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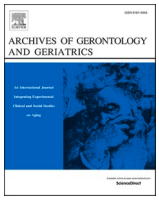

Sarcopenia using muscle mass prediction model and cognitive impairment: A longitudinal analysis from the English longitudinal study on ageing

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HIGHLIGHTS

- Sarcopenia could be a risk factor for dementia in older people.
- Sarcopenia was associated with lower scores in several cognitive domains.
- After adjusting for potential confounders, the presence of sarcopenia was significantly associated with poor verbal fluency.

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ABSTRACT

Background: Literature on the association between sarcopenia and cognitive impairment is largely unclear and mainly limited to non-European populations. Therefore, the aim of this study is to explore if the presence of sarcopenia at the baseline could increase the risk of cognitive impairment in a large cohort of older people participating to the English Longitudinal Study of Ageing (ELSA), over ten years of follow-up.
Methods: Sarcopenia was diagnosed as having low handgrip strength and low skeletal muscle mass index at the baseline, using a muscle mass prediction model; cognitive function was evaluated in the ELSA through several tests. The results are reported in the whole sample adjusted for potential baseline confounders and after matching sarcopenic and non-sarcopenic participants with a propensity score.
Results: 2738 people (mean age: 68.7 years, 54.4% males) were included. During the ten years of follow-up, sarcopenia was associated with significantly lower scores in memory ($p < 0.001$), verbal fluency ($p < 0.001$), immediate word recall ($p < 0.001$), delayed word recall ($p = 0.018$), and in recall summary score ($p < 0.001$). After adjusting for eight potential confounders, the presence of sarcopenia was significantly associated with poor verbal fluency (odds ratio, OR= 1.417, 95% confidence intervals, CI= 1.181–1.700) and in propensity-score matched analyses (OR=1.272, 95%CI= 1.071- 1.511).
Conclusions and implications: Sarcopenia was found to be associated with a significantly higher incidence of poor cognitive status in a large population of elderly people followed up for 10 years, suggesting it may be an important potential risk factor for dementia.

1. Introduction

Dementia is one of the most studied conditions in our society, since more than 50 million people worldwide have dementia, and this number is predicted to triple by 2050 (Rizzi et al., 2014). Aging is often associated with cognitive impairment, an identified risk factor for dementia. Therefore, the prevention of cognitive impairment is imperative: currently there is no effective treatment strategy to "cure" dementia, thus emphasis is being placed on strategies to prevent or delay its onset (Morovic et al., 2019). Sarcopenia, commonly defined as a pathological loss of muscle mass quality and quantity, is common in old age. Its prevalence ranges from 10 to 40% in community-dwelling older adults,

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making this condition very relevant from an epidemiological point of view (Tessier et al., 2022).

Skeletal muscle has an important role as a secretory organ of cytokines and other peptides, denominated myokines, which may have autocrine, paracrine, or endocrine actions and are deeply involved in inflammatory processes (Giudice & Taylor, 2017). Low levels of physical activity promotes an unbalance towards a pro-inflammatory status consequently favouring the vicious circle of sarcopenia, accumulation of fat - especially visceral - and development of cardiovascular diseases, type 2 diabetes mellitus, cancer, depression and finally dementia (Giudice & Taylor, 2017).

Many studies suggest a direct link between loss of physical performance, a component of sarcopenia, and cognitive impairment. For example, a study involving 233 community-dwelling adults from the USA showed how individuals with sarcopenia are more likely to have single and dual impairment in cognitive and physical function (Tolea & Galvin, 2015). Another study conducted in 353 older people from Taiwan reported that sarcopenia was significantly associated with cognitive impairment (Hsu et al., 2014). While these studies advanced our knowledge regarding the possible link between sarcopenia and cognitive impairment, their cross-sectional nature limit the applicability of these findings. A recent longitudinal study, however, confirmed that sarcopenia at the baseline could increase the risk of cognitive impairment during three years of follow-up in a Canadian population of 8279 older people (Tessier et al., 2022). In a large systematic review with meta-analysis including 13 studies for a total of 27,428 patients showed that the prevalence of mild cognitive impairment (MCI) is relatively high in patients with sarcopenia, and sarcopenia may be a risk factor for MCI (Yang et al., 2023). However, they limited their search strategy only to studies written in English and several studies were of a cross-sectional nature (Yang et al., 2023).

