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Sarcopenia-defining parameters, but not sarcopenia, are associated with cognitive domains in middle-aged and older European men

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Abstract

Background Previous research suggests that sarcopenia is associated with lower cognitive functioning. Evidence on the longitudinal relationship between cognition and sarcopenia, according to the revised criteria of the European Working Group on Sarcopenia in Older People (EWGSOP2), is scarce. This study aimed to investigate both cross-sectional and longitudinal associations between sarcopenia and its defining parameters (muscle strength, muscle mass and physical performance) and cognitive performance in middle-aged and older men.

Methods This was a secondary analysis of data from the European Male Ageing Study (EMAS), a multicentre cohort study of men aged 40–79 years, recruited from population registers in eight European centres. Cognitive functioning was assessed by using a battery of three neuropsychological tests, measuring fluid intelligence: Rey–Osterrieth Complex Figure (ROCF-Copy and ROCF-Recall), Camden Topographical Recognition Memory (CTRM) and Digit Symbol Substitution Test (DSST). Sarcopenia-defining parameters appendicular lean mass (aLM), gait speed (GS), chair stand test (CST) and handgrip strength (HGS) were measured. Sarcopenia was diagnosed according to the criteria of the EWGSOP2. All measurements were performed at baseline and after a follow-up of 4.3 years. Cross-sectional associations between cognition, sarcopenia-defining parameters and prevalent sarcopenia (EWGSOP2) were analysed. Longitudinally, the predictive value of baseline cognition on decline in sarcopenia-defining parameters, onset of new sarcopenia and vice versa was examined. Linear and logistic regression were used and adjusted for putative confounders.

Results In the whole cohort (n = 3233), ROCF-Copy (β = 0.016; $P < 0.05$), ROCF-Recall (β = 0.010; $P < 0.05$), CTRM (β = 0.015; $P < 0.05$), DSST score (β = 0.032; $P < 0.05$) and fluid cognition (β = 0.036; $P < 0.05$) were significantly and independently associated with GS at baseline. In the Leuven + Manchester subcohorts (n = 456), ROCF-Copy (β = 1.008; $P < 0.05$), ROCF-Recall (β = 0.908; $P < 0.05$) and fluid cognition (β = 1.482; $P < 0.05$) were associated with HGS. ROCF-Copy (β = 0.394; $P < 0.05$), ROCF-Recall (β = 0.316; $P < 0.05$), DSST (β = 0.393; $P < 0.05$) and fluid cognition (β = 0.765; $P < 0.05$) were associated with aLM. The prevalence of sarcopenia in this population was 17.8%. No associations were detected between cognition and prevalent or incident sarcopenia. Longitudinal analysis showed that low ROCF-Copy score at baseline was associated with an increase in CST in men

≥70 years (β = −0.599; $P < 0.05$). In addition, a decrease in ROCF-Recall was associated with a decrease in GS, and a decrease in DSST was associated with an increase in CST (β = 0.155; $P < 0.0001$, β = −0.595; $P < 0.001$, respectively) in persons with the highest change in both cognition and muscle function.

Conclusions Sarcopenia was not associated with cognitive performance in this population, whereas several components of sarcopenia were associated with domain-specific cognitive performance. Longitudinally, baseline and change in subdomains of cognition predicted change in muscle function in specific subgroups.

Keywords Sarcopenia; Cognition; Older adults; Muscle strength; Physical performance; Muscle mass

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Introduction

It is widely acknowledged that chronic diseases associated with ageing negatively impact health and affect the quality of life of older individuals.[1–3] Two common key features of the ageing process are sarcopenia and cognitive decline. In the last decade, growing attention is given to sarcopenia. According to the most recent definition of the European Working Group on Sarcopenia in Older People (EWGSOP2), sarcopenia is a progressive and generalized skeletal muscle disorder.[1] The mean prevalence of sarcopenia in adults aged 65 years or older goes up to 33.0%, depending on different measuring tools and cut-off values for defining low muscle mass and function.[2] Sarcopenia is a public health challenge given its high prevalence and its links to deleterious health outcomes, such as falls, fractures, physical disability and mortality.[2] Another by-product of the ageing process is cognitive decline. Cognitive decline is defined by a deterioration in cognition involving one or more domains, such as language, memory, reasoning and planning.[4] A decline in cognitive function (CF) is a neurodegenerative process that affects more than 50.0% of people over 60 years old and that can progress to dementia in its most severe form.[5]

Previous research suggests that sarcopenia may be associated with cognitive decline.[6] Nonetheless, there are some knowledge gaps regarding this relationship that needs to be addressed. Firstly, most of the available data showing a positive association between sarcopenia and cognitive dysfunction concern cross-sectional studies.[6–9] There is a scarcity of evidence on the temporality and direction of the association between sarcopenia and cognitive functioning. Secondly, most studies exploring this association has been conducted in post-menopausal women using different criteria to define sarcopenia, resulting in sometimes conflicting findings.[7,8] We are aware of only one cross-sectional study that explored the relationship between EWGSOP1-defined sarcopenia and global CF in men aged 71–92 years old.[9] Therefore, there is a lack of studies examining the relationship using the more recent EWGSOP2 definition of sarcopenia and the different subdomains of cognition in middle-aged and older men. Lastly, socio-demographics, lifestyle risk factors and health characteristics can affect both cognitive functioning and sarcopenia and should be considered as putative confounders when exploring this relationship.[8–10]

To overcome abovementioned knowledge gaps in the literature, more well-designed prospective cohort studies are needed to clarify the interrelationship between CF and sarcopenia.[6] Therefore, this study aims to examine associations between sarcopenia, its defining parameters (muscle strength, muscle mass and physical performance) and domain-specific cognitive performance in a cohort of middle-aged and older European men.

Methods

Study design and subjects

This study utilizes data from the European Male Ageing Study (EMAS), a prospective non-interventional cohort study in Europe. The main aim of the EMAS was to investigate biological and psychosocial determinants correlated with the ageing process in middle-aged and older European men. A comprehensive description of this study has been published previously.[11] In short, non-institutionalized men aged 40–79 years were recruited from population-based registers in eight centres: Leuven (Belgium), Santiago de Compostela (Spain), Szeged (Hungary), Tartu (Estonia), Florence (Italy), Łodz´ (Poland), Malmö (Sweden) and Manchester (UK). There were two phases; a cross-sectional survey was performed between 2003 and 2005, and a follow-up investigation was undertaken between 2008 and 2010. For the baseline survey, stratified random sampling was used to obtain equal numbers of men into each of four age bands (40–49, 50–59, 60–69 and 70–79 years). Ethical approval was acquired from each centre in accordance with local institutional guidelines. Written informed consent was provided prior to participation in the study.

