physical frailty and late-life cognitive decline are triggering increasing attentions (1, 2). Physical frailty refers to a medical syndrome of decreased reserve and diminished resistance to stressors and relates to elevated risk of adverse health outcomes (3–5). The biological model of physical frailty comprises five components: unintentional weight loss, low grip strength, exhaustion, low gait speed, and low physical activity (4). A number of previous studies have demonstrated that physical frailty is associated with increased risk of incident dementia (6–8), Alzheimer's disease (9), mild cognitive impairment (10), and cognitive impairment in older adults (11). However, to date, evidence suggesting the associations between physical frailty and decline in global cognitive function amongst non-demented subjects is limited, and the results are conflicting (11–17). Although cross-sectional studies has consistently observed poorer global cognitive performance in pre-frail and frail persons than the non-frail among non-demented older subjects (12, 13), findings from longitudinal studies are inconsistent. Some longitudinal studies reported that physical frailty, in the absence of dementia at baseline, is associated with increased risk of global cognitive decline (11, 16, 17), whereas other studies showed no significant association between physical frailty and cognitive decline at follow-up (14, 15).

Furthermore, most previous studies that investigated the relationships between physical frailty and cognitive decline have assessed global cognitive function using the Mini-Mental State Examination (MMSE) (11, 15–18), which is reported to be insensitive to subtle cognitive changes, as compared with the Montreal Cognitive Assessment (MoCA), another brief and valid cognitive test for global cognition (19, 20). Practically, individuals without functional impairment in activity of daily living would be better assessed by the MoCA as first cognitive screening, rather than the MMSE (21). Also, existing researches that investigated association between physical frailty and global cognitive decline are mostly limited by various assessments used to operationalize original definition of physical frailty.

Therefore, the purpose of this study was to examine the association of baseline physical frailty status with cognitive decline over time in older adults initially free of dementia.

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Accordingly, we used the MoCA to assess global cognition, rather than the MMSE, in a functionally independent community-dwelling older population. Data were drawn from the Sasaguri Genkimon Study (SGS) in which operational definition of physical frailty has been previously validated by using comprehensive physical assessments that were close to the original definition developed by Fried and colleagues (4, 22). Based on our prior work on cross-sectional relationship between global cognitive performance and physical frailty (22), we hypothesized that being frail, but not pre-frailty, at baseline, is associated with decline in global cognitive performance over two years.

Methods

Study Population

The data were drawn from the SGS, a longitudinal study in a suburban community-dwelling Japanese older population. The cohort were recruited from the Sasaguri town of Fukuoka Prefecture. A detailed description of the study design and recruitment methods of the SGS has been reported previously (23, 24). Briefly, there were 31,606 inhabitants in the Sasaguri town, and 5,636 were aged 65 years and older at the time of baseline survey in 2011. Of those, 4,979 older inhabitants who were not identified by the national long-term care insurance system as needing long-term care were considered meeting the inclusion criteria of this cohort. Two waves of data were collected in May to August of 2011 and 2013 and were used in the present study.

Initially, 1,060 participants completed measurements at both baseline and follow-up. Of those, 1,045 participants who were free of dementia, Parkinson's disease, and depression at baseline were included in the present study. Presence of dementia, Parkinson's disease, and depression was defined according to self-reported medical history of having ever been diagnosed by physicians. We excluded 337 subjects without complete data for baseline physical frailty and other covariates, and assessment of global cognitive function at follow up. The final sample consisted of 708 subjects eligible for analysis. The original survey protocols were approved by the Institutional Review Board of Institute of Health Science, Kyushu University, and written informed consent was obtained from all participants.

