Lower Limb Muscle Strength and Muscle Mass Are

Associated with Incident Symptomatic Knee Osteoarthritis:

a Longitudinal Cohort Study

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Abstract

Recent literature suggests that sarcopenia, often represented by low lower limbs muscle mass and strength, can be considered a potential risk factor for knee osteoarthritis (OA), but the available literature is still limited. We therefore aimed to investigate whether sarcopenia is associated with a higher risk of radiographic (ROA) and symptomatic knee OA (SxOA) in a large cohort of North American people in the context of the OA initiative. Sarcopenia at baseline was diagnosed in case of low skeletal muscle mass (i.e., lower skeletal mass index) and poor performance in the chair stands test. The outcomes of interest for this study included ROA (radiographical osteoarthritis) if a knee developed a Kellgren and Lawrence (KL) grade ≥2 at follow-up, and SxOA (symptomatic osteoarthritis) defined as new onset of a combination of painful knee OA. Altogether, 2,492 older participants (mean age: 68.4 years, 61.4% females) were included. At baseline, sarcopenia was present in 6.1% of the population. No significant difference in ROA prevalence was observed between those with and without sarcopenia (p=0.76), whilst people with sarcopenia reported a significant higher prevalence of SxOA (p<0.0001). Using a logistic regression analysis, adjusting for potential confounders at baseline and the diagnosis of sarcopenia during follow-up, sarcopenia was associated with a higher incidence of knee SxOA (odds ratio, OR=2.29; 95%CI [confidence interval]: 1.42-3.71; p=0.001), but not knee ROA (OR=1.48; 95%CI: 0.53-4.10; p=0.45). In conclusion, sarcopenia could be associated with a higher risk of negative knee OA outcomes, in particular symptomatic forms.

# Introduction

Osteoarthritis (OA) is the most prevalent type of arthritis [1] and a very common long-term disabling chronic condition [2] characterized by the deterioration of cartilage in the joints [3]. Evidence suggests that OA is the leading cause of disability worldwide with very high personal, social and economic burdens [4]. The prevalence of OA increases with age and is more common in women, people with obesity and those with joint trauma [5]. The most prevalent musculoskeletal disease in older adults is knee OA which affects at least 19% of American adults aged 45 years or older [6]. Knee OA is characterized by symptomatic and/or radiographic evidence, such as increased pain, functional/joint instability, as well as increased risk of muscle loss and muscle weakness [3]. Deterioration of muscle quality and quantity have been linked to sarcopenia [7; 8], thus putting the adults with knee OA at high risk of developing this condition [9].

Based on the latest revised European consensus on definition and diagnosis [2; 10], sarcopenia is a generalized and progressive muscle disorder with an increased likelihood of a variety of poor health outcomes such as falls and fractures [11; 12; 13], impaired mobility [14] and gradual loss of independence to perform activities of everyday living [15], eventually leading to respiratory and cardiac diseases [16; 17], low quality of life (QoL) [18] and premature death [19; 20]. Moreover, sarcopenia is now recognized to begin earlier in life and is not merely related to ageing as previously presumed [21].

Even though sarcopenia often accompanies OA[22], the association between them is still unclear and due to the conflicting results and insufficient evidence, no agreement has been reached [23; 24]. Considering the increasing evidence of negative health outcomes that are associated with these two conditions [25], we aimed to investigate whether sarcopenia is associated with a higher risk of radiographic (ROA) and symptomatic knee OA (SxOA) in a large cohort of North American people followed-up for 4 years.

**2 Materials and methods**

***2.1 Data source and subjects***

Data for this study were obtained from the Osteoarthritis Initiative (OAI) database (https://nda.nih.gov/oai/). In the OAI, participants were recruited across four clinical sites in the United States of America (Baltimore, MD; Pittsburgh, PA; Pawtucket, RI; and Columbus, OH) between February 2004 and May 2006. In the OAI project, individuals were included if they: (1) had knee OA with knee pain for a 30-day period in the past 12 months or (2) were at high risk of developing knee OA (e.g. obese/overweight, family traits for knee OA) [26]. For the aims of this work, the data were collected at baseline, in the screening evaluations and in subsequent evaluations until four years of follow-up.

