Functional Capacity, Muscle Fat Infiltration, Power Output, and Cognitive Impairment in Institutionalized Frail Oldest Old

Alvaro Casas-Herrero,¹ Eduardo L. Cadore,² Fabricio Zambom-Ferraresi,² Fernando Idoate,³ Nora Millor,⁴ Alicia Martínez-Ramírez,⁴ Marisol Gómez,⁴ Leocadio Rodríguez-Mañas,⁵ Teresa Marcellán,⁶ Ana Ruiz de Gordo,⁶ Mário C. Marques,⁷ and Mikel Izquierdo²

Abstract

This study examined the neuromuscular and functional performance differences between frail oldest old with and without mild cognitive impairment (MCI). In addition, the associations between functional capacities, muscle mass, strength, and power output of the leg muscles were also examined. Forty-three elderly men and women (91.9 ± 4.1 years) were classified into three groups—the frail group, the frail with MCI group (frail + MCI), and the non-frail group. Strength tests were performed for upper and lower limbs. Functional tests included 5-meter habitual gait, timed up-and-go (TUG), dual task performance, balance, and rise from a chair ability. Incidence of falls was assessed using questionnaires. The thigh muscle mass and attenuation were assessed using computed tomography. There were no differences between the frail and frail + MCI groups for all the functional variables analyzed, except in the cognitive score of the TUG with verbal task, which frail showed greater performance than the frail + MCI group. Significant associations were observed between the functional performance, incidence of falls, muscle mass, strength, and power in the frail and frail + MCI groups ($r = -0.73$ to $r = 0.83$, $p < 0.01$ to $p < 0.05$). These results suggest that the frail oldest old with and without MCI have similar functional and neuromuscular outcomes. Furthermore, the functional outcomes and incidences of falls are associated with muscle mass, strength, and power in the frail elderly population.

Introduction

FRAILTY IS AN AGE-ASSOCIATED syndrome characterized by decreases in the functional reserve and resistance to stressors due to changes in several physiological systems.^{1–4} Frailty is increasingly recognized as a highly prevalent entity that is distinct from disability and co-morbidity and that increases the vulnerability of older adults to clinically important outcomes, including functional decline, falls, and institutionalization.^{5–9} One of the cornerstone issues underlying frailty syndrome is sarcopenia (*i.e.*, aging-induced loss of muscle mass) that is exacerbated by decreased physical activity, causing a decline in overall function and leading to frailty.^{10–15} Skeletal muscle power decreases earlier than muscle strength with advancing age.¹⁵ Muscle power seems to be more closely associated with performance on functional

tests than muscle strength in elderly populations.¹⁵ Knowledge about the relationships between skeletal muscle power, strength, mass, and functional capacity could improve the exercise recommendations for this population. Mild cognitive impairment (MCI) is seen as a transitional state between normal cognitive aging and early dementia.^{16–19} Recent studies have shown that older adults with MCI have a higher prevalence of gait impairments than cognitively normal older adults and that having MCI predicts the later development of dementia.^{20,21}

Cognitive impairment has been closely related to frailty because both diseases share some pathophysiological mechanisms and short-term and mid-term consequences (*e.g.*, hospitalization, incidence of falls, disability, institutionalization, and death).²² In addition, muscular and central nervous systems share common pathogenic pathways in the evolution of

¹Division of Geriatric Medicine, Complejo Hospitalario de Navarra, Pamplona, Navarra, Spain.

²Department of Health Sciences, Public University of Navarre, Tudela, Navarre, Spain.

³Radiology Department, Clínica San Miguel, Pamplona, Spain.

⁴Mathematics Department, Public University of Navarre, Pamplona, Spain.

⁵Division of Geriatric Medicine, University Hospital of Getafe, Madrid, Spain.

⁶Casa de Misericordia, Pamplona, Navarra Spain.

⁷University of Beira Interior, Department of Sport Sciences, UBI, Covilhã, Portugal.

disability, probably underlying the negative association between muscle strength and cognitive impairment.^{22,23} It is well known that people with dementia exhibit some of the symptoms of the frailty phenotype, such as a low gait velocity and a low level of physical activity,^{22,24} but the presence of similarities of differences in the physical outcomes in the frail elderly with or without cognitive impairment has not been studied. These differences could be particularly evident during the dual-task gait paradigm.

Gait impairment is one of the most consistent predictors of falls and is a prevalent feature among older adults with cognitive impairment and frailty syndrome.⁹ The traditional gait assessment is not sensitive enough to detect subtle gait impairments. A sensitive method for detecting these early interactions is to measure the effect that a cognitive load (*e.g.*, simultaneous talking or counting while walking) has on gait. Because one study demonstrated that the inability to maintain a conversation while walking ("stops walking while talking") is a marker for future falls in older adults,^{25,26} walking while performing a secondary task (the dual-task paradigm) has become the classic way to assess the interaction between cognition and gait.^{16,20,21,27–29} Dual-task tests reflect executive function, which is an essential cognitive resource for normal walking. However, little attention has been given to the relationship between dual tasks and frailty or to the ability of these tasks to detect subtle differences in gait patterns between frail patients with and without MCI.

This study was designed to compare the muscle mass, strength, and functional performance between the frail elderly with and without MCI using functional tests with a second cognitive task (*e.g.*, verbal and arithmetic tasks). To help understand the possible differences between these two frail groups, we compared them with a group of age-matched elderly subjects without frailty. A second objective was to investigate the associations between functional capacity and muscle strength, power, and mass in the frail elderly.

