*J Nutr Health Aging. 2019;23(6):525-531*

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# SARCOPENIA IS ASSOCIATED WITH COGNITIVE IMPAIRMENT IN OLDER ADULTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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**Abstract:** *Background and Objectives:* There is little evidence in the literature about the possible relationship between sarcopenia and cognition in older adults. Our objective was to investigate the association between cognitive impairment and sarcopenia in older adults living in the community through a systematic review of published studies. *Research Design and Methods:* We performed a systematic review with meta-analysis through Pubmed, LILACS, Scielo and Web of Science databases between March 1, 2001 and December 18, 2018. We included longitudinal and cross-sectional studies that evaluated sarcopenia and cognition as a primary objective. *Results:* Of the 274 studies identified by the systematic review, 10 were included in qualitative analysis (total of 9,703 participants), and 6 were eligible for the meta-analysis (n = 7,045). Mean prevalence of sarcopenia was 10.5%. Cognitive impairment was observed in 269 participants with sarcopenia (40%), compared with 1,616 in non-sarcopenic participants (25.3%). Sarcopenia was significantly associated with cognitive impairment (pooled OR = 2.50, 95% CI = 1.26-4.92; p = 0.008). Heterogeneity across the studies was high and significant ($I^2$ = 84%). *Discussion and Implications:* Our analyzes confirmed that sarcopenic older adults presented a higher prevalence of cognitive impairment. Sarcopenia may represent a risk factor for cognitive decline, but longitudinal studies are needed to explore causality.

**Key words:** Cognitive impairment, cognition, dementia, sarcopenia, older adults.

## Introduction

Sarcopenia is defined as the decrease in muscle mass and function that occurs during aging. This is an important problem in the health of the elderly, resulting in adverse health events, such as physical incapacity (1, 2), reduction in quality of life, and death (3-5). In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) recommended that the presence of low muscle mass along with the presence of low muscle strength (measured by manual grip strength) or low physical performance (measured by walking speed) should be used for the diagnosis of sarcopenia (2). Recently, the International Consensus for Sarcopenia Screening, Diagnosis, and Treatment (ICFSR) has recommended that sarcopenia should be defined as a disease (muscle insufficiency), that could be screened by the SARC-F tool and diagnosed based on low muscle strength, and low physical performance (6). An update of the European consensus was published at the same time (EWGSOP2) highlighting that low muscle strength is a fundamental characteristic of sarcopenia (to the detriment of low muscle mass) and that the loss of physical performance would indicate severe sarcopenia (7).

The prevalence of sarcopenia varies among studies due to differences in diagnostic criteria, age of participants and sociocultural and local origin of the groups evaluated (2). The mean prevalence of sarcopenia in the elderly aged 65 years and over ranges from 6 to 22%. The number of old people with sarcopenia will continue to grow together with the rapid increase in the number and proportion of elderly people worldwide, especially in low- and middle-income countries such as Brazil (8).

Recent studies have suggested that sarcopenia may be associated with poorer cognitive performance, however, there is no consensus in the literature about this relationship. Therefore, the present systematic review aimed to identify studies that investigated the association between cognition and sarcopenia in the elderly. There is a rapid growth of studies published within this area of research in the last 2 years, which would justify a new revision of the theme with a special focus on older adults (9).

## Method

Two researchers (GC, IA) conducted an electronic search for articles indexed in the electronic databases PubMed, SciELO, LILACS and Web of Science from March 1, 2001 until December 18, 2018 according to the Guidelines for Items of Preferential Reports for Systematic Review and Meta-Analysis (PRISMA). The following descriptors were used in each of the selected bases: «Cognition» OR «Cognitive» AND «Sarcopenia» AND «Elderly» OR «Older People». The search was redone with the descriptors translated into Portuguese and Spanish in SciELO and LILACS databases.

*Received February 9, 2019*
*Accepted for publication February 28, 2019*

Published online April 12, 2019, http://dx.doi.org/10.1007/s12603-019-1188-8

### *Inclusion and Exclusion Criteria*

Only those studies that met the following inclusion criteria were selected: (i) it was an original longitudinal and/or cross-sectional study; (ii) included elderly, aged 60 and over; (iii) conducted among community elderly; (iv) included validated and recognized tests that assess cognition and sarcopenia; (v) original research articles developed with humans, in English, Portuguese and Spanish. Review articles, monographs, dissertations, theses, abstracts, chapters or books and point of view or opinion of experts were not included. Case studies, studies with non-elderly adults, adolescents and children, as well as experimental articles and those involving sarcopenic obesity were also excluded.