All participants provided written informed consent. The OAI study was given full ethics approval by the institutional review board of the OAI Coordinating Center, at the University of California in San Francisco.

***2.2 Sarcopenia definition (exposure)***

For the definition of sarcopenia, we used the criteria of the revised European consensus on the definition and diagnosis of sarcopenia [10]. Sarcopenia was defined as a chair stand test time >15 seconds for 5 repetitions (muscle strength parameter) and low skeletal muscle mass (SMM) as reflected by lower skeletal mass index (SMI) (body composition parameter) [10].

SMM was calculated based on the equation proposed by Lee and colleagues [27]: SMM= 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]). SMM was further divided by body mass index (BMI) based on weight and height measured by a trained nurse, to create a SMI [28]. Low SMM was defined as the lowest quartile of the SMI based on sex-stratified values [29].

***2.3 Assessment of knee OA outcomes***

At baseline and during follow-up examinations, individuals had full knee assessments which included both clinical and radiographic examinations. A fixed flexion posterior–anterior radiograph, which was read centrally for Kellgren and Lawrence (KL) grade, was made for all the participants. In addition, participants were asked regarding knee pain, the following question: ‘During the past 30 days, have you had pain, aching, or stiffness in your right/left knee on most days?’.

The outcomes of interest for this study included: (1) ROA (radiographical osteoarthritis) if a knee developed a KL grade ≥2 at follow-up among those without this condition at baseline and (2) SxOA (symptomatic osteoarthritis), defined as the presence of a combination of painful knee OA. The assessment of the knee OA outcomes was made, other than at baseline, at V01 (12 months), V03 (24 months), V05 (36 months), and V06 (48 months).

***2.4 Covariates***

Several covariates at baseline other than age and sex were identified as potential confounding factors based on previous literature [30]. These included: race (whites vs. others); educational attainment (college or higher vs. others); yearly income (< vs > $50,000 or missing data); smoking habits; physical activity evaluated using the total score for the Physical Activity Scale for the Elderly scale (PASE) [31]; Charlson Comorbidity Index score [32], a validated general health measure of self-reported comorbidities; the number of medications used; daily energy intake (in Kcal).

***2.5 Statistical analyses***

Data on continuous variables were normally distributed according to the Kolmogorov-Smirnov test. Data were consequently presented as means and standard deviation values (SD) for quantitative measures, and percentages for all categorical variables by the presence or absence of sarcopenia at baseline. P values were calculated using an independent T test for continuous variables and a chi-square test for categorical parameters.

To assess the association between sarcopenia and the outcomes of interest during follow-up, a logistic regression analysis was applied, since a survival analysis was not possible due to lack of information on the precise date of event. The basic adjusted model included age and gender. The fully adjusted model included all parameters associated with the outcomes of interest (p-value <0.10) or significantly different between sarcopenic and non-sarcopenic subjects (p-value <0.05). Multi-collinearity among covariates was assessed through variance inflation factor (VIF) [33], taking a cut-off of 2 as the criterion for exclusion. No covariates were excluded using this criterion. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated to estimate the strength of the associations between sarcopenia at baseline and incident knee OA outcomes.

A p<0.05 was deemed statistically significant. All analyses were performed using SPSS® software version 21.0 for Windows (SPSS Inc., Chicago, Illinois).

**3 Results**

***3.1 Sample selection***

The OAI database initially included a total of 4,796 participants. We excluded 2,211 individuals since they were less than 60 years of age, 52 since no data regarding body composition or chair stands time were available, and 41 for not having data regarding race. Therefore, 2,492 participants were included, as shown in Figure 1.

**Diagram

Description automatically generated**

***3.2 Descriptive characteristics***

The cohort consisted of 1,529 females (61.4%), with a mean age of 68.4 years (±5.4 years; range: 60-79 years). The prevalence of sarcopenia at baseline was 6.1%, affecting 153 subjects. At baseline, 58% were affected by knee ROA and, of them, 24.4% knee SxOA.