Methods

Experimental design

We designed a cross-sectional study to compare three groups of elderly populations—frail, frail+MCI, and age-matched non-frail elderly. In addition, we assessed the associations between skeletal muscle strength, power, and mass with functional capacity in the frail group to help identify the most relevant physical outcomes needed to prevent disability. Physical evaluations were performed using dynamometry, functional tests (including strength, gait, and balance tests), and computed tomography (CT) of the thigh muscles. Study participants were assessed in their institution on different occasions and were transported to the hospital for the CT assessments. By measuring these variables, we gathered information about the possible physical differences between the frail elderly with and without cognitive impairment symptoms. Prior to data collection, the participants took part in a familiarization procedure for each test.

Participants

The participants were institutionalized oldest-old patients from the Pamplona, Spain, area older than 75 years old. They were included in the three groups (non-frail without MCI,

frail without MCI, and frail with MCI) of the study according to the Fried criteria of frailty or robustness,⁹ and the MCI consensus definition provided by Windbland et al.³⁰ The Fried criteria of frailty was determined by the presence of three or more of the following components: Slowness, weakness, weight loss, exhaustion, and low physical activity.⁹ The specific recommendations for the general MCI criteria include the following: (1) The person is neither normal nor demented; (2) there is evidence of cognitive deterioration shown by either objectively measured decline over time and/or subjective report of decline by self and/or informant in conjunction with objective cognitive deficits; and (3) activities of daily living are preserved and complex instrumental functions are either intact or minimally impaired.³⁰

Participants fulfilled the criteria for MCI if they had a subjective memory complaint, a report of cognitive deterioration from the patient and/or family, objective memory impairment in cognitive tests with the absence of significant functional impairment, and the absence of clinical dementia. Exclusion criteria included dementia, disability (defined as a Barthel index lower than 60) and the inability to walk independently. An age-matched non-frail group was included for physical and functional comparisons. Fifty-six elderly subjects volunteered to take part in this study, completed an ethical consent form, and met the necessary requirements to join the study. After completing the clinical and cognitive evaluations, 43 elderly men and women were finally included into any of the three groups—the frail without MCI group (93.4 ± 3.2 years), the frail with MCI group (frail+MCI) (age, 92.4 ± 4.2 years), and the non-frail group (age, 88.2 ± 4.1 years). The complete physical characteristics of the participants are presented in the Table 1. Women accounted for 67% of the patients (9 of 13, 14 of 20, and 6 of 10 in the frail+MCI, frail and non-frail groups, respectively). For the muscle mass comparisons, only the frail elderly (with and without MCI) were assessed. A subset of frail subjects (*n* = 13) had their one repetition maximum (1RM) strength and muscle power measured in the leg press machine to investigate the

TABLE 1. PHYSICAL CHARACTERISTICS (MEAN ± SD)

	Frail + MCI (n = 13)	Frail (n = 20)	Non-frail (n = 10)
Age (years)	92.4 ± 4.2	93.4 ± 3.2	88.2 ± 4.1
Women/men	9/4	14/6	6/4
Body mass (kg)	60.8 ± 7.7	52.3 ± 12.7	60.5 ± 7.8
Height (cm)	154.3 ± 6.8	151.8 ± 11.7	152.2 ± 2.2
Body mass index (kg · m ⁻²)	24.7 ± 3.8	21.4 ± 3.8	28.3 ± 4.7 [†]
Schooling level			
Basic uncompleted	2	5	2
Basic completed	8	11	6
High School completed	2	3	1
College complete	1	1	1
MEC	23.0 ± 2.5*	28.8 ± 2.9	31.0 ± 2.6

*Significant difference from frail and non-frail groups (*p* < 0.001).

[†]Significant difference from frail group (*p* < 0.01).

MCI, mild cognitive impairment; MEC, Mini-Examen Cognoscitivo.

associations between these variables with functional capacity. All subjects or their legal guardians agreed with their participation in the trial and completed an ethical consent form. The study was conducted according to the Declaration of Helsinki, and was approved by the Ethics Committee of the Public University of Navarra, Spain.

Functional outcomes

The gait velocity was assessed using the 5-meter habitual gait velocity test (GVT) and the timed up-and-go (TUG) test. Starting and ending limits were marked on the floor with tape lines for a total distance of 7 meters. The first and last meter, considered the warm-up and the deceleration phases, respectively, were not included in the calculations for the gait assessment. The TUG test consisted of measuring the time to perform the task of standing up from a sitting position in a chair, walking 3 meters, turning, returning to the chair, and sitting down. The dual-task paradigm was used in the 5-meter habitual GVT and the TUG test. Two trials were used to measure gait velocity while performing a verbal or counting task (verbal GVT and counting GVT, respectively). During the verbal fluency dual-task condition (verbal GVT), we measured the gait velocity while participants were naming animals aloud. During the arithmetic dual-task condition (counting GVT), we measured gait velocity while participants were counting backward aloud from 100 by ones. The velocity and time were measured, and the cognitive score was measured by counting the number of animals named (dual-task with verbal performance) or counting the numbers backward (dual-task with arithmetic performance). Balance was assessed using the Frailty and Injuries: Cooperative Studies of Intervention Techniques-4 (FICSIT-4) tests of static balance—the parallel, semi-tandem, tandem, and one-legged stance tests. The subjects progressed to the hardest test regardless of their success in the easier tests. The ability to stand up from a chair without support (rise from a chair test) was assessed, and the score was determined by the maximum number of rises that the subject was able to complete in 30 sec. Data on the incidence of falls were obtained using questionnaires.