### *Selection of studies*

Two independent authors reviewed the summary of each study, according to the inclusion criteria and later the full text of all selected studies identified by the literature search for eligibility. We included longitudinal and cross-sectional studies that evaluated the association between sarcopenia and cognition as the main or secondary outcome. Disagreements in study selection were judged and resolved by consensus among the involved authors.

### *Data extraction and Quality Assessment*

Two authors (GC, IA) extracted the information according to a predefined protocol for presentation of qualitative data: author and year, study design, sample, country, measurements, objectives, main results. Additionally, the number of participants with and without sarcopenia, and the number of participants with and without cognitive impairment within the former group (sarcopenia versus non-sarcopenia) were extracted from the studies. If this information was not clear inside the manuscript, a corresponding author was contacted via e-mail. Events were considered as presenting cognitive impairment. Risk estimates were calculated as odds ratio (OR) with 95% confidence intervals (95%CI). The same two authors assessed the quality and risk of bias for each study included in the qualitative analysis. An adapted version of the Newcastle-Ottawa Quality Assessment Scale suited for observational studies was used for quality assessment. Each study was evaluated for good standards on two items of sample selection, one item of comparability (which could be scored with up to two stars), and two items of evaluation, yielding a total of 6 stars (points). Disagreements were solved by consensus between the three authors. Cohort studies were evaluated according to the Newcastle-Ottawa Quality Assessment Scale for cohort studies: four items of sample selection, two items of comparability (which could be scored with up to two stars), and three items of evaluation, yielding a total of 9 stars (points). The scale scores varied based on the study design ranging from 0 (lowest grade) to 6 (highest grade) for cross-sectional studies and from 0 to 9 for cohort studies.

### *Data Synthesis and Analysis*

All evidence extracted was described qualitatively and summarized. Results from studies were also analyzed using quantitative estimates of effects by the Mantel-Haenszel method. A random-effects meta-analysis was conducted to estimate the odds ratios of cognitive impairment between sarcopenic and non-sarcopenic participants using the RevMan software, version 5.3 (Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Heterogeneity between the selected studies was measured using Cochran's Q statistic. The I2 statistic was used to quantify the degree of heterogeneity and values below 25% were considered to be low, 25–50% moderate and over 50% high. Confidence interval was set at 95%, and the level of significance was set at less than 5%.

## Results

### *Selection process*

The systematic search of the literature identified 274 articles: Pubmed = 198; LILACS = 18; SciELO = 4; Web of Science = 54. Duplicate articles between the databases consulted (n = 40) were excluded. Of the 234 records, 198 studies were considered irrelevant, and 36 studies remained for full text revision. Twenty-six studies were excluded by the established criteria. Of these, two clinical case studies and one pharmacological study. Nine were excluded due to lack of data on cognition and sarcopenia. Fourteen studies failed to meet the inclusion criteria (age equal to or greater than 60 years, presenting validated instruments that assessed sarcopenia and cognition). The remaining ten studies were considered to have adequate methodological quality and were included for the systematic review (Figure 1).

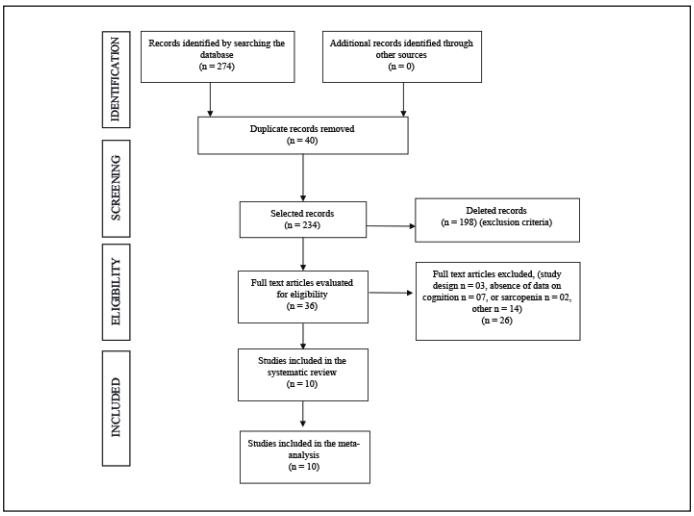
### *Characteristics of the studies and participants*