Since the association between sarcopenia and cognitive impairment is largely unclear and mainly limited to non-European populations, the aim of this study was to explore if the presence of sarcopenia, evaluated using a muscle mass prediction model at the baseline could increase the risk of cognitive impairment at 10-years of follow-up using data from the English Longitudinal Study on Ageing (ELSA).

2. Materials and methods

2.1. Study population

This study is based on data from five waves (Wave 2, Wave 3, Wave 4, Wave 5, and Wave 7) of the ELSA, a prospective and nationally representative cohort of community-dwelling participants from England (Steptoe et al., 2013). Wave 2 (baseline survey) was conducted in 2004-2005; the other waves were conducted every two years, until Wave 7 occurring between 2014 and 2015. The ELSA study was approved by the London Multicentre Research Ethics Committee (MREC/01/2/91). Written informed consent was obtained from all participants.

2.2. Sarcopenia (independent variable)

Since the evaluation of body composition was not carried out in the ELSA, we used a surrogate measures of low fat-free mass, defined as having a low skeletal muscle mass (SMM), as reflected by lower skeletal mass index (SMI). SMM was calculated based on the equation proposed by Lee and colleagues (Lee et al., 2000), i.e.: ASM = 0.244*weight + 7.8*height + 6.6*sex–0.098*age + race–3.3 (where female = 0 and male = 1; race = 0 (White and Hispanic), race = 1.9 (Black), and race = −1.6 (Asian)) (Lee et al., 2000). Next, SMM was divided by body mass index (BMI) based on weight and height measured by a trained nurse, to create the SMI (Studenski et al., 2014). Low SMM was defined as the lowest quartile of the SMI based on sex-stratified values (Tyrovolas et al., 2016). The equation proposed by Lee was already used in the ELSA study (Veronese et al., 2023, 2022, 2021) and validated against gold standard methods, such as Dual-Energy X-ray Absorptiometry in populations having anthropometric characteristics similar to English people (Carnevale et al., 2018; Villani et al., 2014). In these studies, the accuracy of the Lee's equation was overall good (R2=0.86 in Lee et al. 2000 and 0.76 in Villani et al. 2014 and the area the curve was 0.882 in women and 0.826 in men in Carnevale et al. 2018).

According to the newer definition of sarcopenia (Cruz-Jentoft et al., 2019), we used, as indicator of low muscle strength the presence of low handgrip strength defined as <27 kg for men and <16 kg for women using the average value of three handgrip measurements of the dominant hand (Cruz-Jentoft et al., 2019). Grip strength in kilograms was measured by using a Smedley dynamometer (TTM; Tokyo, Japan), with the upper arm being held against the trunk and the elbow in a 90° flexion (Steptoe et al., 2013).

2.3. Outcomes: cognitive tests

Cognitive function was evaluated in the ELSA through several tests, as previously published in detail (Cadar et al., 2021). Briefly: verbal fluency was assessed by asking how many different animals the participants could indicate in 60 s. Memory, as assessed with the word recall summary score, calculated as the sum of immediate and delayed verbal memory. Each participant was presented with a list of 10 nouns on a computer, one every 2 s. Participants were asked to recall as many words as possible immediately and again after a short delay during which they carried out the other cognitive tests. Finally, cognition orient (Summary date naming) was assessed in terms of orientation in time (month, day of month, year, and day of the week) for evaluating temporal orientation.