Table 1 shows the baseline characteristics by the presence of sarcopenia. Compared to the 2,239 participants without sarcopenia, sarcopenic subjects were significantly older, more sedentary, with a lower educational level and were poorer (Table 1). Sarcopenic individuals had a greater number of comorbidities, and they used a higher number of medications. Finally, no significant difference in ROA prevalence was observed between sarcopenic and non-sarcopenic individuals (p=0.76), whilst people with sarcopenia reported a significantly higher prevalence of SxOA (69.4% vs. 49.5%; p<0.0001) than their counterparts (Table 1).

**Table 1. Baseline characteristics of participants according to the presence of sarcopenia.**

|  | **Sarcopenia**  **(n=153)** | **No sarcopenia**  **(n=2239)** | **p-value** |
| --- | --- | --- | --- |
| ***General characteristics*** |  |  |  |
| **Age (years)** | 72.1 (5.3) | 68.2 (5.4) | <0.0001 |
| **Males (%)** | 41.2 | 38.5 | 0.55 |
| **PASE (points)** | 114 (56) | 139 (67) | <0.0001 |
| **Whites (%)** | 88.2 | 83.9 | 0.17 |
| **Smoking (previous/current) (%)** | 43.1 | 51.1 | 0.07 |
| **Graduate degree (%)** | 20.3 | 29.0 | 0.02 |
| **Yearly income (> $50,000) (%)** | 36.3 | 54.8 | <0.0001 |
| **Daily energy intake (Kcal)** | 1334 (565) | 1334 (538) | 0.99 |
| ***Medical conditions*** |  |  |  |
| **BMI (kg/m2)** | 30.8 (5.0) | 28.2 (4.5) | <0.0001 |
| **Charlson co-morbidity index (points)** | 0.79 (1.10) | 0.45 (0.88) | <0.0001 |
| **Number of medications** | 4.14 (2.97) | 3.37 (2.67) | 0.001 |
| ***Osteoarthritis items*** |  |  |  |
| **ROA (%)** | 9.1 | 10.0 | 0.76 |
| **SxOA (%)** | 69.4 | 49.5 | <0.0001 |

Notes: The data are presented as mean (standard deviation) for continuous variables and percentages (%) for categorical outcomes.

Abbreviations: CES-D: Center for Epidemiologic Studies Depression Scale; PASE: Physical Activity Scale for the Elderly; BMI: body mass index; OA: osteoarthritis; ROA: radiographic OA; SxOA: symptomatic knee OA.

***3.3 Sarcopenia and incident knee osteoarthritis outcomes***

During the four years of follow-up, the incidence of ROA was 10.7% and that of SxOA 46.9%. As shown in Table 2, using a logistic regression analysis, adjusting for potential confounders at baseline and the diagnosis of sarcopenia during follow-up, sarcopenia was associated with a higher incidence of knee SxOA (OR=2.29; 95%CI: 1.42-3.71; p=0.001), but not knee ROA (OR=1.48; 95%CI: 0.53-4.10; p=0.45).

**Table 2. Association between baseline sarcopenia and incident knee OA outcomes.**

|  | **N** | **Basic-adjusted model**  **(OR, 95%CI)** | **p-value** | **Fully-adjusted model1**  **(OR, 95%CI)** | **p-value** |
| --- | --- | --- | --- | --- | --- |
| **ROA** | 847 | 1.38 (0.51-3.76) | 0.52 | 1.48  (0.53-4.10) | 0.45 |
| **SxOA** | 1683 | 2.51 (1.56-4.02) | <0.001 | 2.29  (1.42-3.71) | 0.001 |

Notes:

All the data are presented as odds ratios (95% confidence intervals).

1 Basic adjusted model included as covariates age (as continuous) and sex;

2 Fully adjusted model included as covariates, other age and sex: race (whites vs. others); education (degree vs. others); yearly income (categorized as > or < 50,000$ or missing data); smoking habits (current and previous vs. others); Physical Activity Scale for Elderly score (as continuous); Charlson co-morbidity index; number of medications used; energy intake (as continuous).