The characteristics of the longitudinal and cross-sectional studies and the participants' age and education are summarized in Table 1. The studies were conducted involving community dwelling elderly in France (n = 1), Taiwan (n = 1), Brazil (n = 1), China (n = 1), Colombia (n = 1), England (n = 1) and Japan (n = 4). The sample size ranged from 131 to 3,025 (total of 9,703 participants). The mean age of study participants ranged from 69.6 to 82.0 years, with a higher proportion of women, ranging from 47.2% to 100%.

The EWGOSP criteria for the diagnosis of sarcopenia was used by four studies (10-13). One study used both the FNIH and EWGOSP criteria for sarcopenia diagnosis (14). The AWGSP criteria was used in five (15-19) studies. Regarding the evaluation of cognitive impairment, the Mini-Mental State Examination (MMSE) was the most used instrument, being observed in seven studies (10-12, 15-18). One study used the Short Portable Mental Status Questionnaire (13). One study evaluated cognition with the Test Your Memory test (14). One study performed neuropsychological tests to determine

cognitive impairment in addition to the MMSE for the global assessment of cognition (19).

**Figure 1**
Flow diagram of the systematic search




Of the 10 selected studies, only one presented longitudinal analyzes (16). Among the cross-sectional ones, 3 did not find a significant association between sarcopenia and cognitive variables (12, 13, 15). The other studies found significant associations using different methodological strategies.

Gao et al. compared the cognitive performance of sarcopenic to non-sarcopenic individuals and documented significantly lower scores in the MMSE in sarcopenic individuals (17).

Three cross-sectional studies (9, 10, 18), which investigated the association between sarcopenia and cognition through regression analysis, documented the existence of this relationship, as opposed to the findings of other studies (12, 13, 15).

In the SABE study, advanced age, lower MMSE score, low manual grip strength and low walking speed were significantly associated with sarcopenia (10). The study ILAS found no significant association between sarcopenia and global cognitive function, but there was a significant association with verbal fluency performance, with sarcopenic elderly presenting lower fluency (19). Ogawa et al. documented a significant association between sarcopenia and poor cognitive performance among elderly with initial Alzheimer's disease (AD), which was not observed in the cognitively unimpaired group (18).

Sugimoto et al. (11) and Papachristou et al. (14) compared the prevalence of sarcopenia among groups with different degrees of cognitive impairment. Sugimoto et al. reported that the prevalence of sarcopenia was higher among elderly with mild amnestic cognitive impairment (12.5%) and AD (23.3%) compared to elderly cognitively unimpaired individuals (8.6%) (11). Papachristou et al. observed a greater presence of sarcopenia among the elderly with severe cognitive impairment (8%) than among those with mild cognitive impairment (CCL) (41%) (14).

The longitudinal study of Nishiguchi et al. evaluated cognition and sarcopenia among 131 Japanese elderly (121 non-sarcopenic and 10 sarcopenic) at baseline and after 12 months. It was possible to document that after one year, the elderly with sarcopenia showed greater decline in cognition (16).

### *Quality assessment*

Table 2 presents the summary of quality assessment of the cross-sectional studies according to a modified Newcastle-Ottawa scale. Selected studies showed an overall good quality (4-6 stars). Only two studies showed fair quality (3 stars). The only cohort study included also showed good quality (7 stars).

### *Meta-analysis findings*

Of 10 eligible studies for meta-analysis, 4 did not present the information needed in their original publication (12, 15-17). Those authors were contacted several times by electronic correspondence in a 30-day interval. Their data was excluded from the final analysis after no replies. Finally, a total of 673 participants classified as having sarcopenia were compared with 6,372 non-sarcopenic older adults (mean prevalence of 10.5%). Cognitive impairment was observed in 269/673 participants with sarcopenia (40%), compared with 1,616/6,372 similar events among those without sarcopenia (25.3%) (Figure 2). Results showed that cognitive impairment was significantly

**Figure 2**
Random-effects meta-analysis of prevalence of cognitive impairment associated with sarcopenia in older adults