Physical Frailty Measures

Physical frailty was identified according to the five physical frailty components proposed and validated by Fried and colleagues (4): weight loss, low grip strength, exhaustion, slow gait speed and low physical activities. Participants who presented three or more affected components were considered being frail; one to two affected components as being pre-frail; and 0 affected component as non-frail. Accordingly, the cut-off points of low grip strength, slow gait speed and low physical activities were operationalized using the population-based lowest quintile approach, in which participants who scored in the lowest quintile in a given component were classified as being affected in that component. Presence of weight loss was identified with self-reported unintentional weight lost more than 2 to 3 kg in the previous 6 months (25). Low grip strength (kg) was measured using a handhold dynamometer (GRIP-D, T.K.K. 5401, Takei Scientific Instruments Co. Ltd., Niigata, Japan), adjusted for gender and body mass index (kg/m^2). Exhaustion was indicated by a positive answer to either or both of two questions: "Did you feel that everything you did was an effort?" and "Did you feel exhausted without any reason?" in the last one month. Low gait speed was identified with gender- and standing height- stratified time (sec) over 5-meter walking test at one's maximum walking speed. Low physical activity (kcal/kg/day) was objectively assessed using a tri-axial accelerometer (Active Style Pro, HJA350-IT, Omron Healthcare, Inc., Kyoto, Japan). The lowest quintile cut-off points were adjusted for weight and stratified by gender for this low physical activity component. The procedure of this operational definition in SGS has already been completed and reported to have satisfactory internal validity (23).

Cognitive Measures

Global cognitive function was defined based on the Japanese version of MoCA. The Japanese version of the MoCA has been cross-culturally adapted and validated in Japanese population (26). A detailed description of the testing process in the SGS can be found elsewhere (24). The total score of the MoCA is 30 points, with lower scores indicating poorer global cognitive performance when being treated as a continuous measure. As previously validated by Nasreddine and colleagues (27), global cognitive decline was defined as a decrease of at least two points in MoCA scores between baseline and follow-up assessment, which is considered possibly reflecting a true deterioration in global cognition (14, 28).

Other variables

Data on baseline sociodemographic characteristics including number of years of education, living condition ("living alone or not"), smoking ("current smoker or not"), and drinking ("current drinker or not") were collected using questionnaires. Information on age and gender were obtained from the municipality office. Falls were evaluated with one self-reported question of having falls in the past one year. Responses included "yes/no". Polypharmacy was defined as taking four or more medications by a question asking the current number of prescription medicine. Self-reported medical history of having ever been diagnosed with chronic diseases including hypertension, heart disease, stroke, diabetes, minor trauma fracture, chronic pulmonary disease, digestive disease, chronic kidney disease, osteoarthritis or rheumatism, ear trouble, eye trouble, and cancer were also recorded.

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Statistical analysis

Descriptive characteristics were summarized as means and standard deviations (SD) or median and interquartile range (IQR) for continuous variables where appropriate, and percentages for categorical variables. Trends of baseline characteristics across frailty status were tested using the Jonckheere-Terpstra trend test for continuous variables, and the Cochran-Armitage test for categorical variables. The unadjusted means (standard error, SE) of follow-up MoCA scores and least squares means (SE) adjusted for baseline MoCA score were computed according to baseline frailty status using analysis of variance and analysis of covariance, respectively, with multiple comparisons of mean differences between frailty status groups conducted based on Bonferroni correction.

To examine the association between baseline physical frailty and the MoCA scores at follow-up, we conducted multiple linear regression models where follow-up MoCA performance was regressed on baseline frailty status, controlling for baseline MoCA scores and other potential confounders. Of note, in those linear regression models we did not use the difference score (follow-up MoCA score – baseline MoCA score) as the dependent variable, because analyzing difference score does not control for baseline imbalance due to regression to the mean (29). Also, we expected that baseline MoCA scores have an actual causal effect on follow-up MoCA scores. In this case, the model using the "levels" (with each model including follow-up MoCA score as the dependent variable and the baseline MoCA score as a covariate) is preferable to the model using difference scores as the dependent variable (30).

All the multivariate models were adjusted for age, gender, years of education, and the covariates for which p value was < 0.2 in bivariate analysis: living alone, current drinker, falls in the past year, polypharmacy, and number of chronic diseases.