Abbreviations: CI: confidence intervals; OR: odds ratio; ROA: radiographic OA; SxOA: symptomatic knee OA

**4 Discussion**

In this research involving 2,492 older people, we found that the presence of sarcopenia at baseline was significantly associated with a higher risk of symptomatic knee OA, over four years of follow-up.

The overall prevalence of sarcopenia at baseline in our study was just under 10%, which is in accordance to the latest systematic review and meta-analysis of general population studies [34]. The existing literature supports our finding of sarcopenia in older people [35; 36] as well as those with lower educational level and lower income [37], more comorbidities, higher medication intake and more sedentary lifestyle [38; 39].

Other works already explored the potential association between sarcopenia and knee OA outcomes in older people. Recently, Andrews et al. reported that sarcopenia could be associated with a higher risk of sarcopenia, in Health, Aging, and Body Composition participants [40]. Interestingly, our findings did not show any significant difference between ROA prevalence and people with or without sarcopenia, according to the paper of Andrews et al. [40]. However, a significantly higher prevalence of symptomatic knee OA was reported. In another study, whose aim was to explore the prevalence and characteristics of pain associated with sarcopenia, it was found that the prevalence of pain was much higher in participants with sarcopenia than their counterparts [41]. These findings overall suggest that sarcopenia could be associated with higher risk of pain associated to knee OA, indicating the need of early identification of these patients for tailored interventions.

For example, physical exercise interventions could be suggested in people with sarcopenia and without symptomatic knee OA since this kind of intervention is able to prevent further muscle mass loss [42], incident knee OA (in particular forms associated to pain) [43], and pain itself [44].

The strengths of our study are the long duration of follow-up, the several knee OA outcomes assessed, and the large sample size included. However, our findings should be interpreted within some important limitations. First, the participants of the OAI were at high risk or already had knee OA. Thus, our results cannot be extended to the general population. Second, the observational nature of our findings can introduce another bias in our results, although we tried to correct this limitation using analyses adjusted for potential confounders. Finally, body composition was based on a population equation and not on direct assessment. However, this has been validated against gold standard methods such as magnetic resonance imaging and dual-energy X-ray absorptiometry [45].At the same time, sarcopenia was identified using lower limbs performance and muscle mass, whilst handgrip strength is the preferred method for diagnosis sarcopenia [10].

In conclusion, our study suggests that sarcopenia could be associated with a higher risk of negative knee OA outcomes and in particular symptomatic forms. Our findings further suggest the importance of early detection of sarcopenia, in order to implement appropriate preventive treatment against the progression of knee OA.

# 5 Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

# 6 Author Contributions

# Manuscript preparation: Veronese, Stefanac, Al-Daghri, Sabico; critical revision: Maggi, Smith,

# Cooper, Rizzoli, Reginster; data interpretation: Barbagallo, Dominguez; statistical analysis: Veronese

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# 8 Data Availability Statement

The dataset supporting the conclusions of this article is available in https://nda.nih.gov/oai/.

**9 References**

[1] H.S. Picavet, and J.M. Hazes, Prevalence of self reported musculoskeletal diseases is high. Ann Rheum Dis 62 (2003) 644-50.

[2] K.M. Leyland, L.S. Gates, M.T. Sanchez-Santos, M.C. Nevitt, D. Felson, G. Jones, J.M. Jordan, A. Judge, D. Prieto-Alhambra, and N. Yoshimura, Knee osteoarthritis and time-to all-cause mortality in six community-based cohorts: an international meta-analysis of individual participant-level data. Aging clinical and experimental research 33 (2021) 529-545.

[3] D.J. Hunter, and S. Bierma-Zeinstra, Osteoarthritis. Lancet 393 (2019) 1745-1759.

[4] I. Yahaya, T. Wright, O.O. Babatunde, N. Corp, T. Helliwell, L. Dikomitis, and C.D. Mallen, Prevalence of osteoarthritis in lower middle- and low-income countries: a systematic review and meta-analysis. Rheumatol Int 41 (2021) 1221-1231.