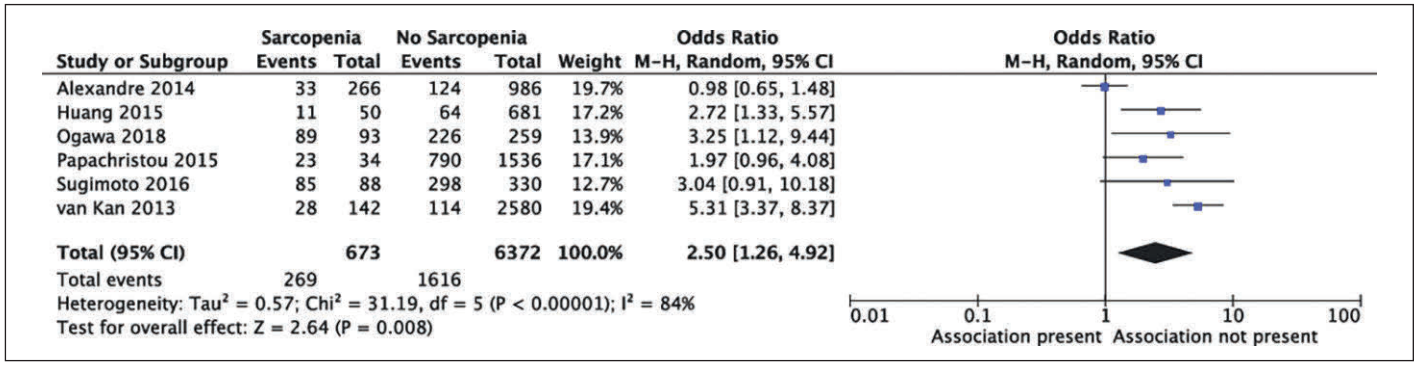


**Table 1**
Qualitative data of the systematic search (n=10 studies)

| **Cross-Sectional Studies** | | | | | |
|---|---|---|---|---|---|
| **Author** | **Sample** | **Country** | **Measurements** | **Objectives** | **Main Results** |
| van Kan et al. (2013) | 3.025 elderly women | France | - Used six criteria to evaluate sarcopenia (Baumgartner, Delmonico, Newman, IWGS, SIG and EWGSOP<br>- Short Portable Mental Status Questionnaire | Whether the operational definitions of sarcopenia are associated with cognition in elderly women in the community. | Prevalence of sarcopenia between 3.3 and18.8%. Despite using 6 different diagnostic criteria to sarcopenia, none had a significant association with cognitive impairment. |
| Alexandre et al. (2014) | 1.149 elderly of both sexes | Brazil | - EWGSOP<br>- MMSE<br>- MNA<br>- GDS<br>- SPPB | Examine the prevalence and factors associated with sarcopenia in elderly residents. | Prevalence of sarcopenia was 16.1% in women and 14.4% in men. Advanced age, cognitive impairment, lower income, smoking, malnutrition and risk for malnutrition were associated with sarcopenia. |
| Nishiguchi et al. (2015) | 273 elderly women | Japan | - Fried phenotype.<br>- MMSE<br>- Scenery Picture Memory Test<br>- AWGS | Determine whether frailty and prefrailty were associated with cognitive decline and sarcopenia in community-dwelling older adults. | Sarcopenia was associated with pre-frailty and frailty, whereas cognitive decline was associated only with frailty. The overall prevalence of sarcopenia was 8%. |
| Gao et al. (2015) | 612 elderly of both sexes | China | - AWGS<br>- MMSE chinese version<br>- MNA<br>- GDS | - To compare the prevalence of sarcopenia in Chinese urban and rural elderly populations.<br>- Identify the risk factors related to sarcopenia, especially to assess whether urban housing is an independent risk factor for sarcopenia. | In rural population, the prevalence of sarcopenia was 13.1%, while in the urban population the prevalence of sarcopenia was 7.0%. Participants with sarcopenia achieved lower MMSE scores. |
| Papachristou et al. (2015) | 1.570 elderly men | England | - Test-Your-Memory<br>- EWGOSP<br>- FNIH | To examine associations of anthropometric characteristics, measures of regional and total body composition assessed by bioelectric impedance, and functional sarcopenia using both definitions of EWGSOP and FNIH, with cognitive impairment. | Prevalence of sarcopenia was 2.7%. Old people with severe cognitive impairment were more likely to present sarcopenia than elderly individuals with mild cognitive impairment. |
| Sugimoto et al. (2016) | 418 elderly of both sexes | Japan | - EWGSOP<br>- National Institute of Neurological and Communicative Disorders and Stroke<br>- Alzheimer's Disease and Related Disorders Association<br>- MMSE | Investigate the prevalence of sarcopenia at various stages of cognitive impairment and examine factors associated with sarcopenia with cognitive decline. | Overall prevalence of sarcopenia was 21.1% (no impairment = 8.6%, amnestic MCI = 12.5%, AD = 23.3%). In both sexes, factors associated with sarcopenia were age and body mass index |
| Huang et al. (2016) | 731 elderly of both sexes | Taiwan | - Version Verbal Learning Test;<br>- Boston Naming Test, Verbal;<br>- Fluency Test, Taylor Complex;<br>- Figure Test, Digits Backward test<br>- Clock Drawing Test;<br>- AWGS | To assess the association between sarcopenia and impairment in different cognitive domains through a community-based, age-matched cohort study. | Overall prevalence of sarcopenia was 6.8%. Sarcopenia was not significantly associated with overall cognitive function, but was significantly associated with impairment in the verbal fluency test. |