Furthermore, logistic regression models were used to estimate the risk for developing cognitive decline by baseline frailty status, with adjustment for those potential confounders listed above, as well as baseline MoCA scores. In subsequent analyses, we tested whether any confounders modified all the associations by individually introducing the interaction term of each confounder with physical frailty.

Finally, we conducted a sensitivity analysis of excluding participants with a history of stroke or MMSE score < 18 points, as those conditions could potentially indicate possible dementias at baseline (4). All the analyses were done using SAS version 9.3 (SAS Institute Inc., Cary, N.C., USA). Significance level was set at $\alpha = 0.05$.

Results

As compared with the final sample of 708 participants, participants excluded from the initial sample were older, more likely to be men and frail, and had poorer global cognitive function and a higher rate of falls in the past one year at baseline than those included in the analysis. There were no significant differences between those excluded and included participants in other characteristics including education, rates of living alone, currently smoker and drinker, polypharmacy, and presence of chronic diseases. Comparisons of characteristics between the excluded and the included participants were made and shown in the Supplemental Table 1.

Figure 1

Mean (Standard error) Montreal Cognitive Assessment (MoCA) scores at follow-up by baseline frailty status
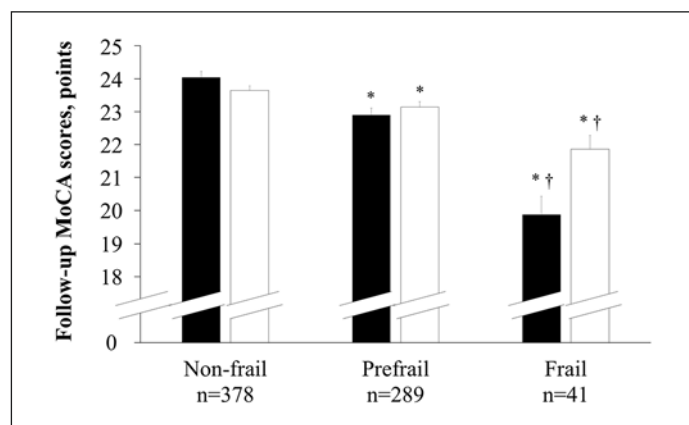
MoCA = Montreal Cognitive Assessment (range 0-30 points). The black bars present unadjusted mean scores. The white bars present least squares means adjusted for baseline MoCA scores; Higher scores on MoCA indicate better global cognitive function; * $p < 0.05$ (v.s. the non-frail group), † $p < 0.05$ (v.s. the pre-frail group) for multiple comparisons of mean differences between frailty status groups based on Bonferroni correction.

In our study population, 40.3% were men. The average age were 72.6 ± 5.5 years old at baseline. Of those, 5.8% were physically frail, and 40.8% were pre-frail. Baseline characteristics of the study sample according to baseline frailty severity were presented in Table 1. Among the three frailty status groups, frail participants was the oldest, and had the least education, the lowest baseline MoCA scores, the greatest number of chronic diseases, the lowest rate of current drinker, the highest rates of living alone, having falls in the past year, polypharmacy, and presence of medical history of hypertension, digestive disease, osteoarthritis or rheumatism, and minor trauma fracture (all p for trend < 0.05). One hundred and fifty nine (22.5%) participants experienced cognitive decline.

Figure 1 displays the unadjusted and adjusted mean and SE of follow-up MoCA scores, according to baseline frailty status. Frail participants had significantly lower mean scores on MoCA at follow-up than pre-frail and non-frail participants. Pre-frail participants had significantly lower mean scores on MoCA at follow-up than non-frail participants. The significance did not alter after adjustment for baseline MoCA scores. Table 2 shows the results of multivariate linear regression models. After full adjustment for baseline MoCA scores and all confounders, being frail at baseline, but not pre-frailty, was significantly associated with a decline in MoCA score (beta = -1.48; 95% confidence interval [CI], -2.37 to -0.59), as compared to non-