Maximal strength and muscle power

Upper (right hand grip) and lower limb (right knee extensors and hip flexors) isometric muscle strength was measured using a manual dynamometer. Maximal dynamic strength was assessed using the 1RM test on the bilateral leg press exercise. The bilateral leg press 1RM was performed using an exercise machine (Exercycle, S.L., BH Group, Vitoria, Spain). On the day of the test, the subjects warmed up with specific movements for the exercise test. Each subject's maximal load was determined with a maximum of five attempts with a 4-min recovery between attempts. After determination of the 1RM values, subjects performed three repetitions at maximal velocity at intensities of 30% and 60% of the 1RM to determine the maximal and mean power and the maximal and mean velocities at these intensities. Two attempts were performed at each intensity, with 2 min of recovery between attempts. During the bilateral leg press actions at the different intensities (30%–60% of 1RM), bar displacement, average velocity ($\text{m} \cdot \text{s}^{-1}$), and mean power (W) were recorded by linking a linear velocity transducer to the weight plates (T-Force System, Ergotech, Murcia, Spain).

Muscle cross-sectional area

The midthigh lower-extremity muscle of the left quadriceps femoris was assessed using a 64-row CT scanner (Siemens Definition AS, Erlangen, Germany). The cross-sectional area (CSA) of the subcutaneous adipose tissue (SAT), intermuscular adipose tissue (IMAT), quadriceps femoris (QF) muscle, adductor muscles, including the adductor longus and magnus, and flexor muscles, including the semitendinosus, semimembranosus, and biceps femoris, were measured. The scans were later analyzed for the CSA (mm^2) of adipose tissue and muscle tissue. Image segmentation of adipose tissue and skeletal muscle CSAs of the abdominal and thigh images was performed using commercially available software (Slice-O-Matic, Tomovision, Montreal, Canada), as previously reported.³¹ The boundaries of the adipose and muscular compartments measured were depicted using a manual cursor. The mean attenuation coefficient values of adipose and muscle within the regions outlined on the images were determined by averaging the CT number (pixel intensity) in Hounsfield units (HU). Skeletal muscle and adipose tissue areas were calculated by the range of attenuation values for skeletal muscle (0–100 HU), high-density muscle (HDM) (30–100 HU), low-density muscle (LDM) (0–29 HU), and adipose (–190 to –30 HU) tissue.³²

Cognitive test

Objective memory impairment was operationalized by the demonstration of memory impairment by neuropsychological testing. For this purpose, the MEC (Mini-Examen Cognoscitivo), an adapted Spanish-validated version for geriatric population of the Mini-Mental State Examination (MMSE),³³ with a sensibility of 90.7% and a specificity of 69% was used. It includes two more items than the MMSE. The maximal score is 35 and cutoff point for cognitive decline is below 28.

Statistical analysis

Descriptive results are reported as the mean $\pm$ standard deviation (SD). The SPSS Statistical Software package (version 17.0) was used to analyze all data. Normal distribution and homogeneity parameters were verified with Shapiro-Wilk and Levene tests, respectively. The differences between groups were assessed using a one-way analysis of variance (ANOVA) with Tukey *post hoc* tests. Retrospective analysis provided using the GPOWER program (version 3.1.7) determined that the number of participants in each group provided a statistical power of over 80% to the differences detected in all variables. Exceptions were observed in the balance and incidence of falls, for which the retrospective statistical power was 75%. The Pearson product moment correlation test was used to investigate possible associations between the variables. In the non-parametric data, a Spearman correlation test was used. Significance was defined as $p < 0.05$.

Results

Rise from a chair, balance, and incidence of falls

The non-frail group showed greater values on the rise from a chair test and a lower incidence of falls compared

with the frail ($p < 0.01$) and frail+MCI ($p < 0.01$) groups (Table 2). The balance score was significantly higher in the non-frail group compared with the frail ($p < 0.01$) and frail+MCI ($p < 0.01$) groups (Table 2).

Gait velocity and dual-task performance

There were significant differences between the groups in all tests related to gait velocity. The non-frail group spent significantly less time performing the TUG test with single and dual tasks (both verbal and arithmetic) compared with the frail ($p < 0.01$) and frail+MCI ($p < 0.01$) groups. The non-frail group performed significantly better in the habitual GVT (5-meter test) than the frail ($p < 0.001$) and frail+MCI ($p < 0.001$) groups. The non-frail group also performed better with the GVT with arithmetic and verbal tasks compared with the frail ($p < 0.01$) and frail+MCI ($p < 0.001$) groups (Table 2).

Although no differences between the frail and frail+MCI groups were observed in the time spent to perform the distance component during the TUG test with dual-task performance, the frail group presented significantly greater cognitive performance than the frail+MCI group in the TUG test with the verbal task because the frail group named a significantly greater ($p < 0.05$) number of animals during this test. No additional physical and cognitive performance differences were observed between the frail and frail+MCI groups during the GVTs (Table 2).

Isometric strength and muscle cross-sectional area

The non-frail group showed greater hand grip and knee extension strength compared with the frail ($p < 0.01$) and frail+MCI ($p < 0.01$) groups and greater isometric hip flexion strength compared with the frail group ($p < 0.001$) (Table 2). No significant differences between the frail and frail+MCI

groups were observed in the muscle CSA of the quadriceps high- and low-density tissue, the CSA of the total quadriceps, or the CSA of the total thigh (Table 2).