[5] G.B.D. Disease, I. Injury, and C. Prevalence, Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 388 (2016) 1545-1602.

[6] R.C. Lawrence, D.T. Felson, C.G. Helmick, L.M. Arnold, H. Choi, R.A. Deyo, S. Gabriel, R. Hirsch, M.C. Hochberg, G.G. Hunder, J.M. Jordan, J.N. Katz, H.M. Kremers, F. Wolfe, and W. National Arthritis Data, Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum 58 (2008) 26-35.

[7] H.T. Kim, H.J. Kim, H.Y. Ahn, and Y.H. Hong, An analysis of age-related loss of skeletal muscle mass and its significance on osteoarthritis in a Korean population. Korean J Intern Med 31 (2016) 585-93.

[8] D.C. Lee, R.P. Shook, C. Drenowatz, and S.N. Blair, Physical activity and sarcopenic obesity: definition, assessment, prevalence and mechanism. Future Sci OA 2 (2016) FSO127.

[9] E. Shorter, A.J. Sannicandro, B. Poulet, and K. Goljanek-Whysall, Skeletal Muscle Wasting and Its Relationship With Osteoarthritis: a Mini-Review of Mechanisms and Current Interventions. Curr Rheumatol Rep 21 (2019) 40.

[10] A.J. Cruz-Jentoft, G. Bahat, J. Bauer, Y. Boirie, O. Bruyere, T. Cederholm, C. Cooper, F. Landi, Y. Rolland, A.A. Sayer, S.M. Schneider, C.C. Sieber, E. Topinkova, M. Vandewoude, M. Visser, M. Zamboni, P. Writing Group for the European Working Group on Sarcopenia in Older, and E. the Extended Group for, Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 48 (2019) 16-31.

[11] H.A. Bischoff-Ferrari, J.E. Orav, J.A. Kanis, R. Rizzoli, M. Schlogl, H.B. Staehelin, W.C. Willett, and B. Dawson-Hughes, Comparative performance of current definitions of sarcopenia against the prospective incidence of falls among community-dwelling seniors age 65 and older. Osteoporos Int 26 (2015) 2793-802.

[12] L.A. Schaap, N.M. van Schoor, P. Lips, and M. Visser, Associations of Sarcopenia Definitions, and Their Components, With the Incidence of Recurrent Falling and Fractures: The Longitudinal Aging Study Amsterdam. J Gerontol A Biol Sci Med Sci 73 (2018) 1199-1204.

[13] C. Beaudart, J.M. Bauer, F. Landi, O. Bruyère, J.-Y. Reginster, and M. Hiligsmann, Experts’ preferences for sarcopenia outcomes: A discrete-choice experiment from a working group of the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) in collaboration with the European Union of Geriatric Medicine Society (EUGMS). Aging clinical and experimental research 33 (2021) 1079-1083.

[14] J.E. Morley, A.M. Abbatecola, J.M. Argiles, V. Baracos, J. Bauer, S. Bhasin, T. Cederholm, A.J. Coats, S.R. Cummings, W.J. Evans, K. Fearon, L. Ferrucci, R.A. Fielding, J.M. Guralnik, T.B. Harris, A. Inui, K. Kalantar-Zadeh, B.A. Kirwan, G. Mantovani, M. Muscaritoli, A.B. Newman, F. Rossi-Fanelli, G.M. Rosano, R. Roubenoff, M. Schambelan, G.H. Sokol, T.W. Storer, B. Vellas, S. von Haehling, S.S. Yeh, S.D. Anker, C. Society on Sarcopenia, and W. Wasting Disorders Trialist, Sarcopenia with limited mobility: an international consensus. J Am Med Dir Assoc 12 (2011) 403-9.

[15] L. Dos Santos, E.S. Cyrino, M. Antunes, D.A. Santos, and L.B. Sardinha, Sarcopenia and physical independence in older adults: the independent and synergic role of muscle mass and muscle function. J Cachexia Sarcopenia Muscle 8 (2017) 245-250.

[16] A.E. Bone, N. Hepgul, S. Kon, and M. Maddocks, Sarcopenia and frailty in chronic respiratory disease. Chron Respir Dis 14 (2017) 85-99.

