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**What Physical Performance measures Predict Incident Cognitive Decline
among Intact Older Adults? A 4.4 year follow up study**

Running head: physical performance and cognitive status

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ABSTRACT

Reductions in physical performance, cognitive impairment (CI) and decline (CD), are common in older age, but few prospective cohort studies have considered the relationship between these domains. In this study we investigated whether reduced physical performance and low handgrip/ lower limbs strength, could predict a higher incidence of CI/CD during a 4-year follow-up among a cohort of elderly individuals. From 3,099 older community-dwelling individuals initially enrolled in the Progetto Veneto Anziani (PRO.V.A.) study, 1,249 participants without CI at the baseline were included (mean age 72.2 years, 59.5 % females). Physical performance measures included the Short Physical Performance Battery (SPPB), 4m gait speed, chair stands time, leg extension and flexion, handgrip strength, and 6-Minute Walking Test (6MWT), categorized in gender-specific tertiles. CI was defined as a Mini-Mental State Examination (MMSE) score below 24; CD a decline of 3 or more points in the MMSE without CI. At baseline, participants developing CI during follow-up scored significantly worse across all physical performance measures compared to those that retained normal cognitive status. After adjusting for potential confounders, a significant trend for MMSE changes was noted for all physical performance tests, except for the SPPB and chair stands time. Multinomial logistic regression revealed that slow gait speed at baseline significantly predicted CD at follow up. Poor SPPB performance and slower gait speed predicted the onset of CI at the follow-up. In conclusion, slow walking speed appears to be the best independent predictor of poor cognitive status over a 4.4-year follow-up, while other items of SPPB were also significantly associated with CI.

Keywords: physical performance; muscle strength; cognition.

INTRODUCTION

Cognitive impairment (CI) is a common condition in older people, affecting about 20% of individuals over 70 years old, and is associated with increased disability, healthcare utilization and mortality.(1)Several risk factors have been elucidated for CI and decline (CD),including aging, low level of formal educational, and several chronic diseases. (2)

Recently, interest has intensified in understanding modifiable lifestyle factors that might influence the development of CD and CI. Among those that have received considerable attention is physical (in)activity (3). Data on physical activity levels are generally collected by means of questionnaires, however, there are inherent difficulties relying purely upon self-report physical activity and function, which are subject to strong recall bias in older people.(4) Data on physical activity whilst useful, indicates how much activity an individual is engaging in and does not reflect an individual's physical performance. Nevertheless, two meta-analyses recently demonstrated that self-reported reduced physical activity level is an independent risk factor for the onset of poor cognitive status. (5,6).The mechanisms linking declining physical and cognitive performance include lower cognitive reserves, changes in the neurotrophic factors in the hippocampus, and the exacerbation of atherosclerotic processes in the cerebral vessels (4,7-10).Whilst these previous studies have been helpful, assessing actual physical performance and muscle strength with objective measurements might offer amore accurate indicator of actual performance, particularly in older people who might have memory complaints and difficulty accurately recalling activity levels. (11)

To date, a paucity of research has considered objective physical performance as a risk factor for future cognitive decline in community dwelling older adults. The research has typically been cross sectional, or prospective with short duration follow up, although walking speed has

been the most common physical performance measure considered (12,16). Two prospective studies have found that handgrip strength was associated with a greater decline in memory tests (2;17), but another study was unable to confirm these findings. (18) There is a paucity of lower limb function tests (e.g. Short Physical Performance Battery) considering CD/CI. To our knowledge one cross-sectional study demonstrated that poor lower limb function correlated strongly with poor cognitive status (19), but these results were only partially confirmed by a prospective study. (20) Moreover, no comprehensive prospective representative study has considered the range of physical performance measures (gait speed, handgrip strength, lower limbs strength) in one study over a period of 4 years or more. Therefore, the data regarding physical performance and the prediction of CD/ CI is equivocal and it remains unclear which measure might be the optimal predictors and offer most clinical utility.

Given the aforementioned limitations and gaps in the literature, the aim of the present study was to examine which objective physical performance measures provide an optimal predictor of incident CD and CI in a representative cohort of elderly individuals over a follow-up of 4.4 ± 1.2 years.

MATERIALS AND METHODS

Data source and subjects

The data included participants from the *Progetto Veneto Anziani* (Pro.V.A.), observational cohort study among community-dwelling Italian older adults aged ≥ 65 years. The study population included 3,099 age- and sex-stratified Caucasian participants (1854 women and 1245 men) randomly selected between 1995 and 1997 using a multistage stratification method. Sampling procedures and data collection methods have been described elsewhere. (21) The only follow-up evaluation was scheduled to occur at 4 years after baseline.

The ethical committees of Padova University and the Local Health Units (USSL) n. 15 and n. 18 of the Veneto Region approved the study protocol, and participants gave their written informed consent.