Relationships between muscle mass, strength, and functional outcomes

In the frail+MCI group, there were significant negative relationships between the individual maximal isometric strengths and the corresponding individual values of functional tests (*i.e.*, TUG, 5-meter gait velocity and dual task performance), as well the incidence of falls, with r values ranging from -0.83 to -0.62 ($p < 0.01$ to $p < 0.05$) (Table 3). In addition, there was a significant positive relationship between the individual maximal isometric hip flexion strength and the corresponding individual values of rise from a chair test ($r = 0.76$, $p < 0.01$) (Table 3). In the frail group, there were significant negative relationships between the individual isometric strengths and the corresponding individual values of functional tests, with r values ranging from -0.62 to -0.43 ($p < 0.01$ to $p < 0.05$) (Table 4). In addition, significant positive associations were observed in the frail group between muscle CSA, the rise from a chair test, and strength performance (r ranging from 0.52 to 0.80 , $p < 0.001$ to $p < 0.05$) (Table 4).

Because no differences were observed between the frail+MCI and frail groups in the physical outcomes and the incidence of falls, we analyzed the correlations between the variables that were associated with these two groups. Significant negative relationships were observed between isometric strength and performance on functional tests and between the functional tests and the incidence of falls, with r values ranging from -0.43 to -0.62 ($p < 0.01$ to $p < 0.05$). Significant positive associations were also observed between

TABLE 2. FUNCTIONAL OUTCOMES, ISOMETRIC STRENGTH, AND MUSCLE CROSS-SECTIONAL AREA

	Frail + MCI (n = 13)	Frail (n = 20)	Non-frail (n = 10)
TUG (sec)	20.1 ± 7.6	19.2 ± 6.5	9.8 ± 2.1*
TUG arithmetic task (sec)	22.9 ± 9.8	24.5 ± 9.3	11.4 ± 2.6*
TUG verbal task (sec)	26.9 ± 10.4	26.5 ± 10.2	12.6 ± 3.6*
Cognitive Score (TUGat)	2.3 ± 0.6	1.9 ± 1.0	2.4 ± 0.5
Cognitive Score (TUGvt)	3.5 ± 1.7	7.1 ± 2.6†	5.0 ± 1.2
5-meter gait test ($\text{m} \cdot \text{s}^{-1}$)	0.80 ± 0.16	0.69 ± 0.25	1.31 ± 0.21*
5-meter gait arithmetic task ($\text{m} \cdot \text{s}^{-1}$)	0.66 ± 0.15	0.56 ± 0.23	1.22 ± 0.29*
5-meter gait verbal task ($\text{m} \cdot \text{s}^{-1}$)	0.56 ± 0.11	0.51 ± 0.22	1.13 ± 0.26*
Cognitive Score (gait velocity-at)	2.5 ± 0.7	2.0 ± 0.9	2.0 ± 0.5
Cognitive Score (gait ability-vt)	4.7 ± 1.9	5.7 ± 1.8	4.4 ± 1.7
Rise from a chair	6.2 ± 3.2	6.3 ± 3.7	13.1 ± 5.7*
Incidence of falls	0.72 ± 0.46	0.95 ± 0.21	0.0 ± 0.0*
Balance score	1.54 ± 0.52	1.31 ± 0.47	2.0 ± 0.5*
Hand grip strength (kg)	15.9 ± 4.3	15.9 ± 4.3	26.8 ± 6.6*
Isometric Knee extension strength (kg)	125.5 ± 34.5	128.6 ± 44.3	216.9 ± 82.2*
Isometric Hip flexion strength (kg)	115.6 ± 27.1	90.5 ± 26.8	152.8 ± 47.2*
CSA QF _{HD} (mm^2)	6487 ± 1129	5588 ± 1581	—
CSA QF _{LD} (mm^2)	1110 ± 391	1123 ± 703	—
CSA QF _{TOT} (mm^2)	7597 ± 940	6711 ± 1693	—
CSA Thigh _{TOT} (mm^2)	15220 ± 3256	13640 ± 3377	—

Comparisons between groups: *Significant different (better performance) from frail+MCI and frail groups. †Significant different (better performance) from frail+MCI group.

TUG, Timed up-and-go; at, arithmetic task; vt, verbal task; CSA, cross-sectional area; QF, quadriceps femoris; HD, high density; LD, low density; TOT, total.

TABLE 3. ASSOCIATIONS BETWEEN FUNCTIONAL TESTS, INCIDENCE OF FALLS, AND ISOMETRIC MUSCLE STRENGTH IN THE FRAIL + MCI SUBJECTS

	Knee extension strength	Hip flexion strength	Hand grip strength	Incidence of falls
TUG	-0.83**	-0.73**	-0.04	0.52
TUG arithmetic task	-0.83**	-0.73**	-0.30	-0.78**
5-meter gait velocity	-0.76**	-0.19	-0.09	0.65**
5-meter gait velocity with arithmetic task	-0.32	-0.20	-0.06	-0.56
Rise from a chair	0.41	0.76**	0.15	0.16
Incidence of falls	-0.62*	-0.39	-0.12	—
Balance	0.38	0.52	0.29	-0.56

Significant correlations: * $p < 0.05$) and ** $p < 0.01$.

MCI, mild cognitive impairment; TUG, timed up-and-go.

muscle CSA, the rise from a chair test, and strength performance ($r = 0.43$ to 0.68 , $p < 0.001$ to $p < 0.05$) (Table 5).

Relationship between muscle power with muscle mass and functional outcomes in the frail group

After assessing the muscle power in a subset of subjects ($n = 13$), we investigated the associations between muscle power and either functional outcomes or muscle mass. Significant negative association was observed between the muscle power output and the corresponding individual values of gait speed ($r = -0.64$, $p < 0.05$) as well as significant positive association was observed between the muscle power output and the corresponding individual values of rising from a chair ($r = 0.66$, $p < 0.05$) (Table 6). Significant positive associations were also observed between muscle mass and maximal power at 30% and 60% of 1RM ($r = 0.59$ – 0.76 , $p < 0.01$).