2.4. Covariates

The selection of covariates was based on their previously reported associations with the exposure (sarcopenia) and outcome (cognitive impairment), and included the following: age; sex; years of education (considered as continuous variable); ethnicity (whites vs. non-whites); marital status (married vs. other status); smoking status (ever vs. never); abdominal obesity defined as a waist circumference, measured by a trained nurse two times, >102 cm in men and >88 cm in women (Grundy et al., 2004); physical activity level (high vs. moderate/low/sedentary): in the ELSA study, for assessing physical activity level, three questions were asked to assess vigorous, moderate, or mild activity in the previous twelve months. To assist in answering the questions, prompt cards with examples of activities categorized by intensity were used (McMullan et al., 2020); the presence of depressive symptoms was assessed through the Center for Epidemiologic Studies Depression Scale (CES-D) (Eaton et al., 2004); the presence of multimorbidity was defined as the presence of ≥2 chronic conditions (Garin et al., 2016). All covariates were assessed at the baseline.

2.5. Statistical analysis

The data were weighted using the person-level longitudinal weight, core sample, wave 2 (https://www.elsa-project.ac.uk/). Participants aged < 60 years at the baseline, those without BMI information at the baseline, and without cognitive tests at follow-up were removed from the sample. Participants in the lowest quartile of all the six cognitive tests at the baseline were excluded as well (incident cases only analysis). Continuous variables were described as mean and standard deviation (SD). Categorical variables were analysed as counts and percentages. Study participants classified by the occurrence of sarcopenia were compared based on demographic characteristics and comorbidity at the baseline (wave 2), using Chi-squared or Fisher exact tests, for categorical variables and *t*-test, for continuous variables.

A matching analysis to minimize the risk of bias was applied. Specifically, the initial unbalance of cognitive test scores at wave 2 between

people with and without sarcopenia was corrected with a case-control 1:3 nearest neighbor matching propensity score without replacement (Rosenbaum & Rubin, 1983). Each sarcopenic subject (treated) was paired with a non-sarcopenic subject (control) that showed the closest propensity score, and the remaining controls were left unmatched and excluded from further analysis. The propensity score was estimated using logistic regression of the treatment on all the covariates. After matching, the quality of matches was assessed through the standardized mean differences (SMD) using the Austin criterion that defines a balanced covariate if SMD < 0.1. (Austin, 2011) Each cognitive test was dichotomized, where 1 corresponded to the first quartile of the test (the worst score) and 0 otherwise. The longitudinal association between sarcopenia at the baseline and the six cognitive tests (memory, immediate word recall, delayed word recall, verbal fluency, Recall Summary Score, and cognition orient) was assessed in the matched dataset using multivariable mixed logistic regression models. The data were then reported as adjusted odds ratios (OR) and 95% confidence intervals (95% CI).

Specifically, data were examined as individuals nested within waves and individual-level covariates as age, gender, BMI, years of education, ever smoker, current smoking status, sarcopenia and multimorbidity were included as fixed effects. The variance components and the intra-class correlation assessed heterogeneity at the individual level. The likelihood ratio test (LRT) statistic was calculated as two times the log-likelihood values between the model with and without the additional random coefficients to test the statistical significance of variance components. Furthermore, a corrected p-value was calculated as half the one obtained from the chi-square distribution, with degrees of freedom equal to the number of additional random parameters. The correction was needed since LRT sampling distribution is non-standard as the null hypothesis of zero variance is on the boundary of the parameter space.

A p-value less than 0.05 was considered statistically significant. All the statistical analyses were performed using STATA/SE 14, and R Language v. 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria) software packages.

3. Results

As shown in Fig. 1, among the 9432 participants initially included in the wave 2 of the ELSA study, we initially excluded 2215 individuals aged less than 60 years and 2333 without information regarding BMI. Of the 4884 remaining participants, 24 prevalent cases having a diagnosis of dementia, 201 having with deteriorated cognitive function at the baseline, and 1921 participants without cognitive tests during the follow-up were excluded (Fig. 1). The eligible sample included 2738 participants aged on average 68.7 ± 6.4 years, and were mainly males (54.4%).