Clinical data

Participants were examined at city hospitals by trained physicians and nurses. Information was collected during a face-to-face interview. Regular physical activity was defined as ≥ 4 h/week in the previous month of at least moderate physical activity (brisk walking, cycling, gardening, dancing, or physical exercising), being 4 h /week the median value of the PRO.V.A. sample. Monthly income was categorized as ≥ 500 vs. < 500 €, being 500 € the median value of the sample as whole. Smoking status was classified as “current” vs. “never”/ “previous” (for at least 1 year in the past). Educational level was categorized as ≥ 5 vs. < 5 years of schooling (which corresponds to the years of compulsory education in Italy when our participants were of school age). Body weight and height were measured by trained physicians, and body mass index (kg/m^2) was calculated. Functional status was assessed using the ADL (activities of daily living) and IADL (instrumental activities of daily living) scores. Any depressive symptoms were assessed with the Geriatric Depression Scale (GDS), a 30-

item self-reporting tool for identifying depression that has been validated for use in the elderly. (22)

The presence of diabetes, cardiovascular diseases (CVD), osteoarthritis, fractures, chronic obstructive pulmonary disease (COPD), hypertension or cancer was ascertained by board-certified physicians involved in the study, who examined all of the clinical information collected for each participant. Additional information collected included disease history, symptoms self-reported using standardized questionnaires, medical and hospital records, blood tests, and a physical examination. (12) We considered CVD as the presence of one of the following: congestive heart failure, angina requiring a stent or angioplasty or hospitalization, myocardial infarction, stroke, atrial fibrillation, or peripheral artery disease. Diabetes was defined as fasting plasma glucose levels ≥ 7.0 mmol/L, HbA1c $\geq 6.5\%$, the use of glucose-lowering drugs, or a history of a 2h post-load glucose ≥ 11.1 mmol/L. (23)

Definition of exposure and outcome

a. Physical performance tests

Physical performance, handgrip strength and lower limbs strength measures were assessed using standardized objective performance tests. Since a significant difference existed between genders for all the parameters investigated ($p < 0.001$), the tertiles for each test were calculated using gender-specific cut-offs. In all the analyses, the cut-off value was included in the lowest tertile, i.e. the first cut-off in the first and the second in the second tertile.

- Short Physical Performance Battery (SPPB)(24) scores were derived from three objective physical function tests. Each test was scored from 0 (inability to complete the test) to 4 (highest level of performance). The scores for all three tests were pooled to obtain a composite score of 0 to 12, higher scores reflecting a better physical function. The cutoffs for dividing the sample into tertiles were 10 and 11 points in men, and 9 and 10 points in

women.

- ✓ Tandem test: participants were asked to maintain their balance in side-by-side, semi-tandem, and full-tandem positions.
- ✓ 4 m walking speed: the best performance achieved in two walks at participants' usual pace along a 4-m corridor was recorded in meters per second. Participants were allowed to use canes or walkers.
- ✓ Chair stands time: participants were asked to stand up and sit down 5 times as quickly as possible, with their hands folded across their chest. The time taken to complete the test, in seconds was recorded.

Since the 4 m walking speed and chair stands time are independent predictors of several negative outcomes in older people (25), these parameters were also considered as separate items in this analysis. The cutoffs used for the 4 m walking speed were 0.82 and 0.95 m/s in males, and 0.71 and 0.83 m/s in females; for the chair stands time, the corresponding cutoffs were 11.3 and 9.2 in males, and 10.3 and 13.0 s in females.

- Leg extension and flexion: knee extensor (quadriceps) and hip flexor (iliopsoas) strength was ascertained using a Nicholas Manual dynamometer (BK-7454, Fred Sammons, Inc.). The highest value recorded between the two legs for quadriceps strength was used in this analysis. (26) The cutoffs for leg extension were 22.1 and 33.3 kg in men, and 16.3 and 23.2 kg in women; for leg flexion, they were 23.4 and 31.0 kg in men, and 15.5 and 21.4 kg in women.
- Handgrip strength: this was measured in kg using a JAMAR hand-held dynamometer (BK-7498, Fred Sammons, Inc.). The best result obtained at three attempts with each hand was used for our analyses. The cutoffs were 34.0 and 39.3 kg in men, and 21.3 and 26.0 kg in women.
- 6-minute walking test(6MWT): participants were asked to walk at their usual pace for 6

minutes, and the distance they covered was recording in meters. (27) The cutoffs were 369 and 444 m in men, and 306 and 374 m in women.

b. Cognitive status

Cognitive status was assessed at the baseline and follow-up by administering the 30-item MMSE. (28,29) The raw MMSE scores obtained in our sample were adjusted for age and formal education using coefficients proposed for the Italian population. (30) CI was defined as adjusted MMSE scores below 24; a decline of 3 or more points in the MMSE, without CI (i.e. MMSE score over 24/30), was defined as CD. (31) Participants at baseline with CI meeting these definitions were excluded from our analyses, thus leaving only cognitively intact older adults.

Statistical analyses

For the continuous variables, normal distributions were tested using the Shapiro-Wilk test. Participants' characteristics were summarized using means ($\pm$ standard deviations) for continuous variables, and counts and percentages for categorical variables, comparing participants with CI, CD or normal cognitive status at the follow-up. Age- and gender-adjusted p values were calculated as follows: the differences between the means of the covariates were analyzed for continuous variables using a general linear model (GLM) and applying the Bonferroni's correction; logistic regression was used for categorical variables.