Study questionnaires and clinical assessments

At baseline, participants completed a short postal questionnaire, which included items concerning demographics, general health, medical conditions, smoking, alcohol consumption and medication use. Data collected on co-morbidities involved self-reported diabetes, bronchitis, asthma, heart condition, high blood pressure, stroke, cancer, prostate disease, kidney disease, liver disease, adrenal disease, thyroid disease, pituitary disease, testicular disease, peptic ulcer and epilepsy. Afterwards, participants attended a research clinic to complete an interviewer-assisted questionnaire and to undergo an assessment of CF (see below). The interviewer-assisted questionnaire included the 21-item Beck Depression Inventory II (BDI-II) to assess the presence and severity of depressive symptoms[12] and the Physical Activity Scale for the Elderly (PASE) to assess physical activity.[13] Physical function was measured using the Reuben's physical performance test (PPT).[14] Height and weight were measured using standard procedures with body mass index (BMI) calculated as weight (kg) divided by height in squared metres. Current prescription and non-prescription medication use were also recorded.

Cognitive function

CF was assessed using a battery of three neuropsychological tests: the Rey–Osterrieth Complex Figure (ROCF) test, the Camden Topographical Recognition Memory (CTRM) and the Digit Symbol Substitution (DSST) test. These cognitive tests were selected on the premise that they were independent of language and culture. The ROCF test consist of two subtests: ROCF-Copy and ROCF-Recall. In the ROCF-Copy task, subjects are instructed to copy a geometric figure as accurately as possible within a 5-min time period. In the ROCF-Recall task, the subjects are asked to reproduce the same figure from memory 30 min after completing the Copy task, without being pre-informed. Scores of 0–2 were assigned to each unit depending on how correctly the units were drawn and arranged. Both ROCF tests (ROCF-Copy and ROCF-Recall) had a maximum score of 36.[15] The CTRM entails the presentation of 30 coloured photographs of outdoor topographical scenes, each for 3 s, which is then followed by a three-way forced recognition component. The score range was 0–30.[16]

The DSST is a subtest modified from the Wechsler Adult Intelligence Scales, where participants are asked to make as many correct symbol-for-digit substitutions as possible within a 1-min time frame.[17] These cognitive tasks assess the domains of visuospatial-constructional ability (ROCF-Copy); visual memory (ROCF-Recall); visual recognition (CTRM); and psychomotor processing speed (DSST).

The cognitive scores on these four tasks were transformed to standardized scores (z-scores) to facilitate comparison across task types. To assess overall fluid cognition, standardized scores of the cognitive tests were then averaged to provide a single metric considered to primarily, though not exclusively, reflect fluid cognition. This method has been used in several studies describing CF.[18,19]

Measurements of the diagnostic components of sarcopenia

Muscle strength

At baseline and follow-up, handgrip strength (HGS) was measured using a Jamar 1 hand-held dynamometer (TEC Inc., Clifton, NJ), where three measurements of maximum strength were taken for both hands and the maximum value was recorded for analysis (in kg).[20] In addition, chair stand test (CST) was used to measure lower extremity muscle strength, in which participants were instructed to rise five consecutive times as fast as possible from a chair (expressed in s).[1]

Physical performance

Physical performance was assessed by gait speed (GS) as part of the Reuben's physical performance test. GS was determined by measuring how many seconds the participant needed to walk a distance of 15.24 m or 50 ft (expressed in m/s).[14]

Muscle mass

Muscle mass assessment was only performed in the Leuven and Manchester cohorts (n = 847). Subjects underwent whole-body dual-energy X-ray absorptiometry (DXA) on QDR 4500A Discovery scanners (Hologic Inc, Bedford, MA, USA). Hologic APEX 4.0 software was used to analyse the scans. The precision error was 0.56% in Manchester (n = 31) and 0.57% in Leuven (n = 20). Appendicular lean mass (aLM), a proxy measure for muscle mass, was measured by the whole body DXA and the skeletal muscle mass index (SMI) was calculated (SMI = aLM/height^2).[21] The devices were cross-calibrated with the European Spine Phantom.[22]

Definition of sarcopenia

Sarcopenia was defined based on the diagnostic criteria issued by the EWGSOP2.[1] According to these criteria, a person with low muscle strength has probable sarcopenia, a person with also low muscle mass has confirmed sarcopenia, and a person with also low physical performance has severe sarcopenia. The EWGSOP2 suggests the following cut-offs for these three criteria for men: low muscle strength when maximal HGS was $<$27 kg or when CST was $>$15 s, low muscle mass when SMI was $<$7.0 kg/m^2 and low physical performance when GS was $\leq$0.8 m/s.[1] We used the term incident

sarcopenia to indicate the presence of sarcopenia at follow-up among those participants who did not have sarcopenia at baseline.

Statistical analysis

Subjects with missing cognitive or muscle data were excluded from the analysis. Descriptive statistics were used to summarize subject baseline characteristics.

For the *cross-sectional analysis*, logistic regression was performed to investigate the association between baseline cognitive scores and prevalent sarcopenia. Subsequently, multivariable linear regression analyses were performed to investigate associations between baseline cognitive scores and each sarcopenia-defining parameter (HGS, CST, GS, aLM). *Longitudinally*, multivariable linear regression was used to explore association between baseline cognitive scores and annual % change in the sarcopenia-defining parameters and vice versa (baseline sarcopenia-defining parameters and annual % change in cognitive scores). In addition, we explored the association between baseline sarcopenia and annual % change in cognitive scores. Vice versa, logistic regression was used to examine the association between baseline cognitive scores and incident sarcopenia. Moreover, associations between annual % change in sarcopenia-defining parameters and annual % change in cognitive scores were examined. These longitudinal analyses were then repeated in subgroups stratified by age (four 10-year age bands) and by quartiles of cognitive scores and sarcopenia-defining parameters. Annual % change was calculated as [(follow-up minus baseline)/baseline] × 100/time (years) between baseline and follow-up measurement. In model 1, the analyses were not adjusted for confounders. Covariates were selected as confounders based on literature review and included in models 2–4. In model 2, analyses was adjusted for age, centre, education, physical activity and BMI. Model 3 was adjusted as model 2 with further adjustment for depression, alcohol consumption and smoking. Model 4 was adjusted as model 3 with further adjustment for co-morbidities and use of psychotropic medications. Results are expressed as standardized β-coefficients and odds ratio with 95% confidence intervals (CI). All statistical analyses were completed using the statistical package Stata SE version 17.0 (StataCorp, College Station, TX, USA).