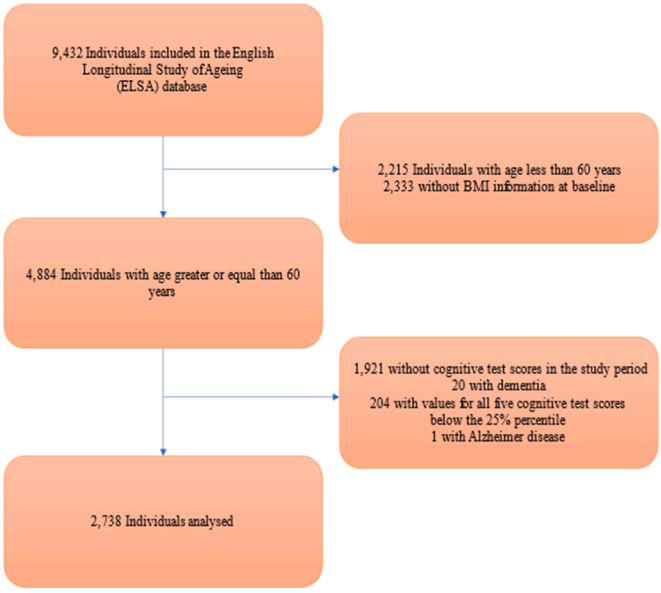

Fig. 1. . Flowchart.

Of the participants, 274 reported sarcopenia, using muscle mass prediction model. Their baseline characteristics compared to their counterparts without sarcopenia ($n = 2464$) are shown in **Supplementary Table 1**. There was no difference in terms of gender among participants with or without sarcopenia, but participants with sarcopenia were significantly older, obese, less educated, or ever smokers. They also reported more frequently high blood pressure, angina, heart murmur, stroke, and cardiovascular conditions. Finally, participants with sarcopenia more frequently reported arthritis, osteoporosis, and cataracts.

As summarized in Fig. 2, during the ten years of follow-up and after matching people with those without sarcopenia using muscle mass prediction model at the baseline evaluation, people affected by sarcopenia at the baseline reported significantly lower scores in memory ($p < 0.001$), verbal fluency ($p < 0.001$), immediate word recall ($p < 0.001$), delayed word recall ($p = 0.018$), and in recall summary score ($p < 0.001$).

Table 1 shows the data of the multivariable logistic regression analysis, in the whole sample and in the propensity score matched samples. Overall, sarcopenia, assessed using a muscle mass prediction model, was significantly associated with a higher incidence of poor cognitive status (defined as the worst quartile) with all the outcomes investigated except for temporal orientation. However, after adjusting for eight potential baseline confounders, the presence of sarcopenia was significantly associated with poor verbal fluency (OR= 1.417, 95%CI= 1.181–1.700, *P*-value<0.001) and poor immediate word recall (OR= 1.239, 95%CI= 1.047–1.465, *P*-value= 0.012) (Table 1). Using the data of the matched samples and after accounting for the baseline confounders, sarcopenia remained significantly associated with poor verbal fluency (OR=1.272, 95%CI= 1.071–1.511, *P*-value=0.006).

4. Discussion

To the best of our knowledge, this is one the first studies attempting to understand the role of sarcopenia, assessed using a muscle mass prediction model, as a putative risk factor for cognitive impairment. Overall, our study on a large cohort of UK older adult participants, demonstrated that the presence of sarcopenia at the baseline was significantly associated with a higher incidence of poor cognitive status, indicating a possible association between these two conditions in older age.

The present findings support previous literature. A Canadian study including 8279 participants has previously identified an association between low muscle mass and cognition in aging (Tessier et al., 2022). The authors showed that older adults with low muscle mass may be at an increased risk for accelerated executive function decline (Tessier et al., 2022). However, the mean scores of both immediate and delayed memory tests increased over 3 years in sarcopenic and non-sarcopenic participants (Tessier et al., 2022), contrary to what we observed in our experience.