Discussion

The major findings of this study were that the frail subjects with MCI did not present different functional outcomes (*i.e.*, gait velocity, rising from a chair, and balance performance), muscle cross-sectional area and muscle quality, as well as

strength/power performance than the frail subjects with preserved cognitive function. A unique finding of the present study was the association between the muscle strength, thigh muscle mass, and especially skeletal muscle power output values with the functional capacity tests in the frail subjects. These results reinforce the need to improve the muscle strength and power in frail subjects to enhance their independence to perform daily activities and reduce their risk of falls. In addition, the performance on the dual-task tests (*e.g.*, gait velocity and TUG) was likely independent of MCI.

Frailty syndrome is an independent predictor of a decline in cognitive function.²⁴ Frail individuals have an increased risk of becoming cognitively impaired, and the decline in cognition over time is more severe in frail subjects as compared with non-frail subjects.^{24,34,35} In addition, impaired physical outcomes, such as altered gait velocity and muscle weakness, are associated with cognitive impairment,²⁴ and these outcomes are physical domains of frailty.⁹ In the present study, no differences were observed between the frail and frail+MCI subjects in terms of physical function and leg muscle CSA, with both groups presenting a lower functional capacity than the non-frail subjects (Table 2). In addition to the functional outcomes, such as gait velocity, balance, and rising from a chair, we assessed muscle strength, CSA, and the incidence of falls. Although these participants were mildly cognitively impaired, the frail+MCI subjects did not present any physical function deficits when compared with cognitively intact frail subjects. From a practical standpoint, the present results suggest that MCI does not alter physical performance in frail individuals, and exercise programs with similar physical demands may be applied in the frail elderly with and without MCI.

A possible explanation for the lack of differences in the functional tests between the two groups is that MCI and frailty are different entities on the same spectrum of disease. Several authors have included cognitive decline in the frailty phenotype because the conditions have similar pathophysiology, similar consequences (*e.g.*, falls, hospitalization, institutionalization, and disability),^{16,23,24,36,37} and similar responses to interventions such as exercise.^{16,23,24,36,37} When tested using dual tasking, MCI gait impairments have been categorized recently (*i.e.*, slowing gait velocity, increased gait variability)

TABLE 4. ASSOCIATIONS BETWEEN FUNCTIONAL TESTS, INCIDENCE OF FALLS, AND ISOMETRIC MUSCLE STRENGTH IN THE FRAIL GROUP

	Knee extension strength	Hip flexion strength	Hand grip strength	Incidence of falls	CSA QF _{HD} (mm ²)	CSA QF _{TOT} (mm ²)	CSA thigh _{TOT} (mm ²)
TUG	-0.30	-0.43*	-0.24	0.26	-0.30	-0.39	-0.44
TUG arithmetic task	-0.21	-0.23	-0.21	0.39	-0.09	-0.07	-0.08
5-meter gait velocity	-0.51*	-0.22	-0.62*	0.37	-0.30	-0.39	-0.43
5-meter gait velocity with arithmetic task	-0.61**	0.06	-0.50*	0.26	-0.28	-0.41	-0.43
Rise from a chair	0.54**	0.43*	0.59*	-0.36	0.59*	0.53*	0.52*
Incidence of falls	-0.26	0.12	-0.36	—	-0.31	-0.26	-0.05
Balance	0.09	0.18	0.17	-0.32	0.23	0.13	-0.03
Hand grip strength (kg)	—	—	—	-0.36	0.65**	0.72***	0.80***
Knee extension strength (kg)	—	—	—	-0.26	0.45	0.62*	0.72***
Hip flexion strength (kg)	—	—	—	0.12	0.49*	0.49*	0.52*

Significant correlations: * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$.

CSA, cross-sectional area; QF, quadriceps femoris; HD, high density; TOT, total; TUG, timed up-and-go.

TABLE 5. ASSOCIATIONS BETWEEN FUNCTIONAL TESTS, INCIDENCE OF FALLS, AND ISOMETRIC MUSCLE STRENGTH IN A WHOLE GROUP OF FRAIL AND FRAIL+MCI SUBJECTS

	<i>Knee extension strength</i>	<i>Hip flexion strength</i>	<i>Hand grip strength</i>	<i>Incidence of falls</i>	<i>CSA QF_{HD} (mm²)</i>	<i>CSA QF_{TOT} (mm²)</i>	<i>CSA thigh_{TOT} (mm²)</i>
TUG	−0.53**	−0.43**	−0.11	0.33	−0.09	−0.10	−0.22
TUG arithmetic task	−0.51**	−0.28	−0.14	0.53*	0.04	0.03	0.04
5-meter gait test	−0.62**	−0.30	−0.33	0.47**	−0.27	−0.37	−0.35
5-meter gait arithmetic task	−0.56**	−0.37*	−0.25	0.29	−0.22	−0.32	−0.37
Rise from a chair	0.55**	0.47**	0.36*	−0.28	0.44*	0.48*	0.51**
Incidence of falls	0.43	−0.25	−0.18	—	−0.18	−0.16	0.02
Balance	0.18	0.37*	0.19	−0.46*	0.16	0.13	−0.07
CSA QF _{HD} (mm ²)	0.35	0.43*	0.62***	−0.18	—	—	—
CSA QF _{LD} (mm ²)	0.27	0.24	0.02	0.1	—	—	—
CSA QF _{TOT} (mm ²)	0.52**	0.46*	0.68***	−0.16	—	—	—
CSA Thigh _{TOT} (mm ²)	0.51**	0.43*	0.68***	−0.07	—	—	—

Significant correlations: * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$.