The proportional hazards assumption was checked by plotting the Schoenfeld residuals versus time. Since the p -values for all physical tests were <0.05 , a multinomial logistic regression was used instead of Cox's regression. Factors known to be associated with physical performance, handgrip and/or lower limbs strength, and/or cognitive status were considered for inclusion in the analysis. The predictors included in the final model were all the variables reaching $p \leq 0.20$ in the univariate analyses or those significantly different across categories of

cognitive status at the follow-up ($p \leq 0.05$), while collinearity among covariates was estimated with the variance inflation factor (VIF). A $VIF \geq 2$ was considered an exclusion criterion, although no variables were excluded based on a violation of VIF. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to compare CI/CD rates across tertiles of physical performance, handgrip and lower limbs strength tests, taking those in the third tertile (best scores) for reference. The estimated mean changes in the MMSE scores recorded at the follow-up, modeled as a continuous variable and adjusted with a GLM that included all the covariates considered in the fully adjusted analysis, were obtained for each tertile. Since a significant difference existed for exposure and outcome parameters, the analyses were also conducted by gender.

All analyses were performed using the SPSS 21.0 for Windows (SPSS Inc., Chicago, Illinois). All statistical tests were two-tailed and statistical significance was assumed for a p -value ≤ 0.05 . We used Bonferroni-correction for the primary outcome, conducting three analyses (total sample, males and females), with $\alpha = 0.05/3$, i.e., $p = 0.017$.

RESULTS

Study flow of participants

At baseline, from 3,099 potentially eligible older adults, 481 participants were excluded since information on their physical performance, handgrip and/or lower limbs strength were lacking. In addition, 855 were excluded because they were diagnosed with CI already at the baseline (MMSE score below 24/30). After excluding a further 129 with missing follow-up data and 385 who died during the follow-up period, our final sample consisted of 1,249 participants (see **Figure 1 for study flow**).

At baseline, excluded participants were more likely to be male (52.2% vs. 40.5%; $p<0.001$), and older (80.6 ± 8.0 vs. 72.2 ± 5.8 ; $p<0.001$) than those cognitive intact and included in our study. The dropouts and the individuals who died had significantly lower MMSE scores (27.1 ± 1.8 vs. 19.2 ± 8.0 points; $p<0.001$) than those included in the study, and they also had worse scores in all the physical performance, handgrip and lower limbs strength measures investigated ($p<0.001$).

Figure 1. Study flow chart

Included participants

The sample consisted of 1,249 community-dwelling elderly subjects without CI at baseline. The mean age of the sample was 72.2 ± 5.8 years [range: 65-96], 59.5% were females, and the mean BMI was 27.8 ± 4.3 kg/m². The mean MMSE score was 27.1 ± 1.8 , while the mean ADL and IADL scores indicated a high level of independence (see table 1).

Sociodemographic and medical factors according to cognitive status at follow up

Tables 1-2 show the participants' baseline characteristics by cognitive status at the follow-up. The group of 254 participants diagnosed with CI during the follow-up was significantly older than the group with CD(n=131) or normal cognitive status (n=864), while the percentage of women was significantly higher only in those with CI compared to subjects with normal cognitive status. After adjusting for age and gender, the group that experienced CI during the follow-up had significantly less formal education, and baseline MMSE than the other two groups. Moreover, those with CI had significantly lower IADL and higher GDS scores than those with normal cognitive status. As for medical conditions, the CI group were significantly more likely to have CVD and COPD than those with normal cognitive status.

Differences in baseline physical performance and cognitive status at follow up

Participants developing CI at the follow-up scored significantly worse than those retaining a normal cognitive status in all the physical performance tests investigated (SPPB, 4 m walking speed, chair stands time, handgrip strength, and 6MWT), but not in lower limbs strength exams (**Tables 1-2**). On the contrary, no significant differences emerged between those with CD and normal cognitive status (**Tables 1-2**).

Table 1. Baseline characteristics of the study sample by cognitive status during the follow-up.

Participants' characteristics	Normal cognitive status (n=864)	Cognitive decline (n=131)	Cognitive impairment (n=254)
Age (years)	71.0 (5.1)	72.4 (5.5)	76.5 (6.4)
Female sex (%)	492 (57.0)	82 (62.6)	169 (66.5)
<i>General and anthropometric characteristics</i>			
Current smokers (n, %)	94 (10.9)	13 (9.9)	21 (8.3)
Formal education > 5 years (n, %)	197 (23.1)	28 (21.5)	21 (8.4)
Monthly income ≥500 € (n, %)	371 (43.6)	62 (48.1)	80 (31.9)
Physical activity ≥4 h/week (n, %)	270 (31.3)	39 (29.8)	70 (27.6)
ADL score	5.6 (0.7)	5.6 (0.8)	5.4 (1.0)
IADL score	7.1 (1.1)	6.8 (1.2)	6.4 (1.5)
BMI (kg/m ²)	27.9 (4.3)	27.8 (4.3)	27.6 (4.4)
GDS (score)	8.9 (4.6)	9.0 (4.7)	9.9 (4.9)
MMSE (score)	27.2 (1.7)	28.7 (1.0)	25.9 (1.6)
<i>Medical conditions</i>			
Hypertension (n, %)	607 (70.3)	97 (74.0)	182 (71.7)
Diabetes (n, %)	117 (13.6)	14 (10.7)	41 (16.1)
CVD (n, %)	113 (13.1)	18 (13.7)	55 (21.7)
Osteoarthritis (n, %)	222 (25.7)	43 (32.8)	95 (37.4)
Fractures (n, %)	63 (7.3)	16 (12.2)	25 (9.8)
COPD (n, %)	60 (7.0)	10 (7.6)	32 (12.6)
Cancer (n, %)	51 (5.9)	11 (8.4)	10 (3.9)
<i>Physical performance tests</i>			
Short physical performance battery (points)	10.0 (2.1)	9.7 (2.3)	8.4 (2.5)
4 m walking speed (m/s)	0.85 (0.17)	0.80 (0.24)	0.72 (0.19)
Chair stands time (s)	11.7 (5.8)	12.1 (4.2)	13.8 (5.4)
Leg extension (kg)	24.6 (10.2)	24.0 (10.5)	21.3 (12.2)
Leg flexion (kg)	22.4 (9.7)	21.9 (9.6)	20.2 (8.9)
Handgrip (kg)	29.1 (9.4)	27.3 (8.3)	24.2 (8.1)
6-minute walking test (m)	377.1 (88.3)	362.5 (99.8)	310.6 (93.1)