| Samper-Ternent et al. (2017) | 1442 elderly of both sexes | Colombia | - Fried phenotype<br>- EWGOSP<br>- MMSE | To estimate the prevalence of frailty and sarcopenia among the elderly in Colombia and to identify variables associated with these conditions. | Prevalence of sarcopenia was 11.5%. Scores in the MMSE were not associated with sarcopenia. |
| Ogawa et al (2018) | 352 elderly of both sexes | Japan | - DSM-5<br>- MMSE<br>- AWGS | To identify differences in the prevalence of sarcopenia among elderly with normal cognition and various stages of AD.<br>To evaluate the relation of mass and muscular strength of the upper and lower extremities and gait speed with dementia severity.<br>Identify factors associated with sarcopenia. | prevalence rate of sarcopenia was significantly higher in early AD, mild AD, and moderate AD than in NC (11% in NC, 36% in early AD, 45% in mild AD, and 60% in moderate AD of the female group, and 13% in NC, 41% in early AD, 47% in mild AD, and 47% in moderate AD of the male group)<br>Older age, lower BMI and lower MMSE score were associated with sarcopenia in patients with AD. |
| **Longitudinal Studies** | | | | | |
| Nishiguchi et al. (2016) | 131 elderly of both sexes | Japan | - MMSE<br>- AWGS | To determine if sarcopenia is an independent risk factor for cognitive impairment in the elderly in the community | The prevalence of sarcopenia was 7.6%. The rate of change in the MMSE scores between baseline and one-year follow-up was significantly higher for the sarcopenic group |

**Table 2**
Quality assessment of cross-sectional studies

| | van Kan et al. (2013) | Alexandre et al. (2014) | Nishiguchi et al. (2015) | Gao et al. (2015) | Papachristou et al. (2015) | Sugimoto et al. (2016) | Huang et al. (2016) | Samper-Ternent et al. (2017) | Ogawa et al (2018) |
|---|---|---|---|---|---|---|---|---|---|
| *Sample selection* | | | | | | | | | |
| Criteria for sarcopenia and cognitive impairment<br>1) Use of validated criteria or instrument *; 2) Without validated criteria or instrument; 3) No description | * | * | * | * | * | * | * | * | * |
| Representativeness and selection of participants<br>1) Participants with sarcopenia and cognitive impairment from specific area, community, clinic, hospital, or sample calculation *; 2) No clear data on selection of participants; 3) Not stated | * | * | * | - | * | * | * | * | * |
| *Comparability on the basis of design or analysis* | | | | | | | | | |
| Control for confounders<br>1) The association between sarcopenia and cognitive impairment was adjusted for 1 confounder *; 2) The association between sarcopenia and cognitive impairment was adjusted for 2 or more confounders **; 3) No adjustments described | ** | * | ** | * | ** | ** | ** | - | * |
| *Evaluation of the association* | | | | | | | | | |
| Analysis of the association | * | * | * | - | * | * | * | - | * |
| 1) Description of the number of participants with both sarcopenia and cognitive impairment *; 2) No clear description of the number of participants with both sarcopenia and cognitive impairment; 3) No description of any data | | | | | | | | | |
| Statistical analysis | * | * | * | * | * | * | * | * | * |
| 1) Appropriate tests to evaluate the association *; 2) Not appropriate tests to evaluate the association; 3) No clear information | | | | | | | | | |
| TOTAL | 6 | 5 | 6 | 3 | 6 | 6 | 6 | 3 | 4 |