MCI, mild cognitive impairment; CSA, cross-sectional area; QF, quadriceps femoris; HD, high density; LD, low density; TOT, total; TUG, timed up-and-go.

and show specific associations with executive function and the risk of falls.^{20,21} This categorization of gait impairment in the frail or frail+MCI has not yet been studied using the dual-task paradigm.

Recently, Montero-Odasso et al.²¹ showed that frailty is associated with low performance in several quantitative gait parameters beyond velocity, including high stride time gait variability. In addition, this variable is the most sensitive and is a stronger marker of the risk of falls than gait velocity.^{20,21} Indeed, in the present study, the decrease in gait velocity with arithmetic tasks (dual-task cost) during the TUG test was strongly associated with the risk of falls ($r = 0.78$, $p < 0.01$; Table 3). From this perspective, we hypothesized that differences in stride time gait variability could help distinguish the frail and frail with MCI elderly, which was not observed in the present study.

Although no differences between the frail and frail+MCI groups were observed in the time spent during the TUG with a verbal task, the cognitive score during the TUG with a verbal task (*i.e.*, a greater number of animals named) was greater in the frail group, which is likely associated with the cognitive deficits of MCI participants.^{20,21} Our results suggest that the time spent during dual tasks may not be sen-

sitive enough to detect a worse gait ability in the frail+MCI subjects, and the cognitive score must be considered. The absence of differences in the gait speed during the dual task tests could be related the small sample size, and this constitutes a limitation of the present study.

Sarcopenia is one of the main pathophysiological issues underlying the frailty syndrome and results in a severe decline in functional capacity^{10,11}; however, no studies have directly assessed the relationship between the leg CSA and functional outcomes in the frail elderly. A unique finding of the present study was the relationship observed between the quadriceps and the total thigh muscle CSA with the rising from a chair test performance, especially in the frail individuals ($r = 0.44$ – 0.59 ; Tables 4 and 5). Furthermore, the muscle CSA was strongly associated with the hand grip strength in the frail subjects, and this variable has been described as a useful predictor of all-cause mortality in older populations.³⁸ Physical inactivity is a main contributor to muscle weakness, and consequently, sarcopenia generates more reduced physical activity and functional capacity, leading to disability and mortality. Nevertheless, another interesting finding of the present study was that the association between muscle CSA and functional outcomes was observed in the frail group, but not in the frail+MCI group. A plausible explanation for this result is that in frail+MCI subjects, not only the neuromuscular function, but also the cognitive function influences the functional capacity.

Skeletal muscle power and strength in elderly people are important for the completion of activities of daily living (ADL) performance, such as rising from a chair, walking, and climbing stairs, and for reducing the incidence of falls.^{28,29,39–42} This study found important associations between muscle strength and muscle power with functional outcomes (*e.g.*, gait ability and rising from a chair) and the incidence of falls in the frail elderly. It is important note that muscle power was assessed at a low to moderate intensity (*i.e.*, 30% and 60% of 1RM, respectively), and both intensities were associated with functional outcomes. On the basis of these results, we suggest that the functional capacity in frail elderly could be improved by performing resistance training at a high speed of motion and using a low intensity of training, such as 30% of the maximal load. This result is especially important in frail

TABLE 6. ASSOCIATIONS BETWEEN MUSCLE POWER, FUNCTIONAL TESTS, AND MUSCLE CROSS-SECTIONAL AREA IN THE LOWER GROUP OF FRAIL SUBJECTS

	<i>Peak power at 30% of 1RM</i>	<i>Peak power at 60% of 1RM</i>
Raise from a chair	0.24	0.69*
5-meter gait velocity with arithmetic task	−0.64*	−0.52
Hand grip strength (kg)	0.76***	0.56
CSA QF _{HD} (mm ²)	0.12	0.10
CSA QF _{LD} (mm ²)	0.72*	0.59*
CSA QF _{TOT} (mm ²)	0.39	0.42
CSA Thigh _{TOT} (mm ²)	0.76**	0.59*

Significant correlations: * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$.

1RM, one repetition maximum; CSA, cross-sectional area; QF, quadriceps femoris; HD, high density; LD, low density; TOT, total.

subjects, who may need more frequent and longer training sessions to perform exercises at higher loads, but urgently need to improve their functional capacities to prevent adverse outcomes like falls, hospitalizations, disability, or even death.

To summarize, the results here showed that the frail subjects with MCI did not present different physical outcomes than the frail subjects with preserved cognitive function. Functional outcomes, such as gait velocity, rising from a chair, balance performance, and the incidence of falls, were associated with muscle mass, strength, and power performance in the frail elderly. On the basis of the present results, we suggest that in addition to strength stimulation, power and velocity of motion with light loads (30% of 1RM) must be stimulated to improve functional capacity in the frail elderly.

Acknowledgments

This work was supported in part by the Spanish Department of Health and Institute Carlos III of the Government of Spain (Spanish Net on Aging and Frailty [RETICEF]), Department of Health of the Government of Navarre and Economy and Competitiveness Department of the Government of Spain, under grants numbered RD12/043/0002, 87/2010, and DEP2011-24105, respectively. This project is also funded in part by the European Commission (FP7-Health, Project reference 278803).

Author Disclosure Statement

No competing financial interests exist.