Numbers are mean (standard deviations) for continuous and number (percentages) for categorical variables, respectively.

Abbreviations: ADL: activities of daily living; IADL: instrumental activities of daily living; BMI: body mass index; GDS: Geriatric Depression Scale; MMSE: Mini Mental State Examination; CVD: cardiovascular disease; COPD: chronic obstructive pulmonary disease.

Table 2. Results of the univariate analysis by cognitive status during the follow-up.

Participants' characteristics	p-value between CD and normal status	p-value between CI and normal status	p-value between CI and CD	p-value overall comparisons
Age (years)	0.01	<0.001	<0.001	<0.001 [†]
Female sex (%)	0.16	0.01	0.22	<0.001 [†]
<i>General and anthropometric characteristics</i>				
Current smokers (%)	1.00	0.54	1.00	0.41
Formal education > 5 years (%)	1.00	<0.001	<0.001	<0.001
Monthly income ≥500 € (%)	0.51	0.09	0.02	0.02
Physical activity ≥4 h/week (%)	1.00	1.00	1.00	0.97
ADL score	0.07	0.06	0.67	0.16
IADL score	0.42	<0.001	0.27	<0.001
BMI (kg/m ²)	1.00	1.00	1.00	0.98
GDS (score)	1.00	0.05	0.29	0.05
MMSE (score)	<0.001	<0.001	<0.001	<0.001
<i>Medical conditions</i>				
Hypertension (%)	1.00	1.00	1.00	0.87
Diabetes (%)	1.00	0.87	0.45	0.33
CVD (%)	1.00	0.03	0.39	0.04
Osteoarthritis (%)	0.72	0.69	1.00	0.31
Fractures (%)	0.30	0.63	1.00	0.25
COPD (%)	1.00	0.03	0.48	0.03
Cancer (%)	0.54	0.18	0.96	0.18
<i>Physical performance tests</i>				
Short physical performance battery (points)	1.0	<0.001	0.002	<0.001
4 m walking speed (m/s)	0.25	<0.001	0.07	<0.001
Chair stands time (s)	1.00	0.04	0.33	0.04
Leg extension (kg)	1.00	0.92	1.00	0.58
Leg flexion (kg)	1.00	0.90	0.87	0.49
Handgrip (kg)	0.60	<0.001	0.33	0.001
6-minute walking test (m)	1.0	<0.001	0.005	<0.001

*Unless otherwise specified, *p* values were adjusted for age and gender using a general linear model or logistic regression, both with the Bonferroni's correction, as appropriate. [†] Not adjusted for age or gender, respectively.

Abbreviations: ADL: activities of daily living; IADL: instrumental activities of daily living; BMI: body mass index; GDS: Geriatric Depression Scale; MMSE: Mini Mental State Examination; CVD: cardiovascular disease; COPD: chronic obstructive pulmonary disease.

Analyzing the adjusted changes in MMSE score during the follow-up (**Figure 2**), there was a significant trend towards an association with all the measures investigated, except for the SPPB and chair stands time.

Figure 2. Changes in MMSE scores during the follow-up by baseline physical performance tertiles: the PRO.V.A. study

Notes:

The tertiles were defined as follows: short physical performance battery: (T1 $\leq$ 10, T2: 11; T3>11 for men; T1 $\leq$ 9, T2:9-10; T3:>10 points for women); 4 m walking speed: (T1 $\leq$ 0.82, T2: 0.82-0.95; T3>0.95 for men; T1 $\leq$ 0.71, T2:0.71-0.83; T3: >0.83m/s for women); chair stands time: (T1 $\geq$ 11.3, T2: 11.3-9.2; T3<9.2 for men; T1 $\geq$ 10.3, T2: 10.3-13; T3: <13 seconds for women); leg extension: (T1 $\leq$ 22.1, T2: 22.1-33.3; T3>33.3 for men; T1 $\leq$ 16.3, T2: 16.3-23.2; T3: >23.2Kg for women); leg flexion: (T1 $\leq$ 23.4, T2: 23.4-31.0; T3>31.0 for men; T1 $\leq$ 15.5, T2:15.5-21.4; T3: >21.4 Kg for women); 6 minute walking test: (T1 $\leq$ 369, T2: 369-444; T3>444 for men; T1 $\leq$ 306, T2:306-374; T3: >374meters for women); handgrip strength: (T1 $\leq$ 34.0, T2: 34.0-39.3; T3>39.3 for men; T1 $\leq$ 21.3, T2:21.3-26.0; T3: >26.0 Kg for women).