associated with sarcopenia (pooled OR = 2.50, 95%CI = 1.26 – 4.92 p = 0.008), as shown in Figure 2. Heterogeneity across the studies was high and significant (I2 = 84%).

## Discussion

In this systematic review of the literature, we considered the relationship between sarcopenia and cognition, summarizing data from 9 cross-sectional studies and 1 longitudinal study involving older adults living in the community. Among the 10 selected studies, one reported lower cognitive performance among sarcopenic seniors, 3 found a significant association between sarcopenia and cognitive performance, 3 studies did not identify this association, 2 studies reported a higher prevalence of sarcopenia with higher degrees of cognitive impairment, and 1 longitudinal study reported greater cognitive decline at one-year follow-up among the sarcopenic patients. The results of this review suggest that there is a significant association between the two examined conditions, which may be of higher magnitude in the context of greater cognitive impairment. A random-effects meta-analysis showed an OR of 2.5 for cognitive impairment in sarcopenic older adults.

Sarcopenia and cognition seem to share the influence of various risk factors. It has been observed in several studies in this review that modulatory factors, such as depression, can influence the association between sarcopenia and cognition (10, 17). In another study, sarcopenia was associated with mild cognitive impairment and depression in elderly Korean women living in the community (20). Malnutrition was also one of the recurrent factors associated with sarcopenia (10, 17) and there are studies that indicate the influence of nutritional pattern on the cognition of the elderly (21). In fact, there is data indicating that there is a decline in the intake of essential foods in the elderly, which may be important for the loss of muscle mass and strength (22), with possible implications for sarcopenia and cognition. Furthermore, muscular functional impairment may be an important key factor in the association between sarcopenia and cognitive impairment. Most sarcopenia diagnostic criteria take a muscular functional variable into diagnostic consideration, and cognitive impairment frequently

implicates in global disability, including physical, motor and gait components (23).

The biological processes underlying a possible association between sarcopenia and cognitive impairment are unclear, but there are several plausible hypotheses. First, successive lifestyle changes, including disability and physical inactivity, can be associated with both conditions. There is a significant relationship between physical activity and functional capacity (24), and physical decline has been consistently associated with future cognitive decline. Second, physical inactivity caused by sarcopenia may result in reduced expression of brain derived neurotrophic factor (BDNF) and insulin growth factor 1(IGF-1), suggesting that they play a role in learning and neural plasticity (25, 26). Serum levels of BDNF and IGF-1 are associated with physical activity (27, 28). Therefore, sarcopenia triggers physical inactivity that in turn could affect the expression of these factors leading to future cognitive decline. In addition, chronic excessive age-related inflammation and oxidative stress are considered mechanisms shared by sarcopenia and cognitive impairment, which may serve as intervening factors (29, 30). Furthermore, mediators such as cognitive frailty, cerebral white-matter hyperintensities and geriatric depression can negatively influence the association between the presence of sarcopenia in cognitively impaired older adults (31).

This review had limitations. The articles selected for review included only community residents, which limits the generalization of findings for clinical or hospital samples, which present with a greater level of comorbidity, depression, polypharmacy, and functional loss. Most of the selected studies were cross-sectional, so causal relationships could not be examined in nine of the ten selected studies. Additionally, heterogeneity between studies was high. Unfortunately, data from 3 cross-sectional studies could not be included since the authors provided no information. However, at least two of these studies present only fair quality.

In conclusion, sarcopenia showed a positive and significant association with cognitive impairment according present data from mostly cross-sectional studies. Longitudinal studies are needed to investigate mechanisms that could better explain the association between sarcopenia and cognition.

*Acknowledgement:* Prof. Aprahamian receives National public grant level 2 from the National Council for Scientific and Technological Development (Ministry of Science, Technology, Innovation and Communications, Brazil).

*Conflict of Interest:* The authors have no conflict of interest to report.

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