Results

Subjects

A total of 3369 middle-aged and older European men participated in the EMAS. An overview of the different analyses and corresponding sample groups can be found in *Figure* 1. The final sample consisted of 3233 men in the whole cohort and 460 men in the Leuven and Manchester cohorts. Baseline characteristics of the study participants are shown in *Table* 1. Overall, the mean age of the participants was 59.9 years, mean BMI was 27.7 kg/m^2, the average age of leaving education was 20.9, and 32.2% of the subjects had two or more co-morbidities. The follow-up measurements were performed a median of 4.3 years after the baseline survey.

Change in sarcopenia-defining parameters and cognitive performance

The mean sarcopenia-defining parameters and cognitive scores at baseline and follow-up are listed in *Table* 1. There were a significant decrease in GS and aLM ($P < 0.001$) and a significant increase in CST ($P < 0.001$) but no significant change in HGS ($P = 0.476$) between baseline and follow-up. There was a significant improvement in mean scores on the CTRM ($P < 0.05$) between baseline and follow-up, whereas subjects on average showed a significant decrease in performance on ROCF-Copy and DSST (all $P < 0.001$). No significant change in mean score on the ROCF-Recall was observed ($P = 0.097$).

Cognitive performance and sarcopenia as a construct (EWGSOP2)

The prevalence of sarcopenia was 17.8% based on the EWGSOP2 criteria with 71 (15.6%) of the participants having probable sarcopenia, 9 (2.0%) having confirmed sarcopenia and 1 (0.2%) having severe sarcopenia. No associations were found between cognition and prevalent sarcopenia (*Table* 2). Of the 375 participants without sarcopenia at baseline, 66 participants were classified as having incident sarcopenia after 4.3 years of follow-up. Longitudinally, baseline cognitive scores were not predictive for incident sarcopenia (*Table* 3). Vice versa, having sarcopenia at baseline was not associated with cognitive change (*Figure* S1).

Baseline cognitive performance and sarcopenia-defining parameters

Figure 2 summarizes the results from the regression models of baseline cognitive scores (ROCF-Copy, ROCF-Recall, CTRM, DSST, fluid cognition) and the four individual sarcopenia-defining parameters [GS, CST and (in Leuven and Manchester) HGS and aLM]. In the fully adjusted model (model 4), all cognitive scores were positively associated with GS. Thus, participants with higher cognitive performance also tended to have a faster GS. In addition, ROCF-Copy, ROCF-Recall and overall fluid cognition were significantly associated with HGS, whereas ROCF-Copy, ROCF-Recall DSST and overall fluid cogni-

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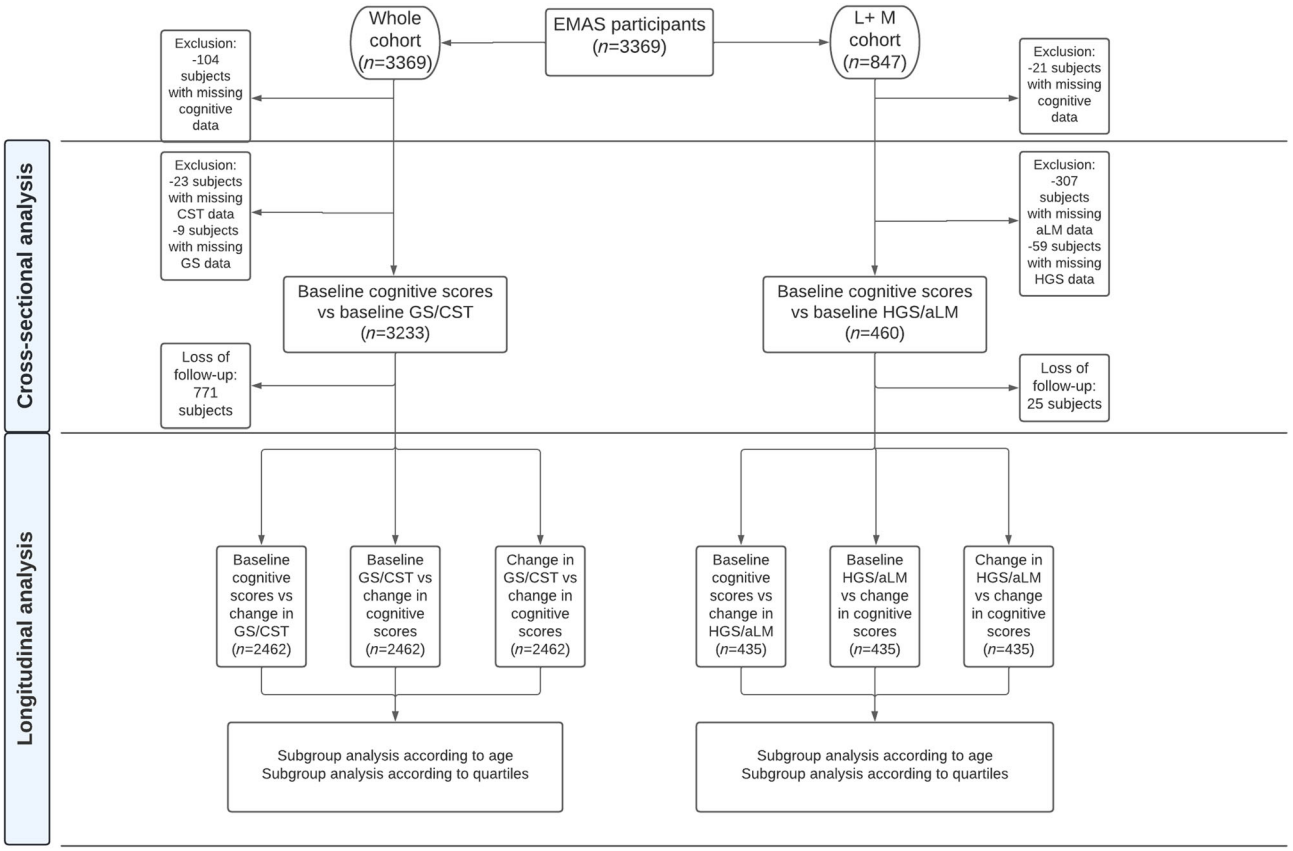

Figure 1 Overview of the analyses and corresponding study population.

tion were significantly associated with aLM. Notably, the significant association between the cognitive scores and CST did not persist after adjustment for confounders.