References

- Campbell AJ, Buchner DM. Unstable disability and the fluctuations of frailty. *Age Ageing* 1997;26:315–318.
- Walston J, Fried LP. Frailty and the older man. *Med Clin North Am* 1999;83:1173–1194.
- Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. *J Gerontol A Biol Sci Med Sci* 2007;62:722–727.
- Rodríguez Mañas L, Féart C, Mann G, Viña J, Chatterji S, Chodzko-Zajko W, Gonzalez-Colaço Harmand M, Bergman H, Carcaillon L, Nicholson C, Scuteri A, Sinclair A, Pelaez M, Van der Cammen T, Beland F, Bickenbach J, Delamarche P, Ferrucci L, Fried LP, Gutiérrez-Robledo LM, Rockwood K, Rodríguez Artalejo F, Serviddio G, Vega E; on behalf of the FOD-CC group (Appendix 1). Searching for an operational definition of frailty: A Delphi Method based Consensus Statement. The Frailty Operative Definition-Consensus Conference Project. *J Gerontol A Biol Sci Med Sci* 2012; Apr 16 [Epub ahead of print].
- Bergman H, Ferrucci L, Guralnik J, Hogan DB, Hummel S, Karunanathan S, Wolfson C. Frailty: An emerging research and clinical paradigm issues and controversies. *J Gerontol A Biol Sci Med Sci* 2007;62:731–737.
- Weiss CO. Frailty and chronic diseases in older adults. *Cin Geriatr Med* 2011;27:39–52.
- Xue Q-L. The frailty syndrome: Definition and natural history. *Clin Geriatr Med* 2011;27:1–15.
- Casas-Herrero A, Izquierdo M. Physical exercise as an efficient intervention in frail elderly persons. *An Sist Sanit Navar* 2012;35:69–85.
- Fried LP, Tangen CM, Waltson J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA. Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: Evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;56:146–155.
- Morie M, Reid KF, Miciak R, Lajevardi N, Choong K, Krasnoff JB, Storer TW, Fielding RA, Bhasin S, LeBrasseur NK. Habitual physical activity levels are associated with performance in measures of physical function and mobility in older men. *J Am Geriatr Soc* 2010;58:1727–1733.
- Theou O, Jones GR, Vandervoort AA, Jakobi JM. Daily muscle activity and quiescence in non-frail, pre-frail, and frail older women. *Exp Gerontol* 2010;45:909–917.
- Kim HK, Susuki T, Saito K, Yoshida H, Kobayashi H, Kato H, Katayama M. Effects of exercise and amino acid supplementation on body composition and physical function in community-dwelling elderly Japanese sarcopenic women: A randomized controlled trial. *J Am Geriatr Soc* 2012;60:16–23.
- Villareal DT, Smith GI, Sinacore DR, Shah K, Mittendorfer B. Regular multicomponent exercise increases physical fitness and muscle protein anabolism in frail, obese, older adults. *Obesity* 2011;19:312–318.
- Barnett A, Smith B, Lord SR, Williams M, Baumand A. Community-based group exercise improves balance and reduces falls in at-risk older people: A randomised controlled trial. *Age Ageing* 2003;32:407–414.
- Cadore EL, Rodríguez-Mañas L, Sinclair A, Izquierdo M. Effects of different exercise interventions on risk of falls, gait ability and balance in physically frail older adults. A systematic review. *Rejuvenation Res* 2013;16:105–114.
- Makizako H, Doi T, Shimada H, Yoshida D, Tsutsumimoto K, Uemura K, Susuki T. Does a multicomponent exercise program improve dual-task performance in amnesic mild cognitive impairment? a randomized controlled trial. *Aging Clin Exp Res* 2012; 24:640–644.
- Susuki T, Shimada H, Makizako H, Doi T, Yoshida D, Tsutsumimoto K, Anan Y, Uemura K, Lee S, Park H. Effects of multicomponent exercise on cognitive function in older adults with amnesic mild cognitive impairment: a randomized controlled trial. *BMC Neurology* 2012; 12:128–137.
- Liu-Ambrose T, Nagamatsu LS, Graf P, Beattie BL, Ashe MC, Handy TC. Resistance training and executive functions: A 12-month randomized controlled trial. *Arch Intern Med* 2010;170:170–178.
- Mhaoláin AM, Gallagher D, Crosby L, Ryan D, Lacey L, Coen RF, Coakley D, Walsh JB, Cunningham C, Lawlor B. Frailty and quality of life for people with Alzheimer's dementia and mild cognitive impairment. *Am J Alzheimers Dis Other Dement* 2012;27:48–54.
- Maquet D, Lekeu F, Warzee E, Gillain S, Wojtsik V, Salmon E, Petermans J, Croisier JL. Gait analysis in elderly adult patients with mild cognitive impairment and patients with mild Alzheimer's disease: Simple versus dual task: A preliminary report. *Clin Physiol Funct Imaging* 2010;30:51–56.
- Montero-Odasso M, Muir SW, Speechley M. Dual-task complexity affects gait in people with mild cognitive impairment: the interplay between gait variability, dual tasking, and risk of falls. *Arch Phys Med Rehabil* 2012;93:293–299.
- García-García FJ, Gutiérrez Avila G, Alfaro-Acha A, Amor Andrés MS, De Los Angeles De La Torre Lanza M, Escribano Aparicio MV, Humanes Aparicio S, Larrion Zugasti JL, Gómez-Serranillo Reus M, Rodríguez-Artalejo F, Rodríguez-Mañas L, Toledo Study Group. The prevalence of frailty syndrome in an older population from Spain. The Toledo Study for Healthy Aging. *J Nutr Health Aging* 2011;15:852–865.