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Table 1
Characteristics of the sample according to frailty status at baseline

Variables	Total (n=708)	Baseline frailty status			p for trend†
		Non-frail, n=378 (53.4%)	Prefrail, n=289 (40.8%)	Frail, n=41 (5.8%)	
Age, mean (SD)	72.6 (5.5)	71.2 (4.8)	73.8 (5.7)	78.0 (5.7)	<.001
Men, n (%)	285 (40.3)	154 (41.4)	118 (40.3)	13 (30.2)	0.28
Years of education, mean (SD)	11.4 (2.6)	11.7 (2.6)	11.0 (2.5)	10.7 (2.5)	<.001
Living alone, n (%)	96 (13.6)	41 (11.0)	47 (16.0)	78 (18.6)	0.04
Current smoker, n (%)	52 (7.4)	27 (7.3)	22 (7.5)	3 (7.0)	0.97
Current drinker, n (%)	312 (44.1)	181 (48.7)	114 (38.9)	17 (39.5)	0.01
Falls in the past year, n (%)	129 (18.2)	57 (15.3)	58 (19.8)	14 (32.6)	0.006
Physical frailty components, n (%)					
Weight loss	103 (14.6)	-	85 (29.1)	18 (41.9)	
Low grip strength	118 (16.7)	-	83 (28.3)	35 (81.4)	
Exhaustion	107 (15.1)	-	79 (27.0)	28 (65.1)	
Slow gait speed	87 (12.3)	-	59 (20.1)	29 (65.1)	
Low physical activities	109 (15.4)	-	76 (25.9)	33 (76.7)	
Polypharmacy (≥ 4 medications), n (%)	177 (25.0)	66 (17.7)	90 (30.7)	21 (48.8)	<.001
Number of chronic diseases, median (IQR)	1 (1-2)	1 (1-2)	1 (1-2)	2 (2-3)	<.001
History of chronic diseases, n (%)					
Hypertension	266 (37.6)	125 (33.6)	123 (42.0)	18 (41.9)	0.03
Stroke	23 (3.3)	11 (3.0)	9 (3.1)	3 (7.0)	0.34
Heart disease	85 (12.0)	39 (10.5)	37 (12.6)	9 (20.9)	0.07
Diabetes	88 (12.4)	41 (11.0)	40 (13.7)	7 (16.3)	0.19
Pulmonary disease	28 (4.0)	18 (4.8)	10 (3.4)	0 (0.0)	0.11
Kidney disease	43 (6.1)	24 (6.5)	16 (5.5)	3 (7.0)	0.79
Digestive disease	65 (9.2)	25 (6.7)	28 (9.6)	12 (27.9)	<.001
Osteoarthritis or rheumatism	134 (18.9)	57 (15.3)	58 (19.8)	19 (44.2)	<.001
Minor trauma fracture	28 (4.0)	7 (1.9)	18 (6.1)	2 (7.0)	0.004
Cancer	38 (4.3)	16 (4.3)	18 (6.1)	4 (9.3)	0.12
Ear trouble	63 (8.9)	35 (9.4)	24 (8.2)	4 (9.3)	0.71
Eye trouble	162 (22.9)	78 (21.0)	72 (24.6)	12 (27.9)	0.17
Baseline MoCA score, mean (SD)	22.9 (3.5)	23.4 (3.1)	22.5 (3.6)	20.0 (4.2)	<.001
Cognitive decline, n (%)*	159 (22.5)	77 (20.4)	70 (24.2)	12 (29.3)	0.11

SD = Standard Deviation; IQR = interquartile Range; MoCA = Montreal Cognitive Assessment; * Cognitive decline defined as a decrease of two or more points in MoCA scores at follow-up; † p for trend through non-frail, prefrail and frail groups from the Jonckheere-Terpstra test for continuous variables and the Cochran–Armitage test for categorical variables.