Baseline cognitive performance and change in sarcopenia-defining parameters

Longitudinally, all baseline cognitive scores showed a positive association with annual % change in GS (ROCF-Copy: β = 0.425; ROCF-Recall:β = 0.426; CTRM: β = 0.550; DSST: β = 0.400;overall fluid cognition: β = 0.790, all $P < 0.001$) (*data not shown*). However, after adjusting for age and centre, results lost significance.

Similarly, an association was found between all cognitive scores and annual % change in HGS, although after adjustment for age and centre, this also became insignificant. No significant association between baseline cognitive scores and annual % change in the other sarcopenia-defining parameters (CST and aLM) were found (*data not shown*). However, a stratified longitudinal subgroup analysis by age (10-year age band) revealed that there was a significant inverse association between ROCF-Copy (but not the other cognitive tests) and annual % change in CST in men aged 70 and older, even after full adjustment (β = −0.667, $P = 0.010$) (*Table* 4). No other significant associations were found between baseline cognition and change in sarcopenia-defining parameters in subgroup analyses stratified by 10-year age band (*Tables* S1–S3).

Baseline sarcopenia-defining parameters and change in cognitive performance

When assessing the association between baseline sarcopenia-defining parameters and change in cognitive scores, no significant associations were found. Additionally, no significant associations were found in the stratified subgroup analysis by age (10-year age band) (*data not shown*).

Decline in cognitive performance and decline in sarcopenia-defining parameters

In subgroups with the highest decline in CST and the highest decline in cognitive scores, annual % change in DSST was negatively associated with annual % change in CST, also after full adjustment (β = −0.595, $P < 0.001$). In subgroups with the highest decline in both GS and cognitive scores, a positive

Table 1 Baseline characteristics of EMAS participants

Variable	Mean/median or %	SD/IQR
N = 3233		
Age (years)	59.9	10.9
BMI (kg/m^2)	27.7	4.1
PASE score	91.4	91.4
Age leaving education (years)	20.9	7.6
BDI score	6.8	6.4
Alcohol consumption (≥1 day/week, %)	56.4%	
Ever smoked (%)	70.3%	
Any psychotropic drugs (%)[a]	7.0%	
Co-morbidities (%)[b]		
0 co-morbidities	36.5%	
1 co-morbidities	31.3%	
≥2 co-morbidities	32.2%	
Baseline sarcopenia-defining parameters		
GS (m/s)	1.2	0.4
CST (s)	12.7	4.1
Follow-up sarcopenia-defining parameters		
GS (m/s)	1.1	0.2
CST (s)	13.6	3.4
Baseline cognitive scores (raw scores)		
ROCF-Copy	34.0	4.5
ROCF-Recall	17.0	6.6
CTRM	23.0	8.8
DSST	28.1	4.7
Follow-up cognitive scores (raw scores)		
ROCF-Copy	33.1	8.3
ROCF-Recall	17.8	7.2
CTRM	23.3	9.0
DSST	27.5	4.7
N = 460		
Baseline sarcopenia-defining parameters		
HGS (kg)	44.1	8.9
aLM (kg)	24.9	3.5
Follow-up sarcopenia-defining parameters		
HGS (kg)	44.1	9.0
aLM (kg)	24.4	6.5
Prevalent sarcopenia (EWGSOP2)		
No sarcopenia	375	82.2%
Probable sarcopenia	71	15.6%
Confirmed sarcopenia	9	2.0%
Severe sarcopenia	1	0.2%

Abbreviations: aLM, appendicular lean mass; BDI, Beck Depression Inventory; BMI, body mass index; CST, chair stand test; CTRM, Camden Topographical Recognition Memory; DSST, Digit Symbol Substitution Test; EWGSOP, European Working Group on Sarcopenia in Older People; GS, gait speed; HGS, handgrip strength; PASE, Physical activity Scale for the Elderly; ROCF, Rey–Osterrieth Complex Figure.

[a]Anti-depressants, benzodiazepines, antipsychotics, sedatives.

[b]Co-morbidities considered were: stroke, high blood pressure, bronchitis, heart conditions, diabetes, asthma, cancer, prostate disease, adrenal disease, thyroid disease, pituitary disease, testicular disease, peptic ulcer, epilepsy, liver and kidney conditions.

association was found between annual % change in ROCF-Recall and annual % change in GS ($\beta = -0.155$, $P < 0.001$ after full adjustment). No other significant associations were found between annual % change in cognitive scores and annual % change in other sarcopenia-defining parameters in the subgroup with the highest decline in both parameters (*Table* 5).

Discussion

We used longitudinal data from the EMAS, a prospective cohort study in middle-aged and older men, to clarify the temporal association between sarcopenia, its defining parameters and cognitive functioning. We have found that EWGSOP2-defined sarcopenia was not associated with CF, whereas some of the individual components of sarcopenia (GS, aLM and HGS) were associated with both overall fluid cognition and its subdomains. Our longitudinal analysis suggests that, after 4.3 years of follow-up, baseline and change in cognition may predict decline in muscle function (but not muscle mass) in persons aged 70–79 years and in persons with the worst change in both parameters, respectively.

We detected no association between *EWGSOP2-defined sarcopenia and fluid cognition or its subdomains*, neither in the cross-sectional analysis nor in the longitudinal analysis. A recent systematic review and meta-analysis of cross-sectional studies consistently found an association between sarcopenia and cognitive impairment (pooled OR = 2.25; 95%CI:1.70–2.97).[6] However, results from longitudinal studies are more conflicting. For instance, in a longitudinal cohort of community-dwelling older Mexican adults, having sarcopenia (EWGSOP1) increased the odds of having MCI and decreased scores on the immediate/delayed recall and verbal fluency tests after 8 years of follow-up.[23] Additionally, Beeri *et al*. found that in older adults without dementia, having sarcopenia (EWGSOP1) at baseline was associated with cognitive decline in the domains of episodic and working memory, but not in the domains of visuospatial abilities or perceptual speed (both measures of fluid cognition) after 5.6 years of follow-up.[24] The inconclusive findings from previous and this present study suggest that sarcopenia may only be associated with specific domains of cognition.