Mean changes in MMSE scores were estimated using a general linear model with multivariable adjustments for age, body mass index, preserved activities of daily living and instrumental activities of daily living, baseline scores in the Mini Mental State Examination and Geriatric Depression Scale, presence of: cardiovascular diseases, hypertension, osteoarthritis, fractures, chronic obstructive pulmonary disease, cancer, formal education, physical activity, smoking habits, monthly income. Gender was added

as a covariate for the analyses on the sample as a whole. The p values are p for linear trend across tertiles of physical performance based on a fully-adjusted general linear model.

Using logistic regression analysis and taking participants with the best performance level as the reference, poor performance at 4m walking speed was significantly associated with the onset of CD at the follow-up after adjusting for potential confounders (T1: OR=1.97; 95%CI: 1.13-3.43; p=0.02), particularly in women (T1: OR=2.57; 95%CI: 1.23-5.37; p=0.01) (**Table 3**). The other physical performance tests were not associated with CD at the follow-up.

Table 3. Association between physical performance tests at the baseline and cognitive decline at the follow-up

	<i>Whole sample</i>				<i>Males</i>				<i>Females</i>			
	<i>Unadjusted odds ratio (95%CI)</i>	<i>p – value</i>	<i>Fully-adjusted odds ratio (95%CI)</i>	<i>p – value</i>	<i>Unadjusted odds ratio (95%CI)</i>	<i>p – value</i>	<i>Fully-adjusted odds ratio (95%CI)</i>	<i>p – value</i>	<i>Unadjusted odds ratio (95%CI)</i>	<i>p – value</i>	<i>Fully-adjusted odds ratio (95%CI)</i>	<i>p – value</i>
<i>Short physical performance battery</i>												
T3	1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]	
T2	0.77 (0.47-1.24)	0.30	0.87 (0.51-1.48)	0.60	1.01 (0.49-2.08)	0.97	1.17 (0.53-2.63)	0.70	0.62 (0.31-1.22)	0.16	0.68 (0.31-1.46)	0.32
T1	0.80 (0.53-1.22)	0.28	0.81 (0.47-1.37)	0.42	0.81 (0.39-1.70)	0.58	0.88 (0.35-2.27)	0.80	0.78 (0.47-1.30)	0.34	0.72 (0.36-1.43)	0.35
<i>4 m walking speed</i>												
T3	1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]	
T2	1.18 (0.74-1.88)	0.50	1.21 (0.72-2.03)	0.47	1.09 (0.52-2.32)	0.82	0.88 (0.38-2.03)	0.76	1.25 (0.69-2.27)	0.47	1.50 (0.76-2.97)	0.24
T1	1.44 (0.92-2.26)	0.11	1.97 (1.13-3.43)	0.02	1.28 (0.61-2.70)	0.51	1.33 (0.54-3.30)	0.54	1.54 (0.87-2.72)	0.14	2.57 (1.23-5.37)	0.01
<i>Chair stands time</i>												
T3	1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]	

T2	1.17 (0.74-1.84)	0.50	1.25 (0.75-2.07)	0.39	1.55 (0.74-3.25)	0.25	1.46 (0.64-3.34)	0.37	0.99 (0.55-1.76)	0.96	1.27 (0.64-2.50)	0.50
T1	1.01 (0.63-1.62)	0.96	1.04 (0.60-1.82)	0.88	1.30 (0.60-2.80)	0.50	1.30 (0.53-3.17)	0.57	0.87 (0.48-1.57)	0.64	0.99 (0.47-2.08)	0.97
<u>Leg extension</u>												
T3	1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]	
T2	0.90 (0.57-1.41)	0.64	0.90 (0.53-1.52)	0.70	0.70 (0.33-1.44)	0.32	0.52 (0.22-1.21)	0.13	1.05 (0.60-1.86)	0.86	0.98 (0.51-1.88)	0.95
T1	0.98 (0.63-1.54)	0.94	0.79 (0.48-1.31)	0.36	0.88 (0.43-1.77)	0.71	0.81 (0.35-1.90)	0.63	1.06 (0.60-1.89)	0.83	1.02 (0.50-2.07)	0.96
<u>Leg flexion</u>												
T3	1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]	
T2	0.80 (0.51-1.24)	0.32	0.64 (0.39-1.06)	0.08	1.03 (0.50-2.13)	0.94	0.74 (0.32-1.69)	0.48	0.68 (0.39-1.20)	0.19	0.61 (0.32-1.17)	0.14
T1	0.84 (0.54-1.30)	0.42	0.70 (0.41-1.16)	0.16	1.06 (0.51-2.20)	0.87	0.71 (0.29-1.74)	0.46	0.72 (0.41-1.27)	0.26	0.68 (0.35-1.32)	0.26
<u>Handgrip</u>												
T3	1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]	
T2	0.98 (0.62-1.57)	0.94	0.96 (0.57-1.62)	0.87	1.27 (0.59-2.74)	0.54	1.17 (0.50-2.75)	0.73	0.83 (0.46-1.49)	0.53	0.81 (0.41-1.61)	0.55
T1	1.29 (0.83-2.00)	0.26	1.28 (0.75-2.19)	0.37	1.28 (0.64-2.58)	0.49	1.24 (0.53-2.89)	0.62	1.28 (0.72-2.26)	0.40	1.23 (0.60-2.52)	0.57
<u>6-minute walking test</u>												
T3	1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]	
T2	0.70 (0.44-1.10)	0.12	0.64 (0.38-1.06)	0.08	0.75 (0.37-1.51)	0.41	0.77 (0.35-1.71)	0.52	0.66 (0.36-1.21)	0.18	0.50 (0.28-1.11)	0.17
T1	0.91 (0.59-1.40)	0.65	0.85 (0.48-1.48)	0.56	0.63 (0.30-1.32)	0.22	0.53 (0.20-1.42)	0.21	1.11 (0.64-1.90)	0.72	0.87 (0.42-1.82)	0.71