The present study showed that people with sarcopenia were significantly older, obese, less educated, or ever smokers compared to those without sarcopenia. Importantly, all these conditions may independently increase the risk of cognitive impairment (Singh-Manoux et al., 2018; Sabia et al., 2012; Hayes-Larson et al., 2023). In the ELSA cohort, we found that people affected by sarcopenia reported more frequently symptoms of cardiovascular disease (CVD), such as high blood pressure, angina, heart murmur, and stroke. An recent review showed that sarcopenia is associated with a faster progression of CVD and higher risk of mortality, falls, and reduced quality of life, particularly among older adults (Damluji et al., 2023). In patients affected by sarcopenia, systemic inflammation, oxidative stress, over-activation of ubiquitin-proteasome

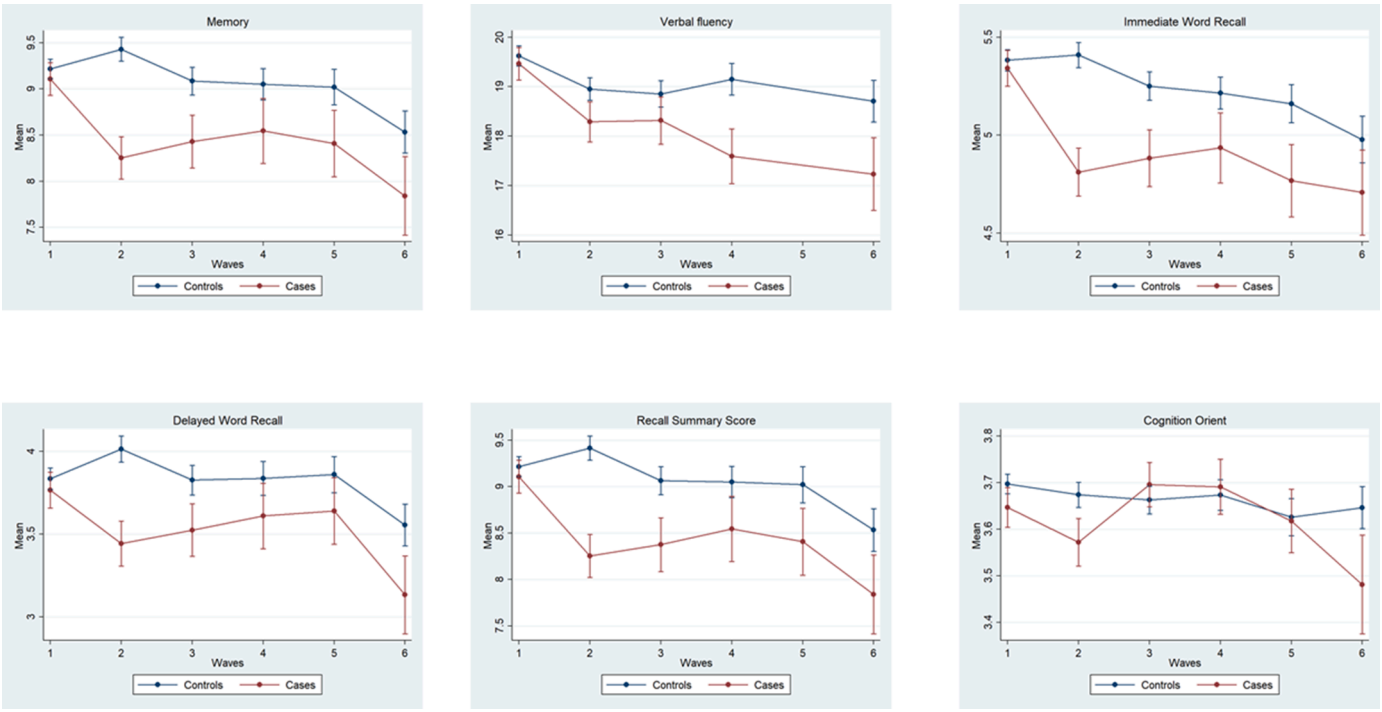

Fig. 2. Cognitive tests' scores by presence or absence of sarcopenia at the baseline.