In addition, also the choice of the sarcopenia definition, study population and the used tools to measure body composition may, at least partly, explain the contradictory findings between our and previous studies.[6] To illustrate this, we firstly used the revised criteria of the EWGSOP2 to define sarcopenia, whereas other studies applied the criteria of the Asian Working Group on Sarcopenia (AWGS) or EWGSOP1.[6] According to the recent systematic review, the association between sarcopenia and cognitive impairment remains consistent independent of the sarcopenia definition used. However, the population-specific sarcopenia criteria used in working group consensus definitions may have a substantial influence on this relationship.[6] Secondly, the relatively good CF of the participants with little to no significant decline after 4.3 years of follow-up may explain the non-associations found. Overall, the cognitive scores of our EMAS participants are largely consistent with adults norms that have been published for the used cognitive test instruments and demonstrates a normative cognitive decline with ageing.[25] It is possible that the used cognitive tests, as a measure of fluid cognition,

Table 2 Cross-sectional association between baseline cognitive scores and prevalent sarcopenia

Cognitive scores (n = 460)	Baseline cognitive scores and prevalent sarcopenia			
	Sarcopenia (EWGSOP2) OR (95%CI)			
	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
ROCF-Copy	0.990 (0.784;1.252)	1.040 (0.796;1.359)	1.035 (0.791;1.354)	1.017 (0.777;1.332)
ROCF-Recall	0.834 (0.657;1.058)	0.941 (0.710;1.249)	0.984 (0.378;1.312)	0.968 (0.725;1.294)
CTRM	0.931 (0.739;1.175)	1.001 (0.755;1.323)	0.997 (0.748;1.330)	1.000 (0.748;1.337)
DSST	0.804 (0.637;1.014)	0.820 (0.610;1.102)	0.842 (0.621;1.140)	0.851 (0.626;1.158)
Fluid cognition	0.796 (0.580;1.093)	0.890 (0.579;1.370)	0.923 (0.594;1.435)	0.911 (0.584;1.421)

Abbreviations: BMI, body mass index; CTRM, Camden Topographical Recognition Memory; DSST, Digit Symbol Substitution Test; EWGSOP, European Working Group on Sarcopenia in Older People; ROCF, Rey–Osterrieth Complex Figure.
[a]No adjustment.
[b]Adjusted for age, centre, education, physical activity, BMI.
[c]Adjusted for age, centre, education, physical activity, BMI, depression, alcohol consumption, smoking.
[d]Adjusted for age, centre, education, physical activity, BMI, depression, alcohol consumption, smoking, co-morbidities, psychotropic medications.

Table 3 Longitudinal association between baseline cognitive scores and incident sarcopenia

Cognitive scores (n = 424)	Baseline cognitive scores and incident sarcopenia			
	Sarcopenia (EWGSOP2) OR (95%CI)			
	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
ROCF-Copy	0.906 (0.721;1.139)	1.036 (0.775;1.385)	1.026 (0.767;1.372)	1.025 (0.766;1.371)
ROCF-Recall	0.974 (0.749;1.267)	1.111 (0.801;1.540)	1.124 (0.807;1.566)	1.123 (0.805;1.566)
CTRM	1.164 (0.882;1.537)	0.998 (0.693;1.438)	1.040 (0.719;1.503)	1.039 (0.719;1.502)
DSST	1.119 (0.857;1.461)	0.917 (0.642;1.310)	0.956 (0.663;1.378)	0.955 (0.660;1.380)
Fluid cognition	1.059 (0.727;1.541)	1.049 (0.625;1.761)	1.096 (0.646;1.860)	1.094 (0.644;1.858)

Abbreviations: BMI, body mass index; ROCF, Rey–Osterrieth Complex Figure; CTRM, Camden Topographical Recognition Memory; DSST, Digit Symbol Substitution Test; EWGSOP, European Working Group on Sarcopenia in Older People.
[a]No adjustment.
[b]Adjusted for age, centre, education, physical activity, BMI.
[c]Adjusted for age, centre, education, physical activity, BMI, depression, alcohol consumption, smoking.
[d]Adjusted for age, centre, education, physical activity, BMI, depression, alcohol consumption, smoking, co-morbidities, psychotropic medications.

may not be sensitive to change and be more prone to ceiling effects.[26] We did not measure the cognitive domains that are typically affected in Alzheimer's disease, such as language, verbal ability or auditive memory. According to Wirth *et al*., only cognition at the dementia-state could be associated with sarcopenia, with the probability that no changes in muscle function may occur at the earlier stages of cognitive impairment.[27] The findings from the study by Beeri *et al*. also suggest that mainly more severe stages of sarcopenia (severe impairments in mass and function) could be associated with incident cognitive impairment.[24] In our study, only 71 participants (17.8%) had sarcopenia, of which most only had low muscle strength but preserved function, and only one participant (0.2%) had severe sarcopenia.

Thirdly, the median age of the participants in this study was 59.9 years old, which is relatively young to study age-related conditions that mostly occur after the age of 65 years old. Though, it is possible that the association seen between some of the sarcopenia-defining parameters and cognition couldbe a forecast for a potential stronger relation between sarcopenia as a construct and cognition, but in a later stage of life (when there is more severe decline in both functions). Therefore, exploring this association in a cohort with older, more severely sarcopenic or more cognitively impaired adults could alter the associations. Further investigation with specifically designed studies is needed to confirm this hypothesis.

Of the individual components of sarcopenia, GS, HGS and aLM were significantly associated with overall fluid cognition and several of its subdomains in the *cross-sectional analysis*. Previous research has consistently shown an association between GS and HGS with CF.[28,29] To illustrate, both Sui *et al*. and Sternäng *et al*. reported that GS and HGS were associated with overlapping domains of fluid cognition.[28,29] This found relationship can be explained by the cognitive processes related to GS and HGS. To clarify, human gait and grip force, even though mainly consisting of automatic motions and regarded as a relatively simple act, is a complicated task that demands the coordinated integration of widespread brain regions. These brain regions include the cerebellum, basal ganglia and motor cortex, the majority of which are also involved in higher-level cognitive processes, such as