Notes:

The tertiles were defined as follows: short physical performance battery: (T1≤10, T2: 11; T3>11 for men; T1≤9, T2:9-10; T3: >10 points for women); 4 m walking speed: (T1≤0.82, T2: 0.82-0.95; T3>0.95 for men; T1≤0.71, T2: 0.71-0.83; T3: >0.83 m/s for women); chair stands time: (T1≥11.3, T2: 11.3-9.2; T3<9.2 for men; T1≥10.3, T2: 10.3-13; T3: <13 seconds for women); leg extension: (T1≤22.1, T2: 22.1-33.3; T3>33.3 for men; T1≤16.3, T2: 16.3-23.2; T3: >23.2 Kg for women); leg flexion: (T1≤23.4, T2: 23.4-31.0; T3>31.0 for men; T1≤15.5, T2: 15.5-21.4; T3: >21.4 Kg for women); 6 minute walking test: (T1≤369, T2: 369-444; T3>444 for men; T1≤306, T2: 306-374; T3: >374 meters for women); handgrip strength: (T1≤34.0, T2: 34.0-39.3; T3>39.3 for men; T1≤21.3, T2: 21.3-26.0; T3: >26.0 Kg for women).

Unless otherwise specified, data are presented as odds ratios and 95% confidence intervals.

Significant results (p≤0.05) are highlighted in bold.

T3 indicates those with the best, T1 those with the worst scores in the physical performance tests.

The **fully-adjusted model** included: age, body mass index, preserved activities of daily living and instrumental activities of daily living, baseline scores in the Mini Mental State Examination and Geriatric Depression Scale (all as continuous variables); presence at the baseline of: cardiovascular diseases, hypertension, osteoarthritis, fractures, chronic obstructive pulmonary disease, cancer (all “yes” vs. “no”); formal education (≥ 5 vs <5 years); physical activity (≥ 4 vs <4 h/week); smoking habits (current vs never/former); monthly income (≥ 500 € vs <500).

Gender was input as a covariate for the analyses on the sample as a whole.

In **Table** , a similar analysis was run taking the onset of CI at the follow-up. The participants with poor SPPB performance (T1: OR=2.11; 95%CI: 1.33-3.36; p=0.002; T2: OR=1.63; 95%CI: 1.01-2.70; p=0.04) at the slowest 4m walking speed (T1: OR=1.52; 95%CI: 1.07-2.37; p=0.03) experienced were significantly more likely to develop CI than those with better performance. These findings were more attenuated in women, in which also low performance at chair stands time (T1: OR=1.70; 95%CI: 1.04-3.00; p=0.03) was associated with future CI. Among the other tests than SPPB, only poor performance at 6MWT (T1: OR=1.89; 95%CI: 1.17-3.06; p=0.01) predicted the onset of CI, particularly in men (T1: OR=2.65; 95%CI: 1.13-6.19; p=0.03) (**Table 4**).

Table 4. Association between physical performance tests at the baseline and cognitive impairment at the follow-up

	<i>Whole sample</i>				<i>Males</i>				<i>Females</i>			
	<i>Unadjusted odds ratio (95%CI)</i>	<i>p – value</i>	<i>Fully-adjusted odds ratio (95%CI)</i>	<i>p – value</i>	<i>Unadjusted odds ratio (95%CI)</i>	<i>p – value</i>	<i>Fully-adjusted odds ratio (95%CI)</i>	<i>p – value</i>	<i>Unadjusted odds ratio (95%CI)</i>	<i>p – value</i>	<i>Fully-adjusted odds ratio (95%CI)</i>	<i>p – value</i>
<i>Short physical performance battery</i>												
T3	1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]	
T2	1.91 (1.21-3.03)	0.006	1.63 (1.01-2.70)	0.04	1.48 (0.69-3.18)	0.32	1.18 (0.51-2.72)	0.70	2.46 (1.38-4.41)	0.002	1.98 (1.03-3.79)	0.04
T1	4.61 (3.11-6.84)	<0.001	2.11 (1.33-3.36)	0.002	5.27 (2.70-10.30)	<0.001	2.08 (0.89-4.89)	0.09	4.43 (2.61-6.92)	<0.001	2.20 (1.24-3.90)	0.007
<i>4 m walking speed</i>												
T3	1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]	
T2	1.35 (0.91-2.02)	0.14	0.91 (0.59-1.43)	0.69	1.12 (0.57-2.19)	0.74	0.78 (0.37-1.66)	0.52	1.54 (0.93-2.54)	0.10	0.92 (0.53-1.63)	0.78
T1	3.69 (2.57-5.29)	<0.001	1.52 (1.07-2.37)	0.03	3.21 (1.76-5.84)	<0.001	1.18 (0.54-0.56)	0.68	4.02 (2.55-6.34)	<0.001	1.69 (1.02-2.70)	0.03
<i>Chair stands time</i>												
T3	1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]	
T2	1.50 (1.02-2.22)	0.04	1.27 (0.81-1.97)	0.30	1.21 (0.62-2.37)	0.58	1.17 (0.54-2.53)	0.68	1.68 (1.03-2.72)	0.04	1.39 (0.80-2.43)	0.24