Table 2
Estimates for Montreal Cognitive Assessment (MoCA) scores at follow-up by baseline frailty status from multiple linear regression models (n=708)

Baseline frailty status	No. of subjects	Model 1		Model 2	
		Beta (95% CIs)	p value	Beta (95% CIs)	p value
Non-frail	378	reference		reference	
Pre-frail	289	-0.29 (-0.70 to 0.13)	0.17	-0.24 (-0.65 to 0.18)	0.27
Frail	41	-1.50 (-2.38 to -0.63)	<.001*	-1.48 (-2.37 to -0.59)	0.001*

CIs = Confidence intervals; Model 1: adjusted for age, gender, years of education and baseline MoCA scores; Model 2: adjusted for Model 1 variables plus the covariates for which p value was < 0.2 in bivariate analysis: living alone, current drinker, falls in the past year, polypharmacy, and number of chronic diseases. *Significant at the p < .05 level.

frailty.

Logistic regression analyses for the associations of baseline frailty status with cognitive decline were shown in Table 3. Compared with being non-frail, being physical frail was associated with an increased risk of experiencing cognitive decline, with an adjusted odds ratio (OR) of 2.28 (95% CI, 1.02 to 5.08). There was no significant association between pre-frailty and cognitive decline. The significance of those associations did not vary with the confounders, since none of interaction terms for physical frailty status and any confounder were significant. Associations remained significant after exclusion of participants with stroke or MMSE score < 18 points (n = 24) from the analyses did not alter the results (results not shown).

Table 3

Odds Ratios (ORs) and 95% confidence intervals (CIs) for cognitive decline according to baseline frailty status from multivariate logistic regression models (n=708)

Baseline frailty status	No. of subjects	Model 1	Model 2
		OR (95% CIs)	OR (95% CIs)
Non-frail (reference)	378	1.00	1.00
Pre-frail	289	1.24 (0.84 - 1.84)	1.21 (0.81 - 1.79)
Frail	41	2.24 (1.02 - 4.90)*	2.28 (1.02 - 5.08)*

Model 1: adjusted for age, gender, years of education and baseline scores of the MoCA; Model 2: adjusted for Model 1 variables plus the covariates for which p value was < 0.2 in bivariate analysis: living alone, current drinker, falls in the past year, polypharmacy, and number of chronic diseases. *Significant at the p < .05 level.

Discussion

This study demonstrated that physical frailty was associated with cognitive decline over a two-year period in non-demented community-dwelling older adults. These findings were observed using both a continuous measure and a categorical measure of cognitive changes as assessed using the MoCA. The results of multivariate linear regression models showed that being physically frail was significantly associated with poorer global cognitive function at follow-up, independent of baseline cognitive function. As compared with non-frail persons, frail persons experienced a statistically significant decrease of 1.48 points in MoCA scores at follow-up after full adjustment for covariates. Although the estimate was slightly smaller, a recent study reported a decrease of 1.8 points in MoCA scores over 3.5 years as clinically meaningful worse in cognitive function (31). Therefore, we may postulate that the observed difference between frail persons and non-frail counterparts over a two-year period reaches potentially clinical significance. The results of logistic regression models showed that being physical frail posed a higher risk of cognitive decline than non-frailty as well. The significant associations were robust in that they were independent of baseline cognitive status and presence of common chronic diseases, and no significant

interaction were observed between physical frailty and any confounder. Further analyses that excluded participants with possible dementia yielded similar results. Unlike previous studies focusing on incidence of dementia, mild cognitive decline, or clinical cognitive impairment in frail subpopulations, this study addressed longitudinal decline in global cognitive function amongst non-demented older adults in relation to baseline frailty severity, suggesting that physical frailty may be an important predictor for cognitive decline that can be sensitively detected by using the MoCA.

Most of previous longitudinal studies, with follow-up period ranging from one to ten years, showed that frail older persons had significantly greater global cognitive decline as evaluated using MMSE or composite cognition measures, than non-frail older adults (9, 11, 17, 18). Our findings extend these prior findings by providing evidence that physical frailty was associated with an increased risk of cognitive decline as assessed using the MoCA. Inconsistently, a recent five-year longitudinal study of 252 non-demented older adults, which assessed global cognition using the MoCA, failed to show significant association between physical frailty and cognitive decline, which was potentially attributed to the small sample size (14).