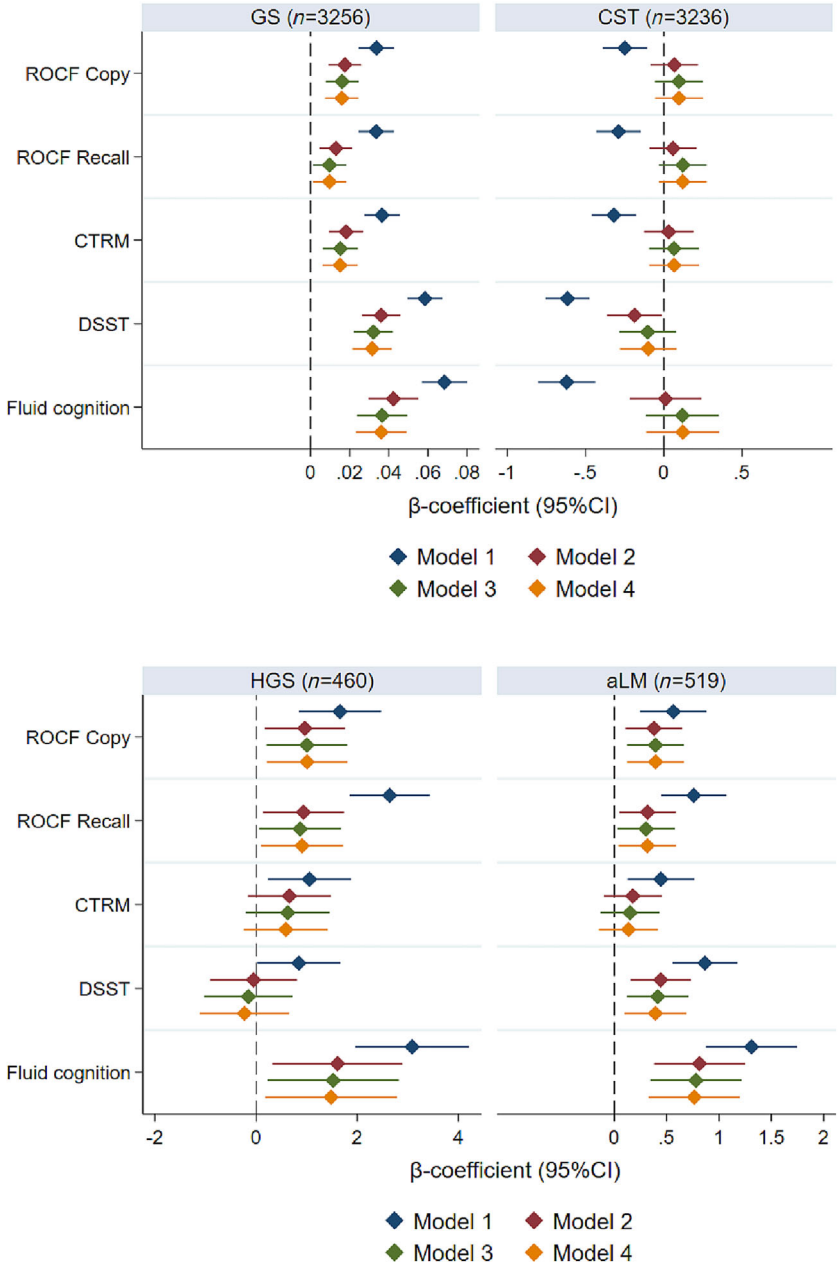

Figure 2 Cross-sectional association between baseline cognitive scores and sarcopenia-defining parameters.

attention, executive functioning and visuospatial ability.[30,31] On the other hand, results from the literature regarding an association between muscle mass and cognition are controversial. For example, an association between low lean mass and cognitive dysfunction has previously been found in 7105 women (75 years and older) of the French EPIDOS cohort.[32] However, in a Chinese study of men and women aged >65 years, an association between lean mass and cognitive impairment was seen in men, but not in women.[33] On the other hand, Bai *et al*. did not find an association between lean muscle mass and cognition in community-dwelling older adults.[10] These conflicting results may be due to the used parameters to measure body composition. For instance, in the study by Bai *et al*., a height-adjusted muscle mass value by the means of SMI was measured, whereas findings from the Chinese study and present study were based on non-adjusted-for-height value of the aLM. Notably, we did not detect associations between CST and measures of fluid cognition in the cross-sectional analysis of this study. Similarly, Wang *et al*.

Table 4 Longitudinal associations between baseline cognitive scores and change in CST, according to age (10 years)

Baseline cognitive scores andchange in sarcopenia-defining parameters				
	Annual % change in CST			
Cognitive scores	β-coefficient (95% CI) 40–49 years (n = 582)	β-coefficient (95% CI) 50–59 years (n = 762)	β-coefficient (95% CI) 60–69 years (n = 658)	β-coefficient (95% CI) 70–79 years (n = 528)
Model 1[a]				
ROCF-Copy	−0.510 (−1.511;0.491)	0.351 (−1.582;2.283)	−0.123 (−0.591;0.345)	**−0.534 (−0.991;−0.077)***
ROCF-Recall	−0.347 (−0.966;0.271)	−0.543 (−1.957;0.871)	−0.123 (−0.666;0.420)	−0.617 (−1.312;0.078)
CTRM	0.555 (−0.157;1.267)	1.410 (−0.074;2.894)	−0.109 (−0.634;0.416)	−0.057 (−0.667;0.552)
DSST	−0.175 (−0.913;0.560)	1.322 (−0.248;2.892)	0.115 (−0.452;0.683)	−0.098 (−0.770;0.575)
Fluid cognition	−0.189 (−1.266;0.889)	1.218 (−0.994;3.429)	−0.131 (−0.850;0.588)	−0.655 (−1.445;0.135)
Model 2[b]				
ROCF-Copy	−0.613 (−1.554;0.328)	−0.314 (−2.166;1.538)	−0.139 (−0.620;0.341)	**−0.696 (−1.208;−0.183)***
ROCF-Recall	−0.344(−0.941;0.253)	−0.009 (−1.345;1.326)	0.319 (−0.392;0.669)	−0.708 (−1.449;0.033)
CTRM	0.196 (−0.517;0.908)	0.871 (−0.554;2.297)	−0.415 (−0.969;0.139)	−0.510 (−1.195;0.175)
DSST	−0.720 (−1.455;0.015)	−0.117 (−1.698;1.463)	−0.332 (−0.946;0.282)	−0.620 (−1.395;0.155)
Fluid cognition	−0.771 (−1.860;0.318)	0.371 (−1.915;2.656)	−0.371 (−1.167;0.426)	−1.250 (−2.156;−0.344)
Model 3[c]				
ROCF-Copy	−0.646 (−1.603;0.311)	−0.273 (−2.133;1.586)	−1.113 (−0.601;0.375)	**−0.674 (−1.189;−0.159)***
ROCF-Recall	−0.342 (−0.950;0.266)	0.020 (−1.326;1.366)	0.192 (−0.350;0.734)	−0.673 (−1.432;0.086)
CTRM	0.162 (−0.569;0.894)	0.894 (−0.536;2.324)	−0.376 (−0.941;0.188)	−0.473 (−1.169;0.222)
DSST	−0.696 (−1.446;0.054)	−0.067 (−1.657;1.523)	−0.264 (−0.905;0.378)	−0.600 (−1.386;0.186)
Fluid cognition	−0.792 (−1.904;0.319)	0.450 (−1.846;2.747)	−0.278 (−1.101;0.546)	−1.198 (−2.116;−0.281)
Model 4[d]				
ROCF-Copy	−0.632 (−1.600;0.334)	−0.278 (−2.140;1.584)	−0.105 (−0.594;0.383)	**−0.667 (−1.184;−0.150)***
ROCF-Recall	−0.333 (−0.943;0.770)	0.025 (−1.323;1.373)	0.192 (−0.350;0.734)	−0.675 (−1.437;0.085)
CTRM	0.173 (−0.561;0.907)	0.895 (−0.538;2.328)	−0.379 (−0.945;0.187)	−0.487 (−1.184;0.210)
DSST	−0.685 (−1.438;0.068)	−0.054 (−1.649;1.542)	−0.283 (−0.927;0.362)	−0.594 (−1.381;0.193)
Fluid cognition	−0.768 (−1.887; 0.351)	0.460 (−1.841;2.761)	−0.280 (−1.105;0.544)	−1.195 (−2.115;−0.275)