T1	2.55 (1.70-3.56)	<0.001	1.42 (0.91-2.22)	0.12	2.47 (1.34-4.56)	0.004	1.14 (0.53-2.44)	0.75	2.45 (1.54-3.91)	<0.001	1.70 (1.04-3.00)	0.03
<u>Leg extension</u>												
T3	1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]	
T2	1.61 (1.13-2.30)	0.008	1.20 (0.78-1.84)	0.15	1.67 (0.91-3.04)	0.10	1.41 (0.70-2.85)	0.33	1.59 (1.02-2.47)	0.04	1.22 (0.72-2.05)	0.47
T1	1.71 (1.20-2.44)	0.003	1.36 (0.90-2.05)	0.41	1.76 (0.97-3.20)	0.07	1.10 (0.51-2.32)	0.83	1.69 (1.08-2.63)	0.02	1.20 (0.70-2.05)	0.51
<u>Leg flexion</u>												
T3	1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]	
T2	1.35 (0.95-1.91)	0.09	1.07 (0.71-1.61)	0.74	1.08 (0.59-1.98)	0.81	0.81 (0.39-1.65)	0.55	1.52 (0.98-2.34)	0.06	1.21 (0.73-2.00)	0.47
T1	1.42 (1.00-2.01)	0.05	0.97 (0.64-1.47)	0.88	1.69 (0.95-2.99)	0.07	0.91 (0.44-1.88)	0.80	1.28 (0.82-1.99)	0.28	0.98 (0.56-1.61)	0.84
<u>Handgrip</u>												
T3	1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]	
T2	1.84 (1.25-2.70)	0.002	1.24 (0.80-1.91)	0.34	1.29 (0.61-2.27)	0.50	0.72 (0.31-1.67)	0.44	1.84 (1.16-2.94)	0.01	1.43 (0.84-2.43)	0.19
T1	2.99 (2.07-4.31)	<0.001	1.42 (0.91-2.22)	0.12	4.24 (2.34-7.66)	<0.001	1.86 (0.91-3.82)	0.10	2.33 (1.45-3.38)	<0.001	1.18 (0.66-2.11)	0.57
<u>6-minute walking test</u>												
T3	1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]		1 [ref.]	
T2	1.95 (1.30-2.93)	0.001	1.42 (0.89-2.24)	0.14	1.70 (0.80-3.63)	0.17	1.07 (0.46-2.49)	0.89	2.08 (1.28-3.38)	0.003	1.47 (0.84-2.58)	0.18
T1	4.19 (2.86-6.14)	<0.001	1.89 (1.17-3.06)	0.01	6.15 (3.14-12.05)	<0.001	2.65 (1.13-6.19)	0.03	3.41 (2.13-5.45)	<0.001	1.47 (0.80-2.72)	0.22

Notes:

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T3 indicates those with the best, T1 those with the worst scores in the physical performance tests.

The **fully-adjusted model** included: age, body mass index, preserved activities of daily living and instrumental activities of daily living, baseline scores in the Mini Mental State Examination and Geriatric Depression Scale (all as continuous variables); presence at the baseline of: cardiovascular diseases, hypertension, osteoarthritis, fractures, chronic obstructive pulmonary disease, cancer (all “yes” vs. “no”); formal education (≥ 5 vs <5 years); physical activity (≥ 4 vs <4 h/week); smoking habits (current vs never/former); monthly income (≥ 500 € vs <500). Gender was input as a covariate for the analyses on the sample as a whole.

DISCUSSION

Our population-based cohort study considering a comprehensive battery of baseline physical performance measures, demonstrated that reduced physical performance is significantly associated with poor cognitive status over a follow-up of 4.4 years in older adults. Specifically, we demonstrated that slow gait speed scores predicted both CD and CI, while lower limbs muscle strength measures do not appear to be associated with poor cognitive status at the follow-up. Therefore, our data suggests that the measurement of gait speed as a single test for the measurement of CI/CD offers the most optimal clinical utility and predictive value.