23. Uemura K, Shimada H, Makizako H, Doi T, Yoshida D, Anan Y, Susuki T. Cognitive function affects trainability for physical performance in exercise intervention among older adults with mild cognitive impairment. *Clin Interv Aging* 2013;8:97–102.
24. Samper-Ternent R, Snih SA, Raji MA, Markides KS, Ottenbacher KJ. Relationship between frailty and cognitive decline in older Mexican Americans. *J Am Geriatr Soc* 2008;56:1845–1852.
25. Uemura K, Doi T, Shimada H, Yoshida D, Tsutsumimoto K, Anan Y, Susuki T. Effects of exercise intervention on vascular risk factors in older adults with mild cognitive impairment: A randomized controlled trial. *Dement Geriatr Cogn Disord Extra* 2012;2:445–455.
26. Lundin-Olsson L, Nyberg L, Gustafson Y. “Stops walking when talking” as a predictor of falls in elderly people. *Lancet* 1997;349:617.
27. Doi T, Makizako H, Shimada H, Yoshida D, Ito K, Kato T, Ando H, Susuki T. Brain atrophy and trunk stability during dual-task walking among older adults. *J Gerontol A Biol Sci Med Sci* 2012;67:790–795.
28. Reid KF, Fielding RA. Skeletal muscle power and functioning in older adults. *Exerc Sport Sci Rev* 2012;40:1–12.
29. Izquierdo M, Ibanez J, Gorostiaga EM, Garrues M, Zuñiga A, Antón A, Larrión JL, Häkkinen K. Maximal strength and power characteristics in isometric and dynamic actions of upper and lower extremities in middle-aged and older men. *Acta Physiol Scand* 1999;167:57–68.
30. Windblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, Nordberg A, Bäckman L, Albert M, Almkvist O, Arai H, Basun H, Blennow K, de Leon M, DeCarli C, Erkinjuntti T, Giacobini E, Graff C, Hardy J, Jack C, Jorm A, Ritchie K, van Duijn C, Visser P, Petersen RC. Mild cognitive impairment beyond controversies, towards a consensus: Report of the International Working Group on Mild Cognitive Impairment. *J Intern Med* 2004;256:240–246.
31. Santanasto AJ, Glynn NW, Newman MA, Taylor CA, Brooks MM, Goodpaster BH, Newman AB. Impact of weight loss on physical function with changes in strength, muscle mass, and muscle fat infiltration in overweight to moderately obese older adults: A randomized clinical trial. *J Obes* 2011; 2011. pii: 516576 doi: 10.1155/2011/516576. Epub 2010 Oct 10.
32. Ross R. Advances in the application of imaging methods in applied and clinical physiology. *Acta Diabetol* 2003;40(Suppl): S45–S50.
33. Lobo A, Ezquerro J, Gómez F, Sala JM, Seva A. El “Mini-Examen Cognoscitivo”: Un test sencillo, práctico, para detectar alteraciones intelectivas en pacientes médicos. *Actas Lus-Esp Neurol Psiquiatr* 1979;3:189–202.
34. Freiburger E, Häberle L, Spirduso WW, Rixt Zijlstra GA. Long-term effects of three multicomponent exercise interventions on physical performance and fall-related psychological outcomes in community-dwelling older adults: A randomized controlled trial. *J Am Geriatr Soc* 2012;60:437–446.
35. Buchman AS, Boyle PA, Wilson RS, Tang Y, Bennett DA. Frailty is associated with incident Alzheimer’s disease and cognitive decline in the elderly. *Psychosom Med* 2007;69: 483–489.
36. McGough EL, Kelly VE, Logsdon RG, McCurry SM, Cochrane BB, Engel JM, Teri L. Associations between physical performance and executive function in older adults with mild cognitive impairment: Gait speed and the timed “up & go” test. *Phys Therapy* 2011;91:1198–1207.
37. Heyn PC, Johnson KE, Kramer AF. Endurance and strength training outcomes on cognitively impaired and cognitively intact older adults: A meta-analysis. *J Nutr Health Aging* 2008;12:401–409.
38. Shields RK, Leo KC, Messaros AJ, Somers VK. Effects of repetitive handgrip training on endurance, specificity, and cross-education. *Phys Therapy* 1999;79:467–475.
39. Izquierdo M, Häkkinen K, Antón A, Garrues M, Ibañez J, Ruesta M, Gorostiaga EM. Maximal strength and power, endurance performance, and serum hormones in middle-aged and elderly men. *Med Sci Sports Exerc* 2001;33:1577–1587.
40. Cadore EL, Izquierdo M, Conceição M, Radaelli R, Pinto RS, Baroni BM, Vaz MA, Alberton CL, Pinto SS, Cunha G, Bottaro M, Kruel LF. Echo intensity is associated with skeletal muscle power and cardiovascular performance in elderly men. *Exp Gerontol* 2012;47:473–478.
41. Pereira A, Izquierdo M, Silva AJ, Costa AM, Bastos E, González-Badillo JJ, Marques MC. Effects of high-speed power training on functional capacity and muscle performance in older women. *Exp Gerontol* 2012;47:250–255.
42. Bottaro M, Machado SN, Nogueira W, Scales R, Veloso J. Effect of high versus low-velocity resistance training on muscular fitness and functional performance in older men. *Eur J Appl Physiol* 2007;99:257–264.

Address correspondence to:

Mikel Izquierdo

Department of Health Sciences

Public University of Navarra (Navarra) SPAIN

Campus of Tudela

Av. de Tarazona s/n.

31500 Tudela (Navarra)

Spain

E-mail: mikel.izquierdo@gmail.com

Received: April 23, 2013

Accepted: July 3, 2013