Abbreviations: aLM, appendicular lean mass; BMI, body mass index; CST, chair stand test; CTRM, Camden Topographical Recognition Memory; DSST, Digit Symbol Substitution Test; GS, gait speed; HGS, handgrip strength; ROCF, Rey–Osterrieth Complex Figure.
[a]No adjustment.
[b]Adjusted for age, centre, education, physical activity, BMI.
[c]Adjusted for age, centre, education, physical activity, BMI, depression, alcohol consumption, smoking.
[d]Adjusted for age, centre, education, physical activity, BMI, depression, alcohol consumption, smoking, co-morbidities, psychotropic medications.
*$P < 0.05$.

detected an association between GS and HGS, but not CST with CF.[34] This lack of association suggests that our study population may had sufficient cognitive capacity to control coordination and standing force that are needed to perform the CST.[35]

In this study specifically, we did not observe any *longitudinal association between sarcopenia-defining parameters and CF* in the whole study population. However, in the subgroup analysis stratified by quartiles, we found that those with the highest decline in GS also had the highest decline in ROCF-Recall. In addition, we also found an association between the highest decline in CST and the highest decline in DSST. These findings suggest that more severe cognitive decline in the specific domains of visual memory and processing speed could potentially be associated with more severe stages of decline in muscle function. Moreover, in the longitudinal analyses in subgroups stratified by 10-year age band, a statistically significant association was found between baseline ROCF-Copy score and change in CST in men aged 70 and older. Notably, the association between baseline ROCF-Recall and change in CST approached the significance level of 5.0% (P = 0.081) in this age group.

These results may suggest that having a better visuospatial-constructional ability and memory (as measured by both ROCF tests) could probably be important for having better muscle strength (as measured by CST).

Interestingly, the longitudinal association between the cognitive domain of visuospatial-constructional ability (ROCF-Copy) and muscle strength was only significant when CST, but not HGS, was used to indicate muscle strength. These incongruent results suggest that muscle strength and muscle functioning do not have the same impact in the relationship between muscle and cognition, a phenomenon that was also seen in other studies.[36,37] Kuh *et al*. provided a possible explanation for these differential patterns of associations: different measures of physical function may differ in their sensitivity to cognitive change, in a way that also depend on age. To illustrate, the more 'brain challenging' functional tasks of GS and CST could be more susceptible to cognitive dysfunction than pure strength measures. For example, the tasks of GS and CST demand not only mental concentration, coordination, balance, strength and muscle power in the lower extremity function but also require integration of motor, sensory and cerebellar activities, whereas handgrip

Table 5 Longitudinal associations between annual % change in cognitive scores and annual % change in sarcopenia-defining parameters, according to quartiles

Annual % change in cognitive scores and annual % change in sarcopenia-defining parameters: Subgroup analyses: association between worst decline in cognitive scores and worst decline in sarcopenia-defining parameters (quartiles)				
Cognitive scores *Subgroup with highest decline in cognitive scores between baseline and follow-up*	Annual % change in CST (n = 3,236) β-coefficient (95% CI) *Subgroup with highest decline in CST between baseline and follow-up*	Annual % change in GS (n = 3,256) β-coefficient (95% CI) *Subgroup with highest decline in GS between baseline and follow-up*	Annual % change in aLM (*n* = 519) β-coefficient (95% CI) *Subgroup with highest decline in aLM between baseline and follow-up*	Annual % change in HGS (n = 460) β-coefficient (95% CI) *Subgroup with highest decline in HGS between baseline and follow-up*
Model 1[a]				
Annual % change in ROCF-Copy	0.207 (−0.074;0.487)	0.007 (−0.154;0.169)	−0.046 (−0.181;0.089)	0.011 (−0.165;0.187)
Annual % change in ROCF-Recall	0.007 (−0.240;0.226)	**0.114 (0.029;0.198)***	−0.057 (−0.143;0.028)	0.072 (−0.096;0.241)
Annual % change in CTRM	−0.474 (−0.877;−0.071)	0.072 (−0.059;0.204)	0.043 (−0.087;0.174)	0.100 (−0.193;0.393)
Annual % change in DSST	**−0.389 (−0.688;−0.090)***	0.019 (−0.085;0.124)	- 0.057 (−0.179;0.065)	−0.036 (−0.274;0.202)
Annual % change in fluid cognition	0.001 (−0.003;0.004)	0.000 (−0.001;0.000)	0.000 (−0.000;0.000)	0.000 (−0.002;0.002)
Model 2[b]				
Annual % change in ROCF-Copy	0.126 (−0.209;0.461)	0.039 (−0.147;0.226)	−0.002 (−0.086;0.081)	−0.005 (−0.194;0.184)
Annual % change in ROCF-Recall	−0.029 (−0.281;0.222)	**0.151 (0.051;0.251)***	−0.046 (−0.101;0.010)	0.114 (−0.050;0.279)
Annual % change in CTRM	−0.391 (−0.860;0.079)	0.115 (−0.027;0.256)	0.012 (−0.079;0.102)	0.030 (−0.283;0.344)
Annual % change in DSST	**−0.605 (−0.952;−0.258)***	−0.016 (−0.138;0.107)	−0.065 (−0.156;0.026)	−0.088 (−0.338;0.163)
Annual % change in fluid cognition	−0.005 (−0.005;0.004)	0.000 (−0.001.0.001)	0.001 (−0.001;0.003)	0.000 (−0.003;0.002)
Model 3[c]				
Annual % change in ROCF-Copy	0.116 (−0.177;0.409)	0.040 (−0.151;0.231)	−0.005 (−0.100;0.091)	0.014 (−0.161;0.189)
Annual % change in ROCF-Recall	−0.028 (−0.281;0.224)	**0.157 (0.055;0.259)***	−0.059 (−0.123;0.005)	0.131 (−0.042;0.303)
Annual % change in CTRM	−0.418 (−0.902;0.066)	0.115 (−0.030;0.260)	0.005 (−0.095;0.105)	0.032 (−0.307;0.372)
Annual % change in DSST	**−0.607 (−0.967;−0.246)***	−0.008 (−0.134;0.118)	−0.057 (−0.158;0.043)	−0.112 (−0.374;0.151)
Annual % change in fluid cognition	−0.000 (−0.005;0.004)	0.000 (−0.001;0.001)	0.000(−0.002;0.003)	−0.001 (−0.003;0.002)
Model 4[d]				
Annual % change in ROCF-Copy	0.150 (−0.133;0.433)	0.036 (−0.154;0.226)	0.008 (−0.097;0.114)	0.007 (−0.203;0.217)
Annual % change in ROCF-Recall	0.011 (−0.253;0.274)	**0.155 (0.052;0.258)***	−0.052 (−0.114;0.010)	0.134 (−0.038;0.306)
Annual % change in CTRM	−0.413 (−0.910;0.083)	0.114 (−0.033;0.261)	0.009 (−0.095;0.113)	−0.040 (−0.372;0.293)
Annual % change in DSST	**−0.595 (−0.948;−0.241)***	−0.007 (−0.134;0.120)	−0.066 (−0.178;0.046)	−0.124 (−00.418;0.171)
Annual % change in fluid cognition	−0.001 (−0.005;0.003)	0.000 (−0.001;0.001)	0.001 (−0.001;0.003)	−0.001 (−0.004;0.002)