Slow gait speed is associated with several negative outcomes in the elderly including falls, cardiovascular diseases and mortality (32,33). Regarding cognition, walking speed seems to be able to predict the onset of poor cognitive status in longitudinal studies (12-16). Since our study is one of the largest to date and we considered a wide range of objective physical performance measures, our results support the notion that slow walking speed precedes the onset of poor cognitive status (16) and might be the most optimal predictor of all performance measures. Moreover, slow gait speed predicts the onset of CD at the follow-up. Since CD is the first step for CI, our findings add credence to the notion that clinicians should incorporate early cognitive assessments among older adults presenting with slow gait speed. The exact reasons why a slowing of gait speed might be associated with CI or CD are not yet fully elucidated, but several mechanisms might account for this. First, gait speed is closely associated with an impaired balance and fear of falling which has been associated with grey matter volume loss, particularly in the left cerebellum and bilateral inferior occipital gyrus (34). Therefore, gait speed may be a more sensitive marker of generalized deterioration in the nervous system typical of aging which could finally reflect reduced cognitive status (34).

Second, slow gait speed and cognitive status share some risk and pathogenic factors (e.g. oxidative stress and inflammation, and sex hormone levels) that may influence the rate of cognitive decline. (2;35) Third, it may be that individuals with slower gait speed were socially more isolated as a result. Since social isolation is an independent predictor of poor cognitive status, this factor could also play a part. (36) Another pertinent factor that might account for this, is that older adults with reduced physical performance are likely to have reduced functional mobility, be at increased risk of falls and therefore avoid more activities due to a fear of falling (37,38) and thus the vicious cycle of inactivity and social isolation develops, potentially increasing the risk of cognitive decline.

A novel finding from our study is that poor SPPB scores were significantly associated with the onset of CI. To date, there is a paucity of research considering SPPB and CI and CD. Previously, a cross-sectional study suggested that low scores on the SPPB were associated with a poor cognitive status (19) whilst one longitudinal study showed that the association between low SPPB score and poor cognitive status was significant, although this effect became weak after correcting for potential confounders. (20)

Our study found that chair stands time predicts the onset of CI, although only in women. To the best of our knowledge, no study assessed the association between this item and cognitive function. Our study should encourage further research investigating the potential association between chair stands and cognition since it is probably the most multidimensional among the tests included in the SPPB. (32) As reported in previous research, higher levels of aerobic fitness were associated with a better preserved cognitive function (39,40) and a lower risk of developing dementia. (41,42) In agreement with these results, we found that low 6MWT values were significantly associated with higher risk of CI, particularly in men. The reasons of

this gender difference are unknown and further research is needed to confirm our findings.

However, although low scores at physical performance predicted the onset of CI and partly of CD, if improving these items corresponds to an improvement in cognitive function is still a matter of debate. In a meta-analysis of randomized controlled trials, the Authors failed to find that aerobic physical activities have any cognitive benefit in cognitively healthy older adults (43). However, the small sample size of the studies included together with the low quality and the short duration limited our knowledge about this topic, encouraging better designed studies (43).

Finally, lower limbs strength and handgrip tests appear not to be associated with cognitive status at the follow-up. Some cross-sectional studies have suggested that leg extension and flexion strength is lower in people with CI (44,45) but, to the best of our knowledge, our study is the first to consider this pertinent question. It is well known that weak lower limbs are significantly associated with various negative outcomes (e.g. falls and functional limitations in ADL), that are common in people with a poor cognitive status too. (46) We could hypothesize that these tests are too complex for older people without cognitive problems at the baseline to see any significant difference in cognitive follow-up status. Handgrip strength would seem to be easier to test. In our study, however, low handgrip scores were not associated with CI or CD contrary to other studies finding a significant association (2;17), but in agreement with another one (18). Since before adjusting for potential confounders low handgrip strength values were strongly associated with the onset of CI and CD, we believe that the confounders for which we have adjusted our analyses could explain the differences with the other surveys present in literature.

Whilst our study is the most comprehensive cohort study investigating physical performance

and cognitive decline in older people to date, some limitations should be considered. The main limitation lies in that the possible causes of any cognitive changes observed over time were not investigated, and participants' neurocognitive functioning was only measured on the strength of the MMSE, which is unable to assess certain cognitive functions. (47)A second limitation concerns the fact that we did not estimate body composition, which could be important because some studies have suggested that a low fat-free mass and a high fat mass could also have a role in older subjects' cognitive status. (48)Third, oxidative stress and inflammatory markers could play an important part in mediating the association between physical performance and cognitive status, but were not assessed here. Fourth, although we divided participants in to two discreet groups (CI and CD), clearly there is some potential overlap between CD and CI which may have influenced our results. The separation of people into CD and CI is somewhat artificial, and future research is required to disentangle the rate of cognitive change in people over a longer period of time to inform clinical practice. Finally, since MMSE values were not available prior to the baseline visit, it is possible that we included people with already CD at the baseline among cognitively intact subjects.

In conclusion, slow walking speed appears to be an independent predictor of cognitive decline and impairment over a 4.4-year follow-up in our sample of elderly people. In addition, some other items of the SPPB were significantly associated with CI. Thus, slow walking speed appears to be a more important indicator for the risk of the development of CI and CD and yields good clinical utility. Since low physical performance is potentially reversible, future high quality studies with a larger sample size are needed to see whether improving muscular strength could have a positive effect on cognitive status too.

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HIGHLIGHTS

- Few studies assessed if low physical performance predicts poor cognitive status.
- In 1,249 participants followed for 4.4 years slow gait speed predicted cognitive decline.
- Slow gait speed predicted the onset of cognitive impairment at follow-up.