Table 1
Association between presence or absence of sarcopenia at the baseline and cognitive tests, using a logistic binary regression analysis.

Domains	All sample Model 1	Model 2	Matched samples Model 1	Model 2
Memory	OR= 1.244, 95%CI= 1.060–1.460, *P*-value=0.008	OR= 1.133, 95%CI= 0.956–1.344, *P*-value=0.150	OR= 0.949, 95%CI= 0.784–1.148, *P*-value=0.589	OR= 1.142, 95%CI= 0.975–1.339, *P*-value=0.101
Verbal fluency	OR= 1.624, 95%CI= 1.371–1.924, *P*-value<0.001	OR= 1.417, 95%CI= 1.181–1.700, *P*-value<0.001	OR= 1.471, 95%CI= 1.188–1.821, *P*-value<0.001	OR=1.272, 95%CI= 1.071 - 1.511, *P*-value=0.006
Immediate Word Recall	OR= 1.365, 95%CI= 1.166–1.598, *P*-value<0.001	OR= 1.239, 95%CI= 1.047–1.465, *P*-value= 0.012	OR= 1.114, 95%CI= 0.922–1.346, *P*-value=0.264	OR= 1.103, 95%CI= 0.822 - 1.209, *P*-value= 0.688
Delayed Word Recall	OR= 1.269, 95%CI= 1.069–1.508, *P*-value= 0.007	OR=1.168, 95%CI= 0.972–1.403, *P*-value= 0.097	OR= 0.873, 95%CI= 0.724–1.054, *P*-value= 0.158	OR=1.003, 95%CI= 0.856 - 1.176, *P*-value= 0.969
Recall Summary Score	OR= 1.244, 95%CI= 1.060–1.460, *P*-value=0.008	OR=1.135, 95%CI= 0.957–1.345, *P*-value= 0.145	OR= 0.948, 95%CI= 0.783–1.147, *P*-value=0.582	OR=1.143, 95%CI= 0.976 - 1.340, *P*-value= 0.098
Temporal orientation	OR= 1.173, 95%CI= 0.997–1.380, *P*-value= 0.054	OR= 1.103, 95%CI= 0.928–1.310, *P*-value= 0.265	OR= 0.878, 95%CI= 0.723–1.067, *P*-value= 0.191	OR= 1.231, 95%CI= 0.707 - 1.048, *P*-value= 0.135

Model 1 adjusted only for age and sex; model 2 adjusted for age, sex, BMI, comorbidity, years of education, smoking habits, physical activity, waist circumference. All data are reported as odds ratios (ORs) with their 95% confidence intervals (CIs) and correspondent *p*-values.

system, endothelial dysfunction, lowering muscle blood flow, impaired glucose tolerance, hormonal changes, and physical inactivity possibly contribute to CVD-related sarcopenia (Sasaki & Fukumoto, 2022).

However, the association between sarcopenia, assessed using a muscle mass prediction model, and poor cognitive status was independent from these confounders evaluated at the baseline. After using the data of the matched samples and after accounting for the baseline confounders, sarcopenia remained significantly associated with poor verbal fluency. This finding was previously reported by a Chinese study of 371 older people where sarcopenia was only associated with an impaired verbal fluency test (Huang et al., 2016); another study carried out in the US on a sample of 496 people a poor verbal fluency was associated with slowness and weakness, predictors of cognitive impairment (Salinas-Rodríguez et al., 2021), but they only analysed non-European population. We can justify these findings using several explanations. First, skeletal muscle has shown a role as an endocrine organ maintaining cognitive executive functions: muscle contraction through exercising could stimulate the release of cytokine such as IL-6, IL-8, IL-15, and Brain-Derived Neurotrophic Factor (BDNF) with anti-inflammatory effects and could explain the potential protective effect of preserving muscle mass for brain health (Pratesi et al., 2013). Further to this theory, insulin resistance, oxidative stress, and low-grade chronic elevation of pro-inflammatory markers may be involved in both pathogenesis of sarcopenia and cognitive impairment (Dalle et al., 2017). Moreover, a review based on imbalanced myokine secretion and vascular dysfunction as cause of connection between cognitive impairment and sarcopenia reported that sarcopenia itself showed alteration of the gut microbiome related to reduced muscle protein synthesis induced