Abbreviations: aLM, appendicular lean mass; BMI, body mass index; CST, chair stand test; CTRM, Camden Topographical Recognition Memory; DSST, Digit Symbol Substitution Test; GS, gait speed; HGS, handgrip strength; ROCF, Rey–Osterrieth Complex Figure.

[a]No adjustment.

[b]Adjusted for age, centre, education, physical activity, BMI.

[c]Adjusted for age, centre, education, physical activity, BMI, depression, alcohol consumption, smoking.

[d]Adjusted for age, centre, education, physical activity, BMI, depression, alcohol consumption, smoking, co-morbidities, psychotropic medications.

*$P < 0.05$.

consists of a simpler motor task.[36] Additionally, it may also be possible that CF could predict change in CST in an earlier stage of life (70–79 years old), whereas change in upper body strength could only be predicted later on in life (e.g. 80 years and older).

Other longitudinal studies have also explored the association between diagnostic components of sarcopenia and CF. Nonetheless, the temporal direction of this relationship remain inconclusive. The mixed findings from the literature suggest that the relationship between physical and cognition may be a complex bidirectional relationship, because some studies report a unidirectional association from cognition to subsequent physical decline[38] and others report the opposite association of physical function to subsequent cognitive decline.[35] For example, the study by Beeri *et al*. found that GS and HGS, as measures of muscle function, were associated with incident cognitive decline, Alzheimer's disease and MCI, whereas muscle mass was not significantly associated with incident MCI or cognitive decline.[24] Moreover, results from another longitudinal study showed that GS was associated with overall CF and the domain of working memory, whereas HGS was associated with the specific domain of delayed recall and perceptual speed.[23] In addition, in a subsample of the EPIDOS cohort (n = 181), van Kan *et al*. detected no association between percentage changes in muscle mass or gait speed with CF after 7 years of follow-up.[39] Similar to the results from the EPIDOS cohort and the study by Beeri *et al*., we have found no association between muscle mass and cognition in the longitudinal analysis.[24] These longitudinal findings may provide additional support to the hypothesis that muscle function, rather than muscle mass, is more clinically relevant for indicating poorer cognition and other adverse health outcomes in older adults.[1,24]

The originality of the present study relies on the evaluation of EWGSOP2-defined sarcopenia and its parameters in relation with overall fluid cognition and its subdomains. To our knowledge, this study pioneers in assessing longitudinal associations between domain-specific CF and incident sarcopenia. Another strength of this study is the recruitment of a large representative sample from population-based registers from different European countries, across different adult age groups. Lastly, our study systematically adjusted for numerous putative confounders that previously have been shown to be associated with both conditions.[8–10]

There are some limitations in this study that must be highlighted. First, the current study sample consisted of relatively young, healthy and high-functioning community-dwelling male adults.

Therefore, the generalizability of the results is limited. For instance, our findings might not be applicable to women, different settings and age categories and other demographic health profiles. Secondly, because ability to provide informed consent was an inclusion criteria, older adults with severe cognitive impairment or dementia were excluded from this study. Thirdly, we cannot rule out the possibility that variation in individual characteristics such as genetics, hormonal and lifestyle factors might have influenced our findings. Moreover, it has been suggested that the co-existence of sarcopenia and obesity—sarcopenic obesity—may have an exacerbating effect on CF than either alone.[40] Unfortunately, we could not assess the relationship between sarcopenic obesity and CF, since the number of obese subjects with reduced muscle mass or function were very small in our study. Further studies are required to clarify this relationship. In addition, the prospective cohort design of the present study did not allow us to examine any causality in the studied relationships. Finally, we also acknowledge the limitation of multiple testing in this present study, but because of the exploratory nature of this study, no correction for multiple testing was made.

In conclusion, sarcopenia as a construct was not found to be associated with cognition in this cohort of community-dwelling older men. However, some of the individual components of sarcopenia (muscle function and muscle mass) were associated with overall fluid cognition and/or its specific subdomains. Our longitudinal analysis suggests that, in specific subgroups, baseline and change in cognition could predict decline in muscle function. Our findings extend the growing body of evidence that cognitive decline in concomitant with loss of physical functioning, independent of the coexisting sarcopenia, can pose high threat to the independence of older adults. Hence, a comprehensive physical function assessment could be valuable in older adults with cognitive decline.

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Conflict of interest

All authors declare that they have no conflicts of interest related to this manuscript.

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Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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