[17] G. Bahat, and B. İlhan, Sarcopenia and the cardiometabolic syndrome: A narrative review. European Geriatric Medicine 7 (2016).

[18] C. Beaudart, E. Biver, J.Y. Reginster, R. Rizzoli, Y. Rolland, I. Bautmans, J. Petermans, S. Gillain, F. Buckinx, N. Dardenne, and O. Bruyere, Validation of the SarQoL(R), a specific health-related quality of life questionnaire for Sarcopenia. J Cachexia Sarcopenia Muscle 8 (2017) 238-244.

[19] S.L. De Buyser, M. Petrovic, Y.E. Taes, K.R. Toye, J.M. Kaufman, B. Lapauw, and S. Goemaere, Validation of the FNIH sarcopenia criteria and SOF frailty index as predictors of long-term mortality in ambulatory older men. Age Ageing 45 (2016) 602-8.

[20] T.Y. Wu, C.K. Liaw, F.C. Chen, K.L. Kuo, W.C. Chie, and R.S. Yang, Sarcopenia Screened With SARC-F Questionnaire Is Associated With Quality of Life and 4-Year Mortality. J Am Med Dir Assoc 17 (2016) 1129-1135.

[21] A.A. Sayer, H. Syddall, H. Martin, H. Patel, D. Baylis, and C. Cooper, The developmental origins of sarcopenia. J Nutr Health Aging 12 (2008) 427-32.

[22] G. Bouchouras, G. Sofianidis, G. Patsika, E. Kellis, and V. Hatzitaki, Women with knee osteoarthritis increase knee muscle co-contraction to perform stand to sit. Aging clinical and experimental research 32 (2020) 655-662.

[23] K.K. Ho, L.C. Lau, W.W. Chau, Q. Poon, K.Y. Chung, and R.M. Wong, End-stage knee osteoarthritis with and without sarcopenia and the effect of knee arthroplasty - a prospective cohort study. BMC Geriatr 21 (2021) 2.

[24] T.L. Jones, M.S. Esa, K.H.C. Li, S.R.G. Krishnan, G.M. Elgallab, M.S. Pearce, D.A. Young, and F.N. Birrell, Osteoporosis, fracture, osteoarthritis & sarcopenia: A systematic review of circulating microRNA association. Bone 152 (2021) 116068.

[25] A. Cieza, K. Causey, K. Kamenov, S.W. Hanson, S. Chatterji, and T. Vos, Global estimates of the need for rehabilitation based on the Global Burden of Disease study 2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 396 (2021) 2006-2017.

[26] G.A. Eby, and K.L. Eby, Rapid recovery from major depression using magnesium treatment. Medical Hypotheses 67 (2006) 362-370.

[27] R.C. Lee, Z. Wang, M. Heo, R. Ross, I. Janssen, and S.B. Heymsfield, Total-body skeletal muscle mass: development and cross-validation of anthropometric prediction models. The American journal of clinical nutrition 72 (2000) 796-803.

[28] S.A. Studenski, K.W. Peters, D.E. Alley, P.M. Cawthon, R.R. McLean, T.B. Harris, L. Ferrucci, J.M. Guralnik, M.S. Fragala, A.M. Kenny, D.P. Kiel, S.B. Kritchevsky, M.D. Shardell, T.T. Dam, and M.T. Vassileva, The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. J Gerontol A Biol Sci Med Sci 69 (2014) 547-58.

[29] S. Tyrovolas, A. Koyanagi, B. Olaya, J.L. Ayuso-Mateos, M. Miret, S. Chatterji, B. Tobiasz-Adamczyk, S. Koskinen, M. Leonardi, and J.M. Haro, Factors associated with skeletal muscle mass, sarcopenia, and sarcopenic obesity in older adults: a multi-continent study. J Cachexia Sarcopenia Muscle 7 (2016) 312-21.

[30] K.D. Allen, and Y.M. Golightly, Epidemiology of osteoarthritis: state of the evidence. Current opinion in rheumatology 27 (2015) 276-283.