Evidence on the association between physical pre-frailty and cognitive decline are also conflicting in prior studies (11, 12). We found that the intermediate physical frail status, the pre-frailty, was not significantly associated with a higher risk for cognitive decline, as compared with non-frailty. This observation suggests that cognitive function are more likely to be maintained when deficits in physical function are not sufficiently severe to warrant a diagnosis of frailty. Indeed, all older adults experienced cognitive decline, and there are wide individual variabilities in the magnitude and the timing of exhibiting cognitive decline (32). Further studies are necessary to investigate the trajectory of cognitive ability amongst the frail, as well as the pre-frail subpopulations.

To date, the basis for the association between physical frailty and global cognitive decline is still uncertain. The observed association might be attributable to systematic physiologic alterations that occur with aging and/or correlated with common pathological pathways, such as oxidative stress (33), inflammation (34), and hormonal dysregulation (35). Other common risk factors, such as malnutrition and cardiovascular risk, have been used to explain the observed associations between physical frailty and cognitive decline (1). Our results also support a recently proposed clinical entity, "cognitive-frailty", hypothetically defined as the presence of both physical frailty and cognitive impairment but in the absence of dementia (36). The cognitive-frailty construct notionally defines reduced cognitive reserve related to physical frailty with a potential reversibility of clinical representation. Individuals with cognitive-frailty have been recently reported to have worse cognitive function than individuals with cognitive impairment and without physical frailty (37).

Interpretations of the present findings should be cautious in concluding causality between frailty and global cognitive decline. Practically, physical frailty often occurs in the absence of cognitive decline, and vice versa. Also, it is speculated that physical frailty and cognitive decline are merely two manifestations of common underlying brain pathological damage (1, 38), which was recently supported by the findings of Buchman and colleagues in showing an independent significant association between Alzheimer's disease pathology, macroinfarcts, and nigral neuronal loss with simultaneous worsening physical frailty and cognition (39). Although the intrinsic mechanisms underlying this link are not fully understood, the present findings raised the possibility that physical frailty may be a useful predictor for cognitive decline in community-dwelling older adults. It will also be of great practical significance to explore shared modifiable risk/protective factors of physical frailty and cognitive decline towards preventing or ameliorating the progression of both of the two conditions in older adults, since both of them are not irreversible.

This study has several important limitations. Firstly, generalizability of the results is limited because of the non-representative sample, thus our observations need to be confirmed in other populations. Secondly, exclusion of participants from the initial sample may have led to potential selection bias and distorted the association. The exclusion were mainly due to incomplete data on either physical frailty or cognitive tests, or both. As shown in the results of comparisons between those excluded with available data and those included, those excluded participants simultaneously presented severer physical and cognitive deficits at baseline than those included individuals. Thus, the observed association in the final sample would be weakened, and biased toward the null hypothesis. Therefore, the true association may be stronger than that found in this study. Thirdly, the possibility of undiagnosed dementia cannot be ruled out. However, the similar results from sensitivity analysis of excluding possible dementia might, to some extent, increase the robustness of the findings.

Several strengths of this studies increase confidence in the present findings, which include well-characterized cohort of functional community-dwelling older adults without long-term care, the previously validated operational definition of physical frailty in this cohort which was close to original frailty definition (4), and the use of the MoCA test which is sensitive to subtle changes in global cognition (27).

Conclusions

Physical frailty at baseline was associated with a decline in global cognitive function in this non-demented older sample over a period of two years. Physically frail older community-dwellers should be closely monitored for cognitive decline that can be sensitively captured by using the MoCA. Future investigations of common risk/protective modifiable factors of physical frailty and cognitive decline may of great practical significance towards prevention of both physical frailty and cognitive decline.

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