by anabolic stimulus and chronic inflammation (Jo et al., 2022). There is a growing body of evidence that underlines a relationship between the presence of social frailty and negative outcomes, in particular cognitive issues (Ragusa et al., 2022). Social isolation and the lack of physical activity, very common outcomes for older people affected by cognitive decline, are usually associated with an increased risk of possible sarcopenia (Hu et al., 2023). Interestingly, the participants' social and participatory life were found to be crucial determinants of the maintenance of cognitive functions among older adults (Miceli et al., 2019).

Frailty was usually associated with decrease of cognitive function: new evidence corroborating the existence of distinct physical frailty subtypes related with aging. Mobility-subtype frailty was significantly associated with functional declines and progression of multimorbidity (Huang et al., 2020). Furthermore, higher risk of cognitive impairment is very common in the prefrail and frail individuals. The incremental impact of frailty on cognition and the susceptibility of non-memory domain may provide a new view in evaluating the pathogenesis of the relationship between frailty and cognitive impairment (Wu et al., 2015).

Increasing muscle mass may be an effective intervention to prevent cognitive decline; nutrition therapy with exercise training may be particularly beneficial from a pathophysiological perspective in terms of decreasing protein breakdown and improving muscle function (Ali & Garcia, 2014). Physical activity could decrease global cognitive decline and behavioral symptoms in people with cognitive impairment or dementia (Demurtas et al., 2021). Its benefits on cognitive function can be attributed to its effects on working memory; even aerobic exercise at moderate intensity or above and a total training duration of $>$ 24 h could have more pronounced effects on cognitive issues (Law et al., 2020).

The findings of this work must be interpreted within its limitations. First, the ELSA study did not analyze psychomotor speed or executive function as cognitive tests. Second, the ELSA study predominantly consists of those of a Caucasian ethnicity, avoiding the part of population that could be, paradoxically, more exposed to cognitive impairment. Third, objective measures of body composition were not performed: consequently, we used surrogates of low fat-free mass based on anthropometric parameters. Although a direct assessment of body composition was not made, the equation proposed by Lee and colleagues has a good agreement with the gold standard tool for evaluating body composition, i.e. DXA (González-Mendoza et al., 2019). Fourth, some variables such as physical activity level and depressive symptoms were self-reported that could be subject to recall bias and social desirability bias. Moreover, we did not consider their inherent changes during the follow-up time that may strongly affect our results. Fifth, the exclusion of participants who did not have BMI information, cognitive tests at follow-up, or those in the lowest quartile of cognitive test scores at baseline may introduce a selection bias.

In conclusion, our research demonstrated a significant association between sarcopenia, assessed using a muscle mass prediction model, at baseline and higher incidence of poor cognitive status in a population of older people. Cognitive impairment is constantly rising in our society and prevention efforts should be an important aim for all clinicians. Identifying older people with sarcopenia and developing interventions to manage or reverse the condition may contribute to this. However, further longitudinal and experimental research is needed to either confirm or refute the present findings before concrete recommendations can be made.

CRediT authorship contribution statement

Laura Maniscalco: Writing – original draft. **Nicola Veronese:** Writing – original draft. **Francesco Saverio Ragusa:** Writing – original draft. **Laura Vernuccio:** Writing – review & editing. **Ligia J. Dominguez:** Writing – review & editing. **Lee Smith:** Writing – review & editing, Supervision. **Domenica Matranga:** Writing – review & editing. **Mario Barbagallo:** Writing – review & editing, Supervision.

Declaration of Competing Interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.archger.2023.105160.

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