[31] R.A. Washburn, E. McAuley, J. Katula, S.L. Mihalko, and R.A. Boileau, The physical activity scale for the elderly (PASE): evidence for validity. Journal of clinical epidemiology 52 (1999) 643-51.

[32] J.N. Katz, L.C. Chang, O. Sangha, A.H. Fossel, and D.W. Bates, Can comorbidity be measured by questionnaire rather than medical record review? Medical care 34 (1996) 73-84.

[33] J. Miles, Tolerance and variance inflation factor. Wiley StatsRef: Statistics Reference Online (2009).

[34] G. Shafiee, A. Keshtkar, A. Soltani, Z. Ahadi, B. Larijani, and R. Heshmat, Prevalence of sarcopenia in the world: a systematic review and meta- analysis of general population studies. J Diabetes Metab Disord 16 (2017) 21.

[35] J.D. Walston, Sarcopenia in older adults. Curr Opin Rheumatol 24 (2012) 623-7.

[36] R.M. Dodds, J.C. Murray, S.M. Robinson, and A.A. Sayer, The identification of probable sarcopenia in early old age based on the SARC-F tool and clinical suspicion: findings from the 1946 British birth cohort. Eur Geriatr Med 11 (2020) 433-441.

[37] M.A. Perez-Sousa, J.D. Pozo-Cruz, C.A. Cano-Gutierrez, M. Izquierdo, and R. Ramirez-Velez, High Prevalence of Probable Sarcopenia in a Representative Sample From Colombia: Implications for Geriatrics in Latin America. J Am Med Dir Assoc 22 (2021) 859-864 e1.

[38] J. Pacifico, M.A.J. Geerlings, E.M. Reijnierse, C. Phassouliotis, W.K. Lim, and A.B. Maier, Prevalence of sarcopenia as a comorbid disease: A systematic review and meta-analysis. Exp Gerontol 131 (2020) 110801.

[39] G. Gong, W. Wan, X. Zhang, Y. Liu, X. Liu, and J. Yin, Correlation between the Charlson comorbidity index and skeletal muscle mass/physical performance in hospitalized older people potentially suffering from sarcopenia. BMC Geriatr 19 (2019) 367.

[40] J.S. Andrews, L.S. Gold, M. Nevitt, P.J. Heagerty, and P.M. Cawthon, Appendicular lean mass, grip strength, and the development of knee osteoarthritis and knee pain among older adults. ACR open rheumatology 3 (2021) 566-572.

[41] K. Maruya, H. Fujita, T. Arai, R. Asahi, Y. Morita, and H. Ishibashi, Sarcopenia and lower limb pain are additively related to motor function and a history of falls and fracture in community-dwelling elderly people. Osteoporos Sarcopenia 5 (2019) 23-26.

[42] A. Escriche-Escuder, I.J. Fuentes-Abolafio, C. Roldán-Jiménez, and A.I. Cuesta-Vargas, Effects of exercise on muscle mass, strength, and physical performance in older adults with sarcopenia: A systematic review and meta-analysis according to the EWGSOP criteria. Experimental Gerontology (2021) 111420.

[43] A.-K.R. Osthoff, C.B. Juhl, K. Knittle, H. Dagfinrud, E. Hurkmans, J. Braun, J. Schoones, T.P.V. Vlieland, and K. Niedermann, Effects of exercise and physical activity promotion: meta-analysis informing the 2018 EULAR recommendations for physical activity in people with rheumatoid arthritis, spondyloarthritis and hip/knee osteoarthritis. RMD open 4 (2018) e000713.

[44] L.J. Geneen, R.A. Moore, C. Clarke, D. Martin, L.A. Colvin, and B.H. Smith, Physical activity and exercise for chronic pain in adults: an overview of Cochrane Reviews. Cochrane Database of Systematic Reviews (2017).

[45] R.C. Lee, Z. Wang, M. Heo, R. Ross, I. Janssen, and S.B. Heymsfield, Total-body skeletal muscle mass: development and cross-validation of anthropometric prediction models. The American journal of clinical nutrition 72 (2000) 796-803.