

# Sarcopenia: A Time for Action. An SCWD Position Paper

Juergen Bauer<sup>1</sup>, John E. Morley<sup>2\*</sup>, Annemie M.W.J. Schols<sup>3</sup>, Luigi Ferrucci<sup>4</sup>, Alfonso J. Cruz-Jentoft<sup>5</sup>, Elsa Dent<sup>6,7</sup>, Vickie E. Baracos<sup>8</sup>, Jeffrey A. Crawford<sup>9</sup>, Wolfram Doehner<sup>10,11,12</sup>, Steven B. Heymsfield<sup>13</sup>, Aminah Jatoi<sup>14</sup>, Kamyar Kalantar-Zadeh<sup>15</sup>, Mitja Lainscak<sup>16</sup>, Francesco Landi<sup>17,18</sup>, Alessandro Laviano<sup>19</sup>, Michelangelo Mancuso<sup>20</sup>, Maurizio Muscaritoli<sup>19</sup>, Carla M. Prado<sup>21</sup>, Florian Strasser<sup>22</sup>, Stephan von Haehling<sup>23,24</sup>, Andrew J.S. Coats<sup>25</sup> & Stefan D. Anker<sup>10,11,12</sup>

<sup>1</sup>Center for Geriatric Medicine, Heidelberg University, Heidelberg, Germany, <sup>2</sup>Division of Geriatric Medicine, Saint Louis University School of Medicine, St. Louis, USA, <sup>3</sup>Department of Respiratory Medicine, Research School NUTRIM, Maastricht University Medical Center, Maastricht, The Netherlands, <sup>4</sup>Longitudinal Studies Section, Translational Gerontology Branch, National Institute on Aging, National Institutes of Health, Baltimore, MD, USA, <sup>5</sup>Servicio de Geriatria, Hospital Universitario Ramón y Cajal (IRYCIS), Madrid, Spain, <sup>6</sup>Torrens University Australia, Adelaide, Australia, <sup>7</sup>Baker Heart and Diabetes Institute, Melbourne, Australia, <sup>8</sup>Division of Palliative Care Medicine, Department of Oncology, University of Alberta, Edmonton, AB, Canada, <sup>9</sup>Duke Cancer Institute, Duke University, Durham, NC, USA, <sup>10</sup>BIH Center for Regenerative Therapies (BCRT), Charité Universitätsmedizin Berlin, Berlin, Germany, <sup>11</sup>Department of Cardiology (Campus Virchow-Klinikum), Charité-Universitätsmedizin Berlin, Berlin, Germany, <sup>12</sup>German Center for Cardiovascular Research (DZHK), partner site Berlin, Germany, <sup>13</sup>Pennington Biomedical Research Center, LSU System, Baton Rouge, LA, USA, <sup>14</sup>Department of Oncology, Mayo Clinic, Rochester, MN, USA, <sup>15</sup>Division of Nephrology and Hypertension, University of California Irvine Medical Center, Orange, CA, USA, <sup>16</sup>Division of Cardiology, General Hospital Murska Sobota, Murska Sobota, Slovenia, <sup>17</sup>Institute of Internal Medicine and Geriatrics, Università Cattolica del Sacro Cuore, Rome, Italy, <sup>18</sup>Fondazione Policlinico Universitario 'Agostino Gemelli' IRCCS, Rome, Italy, <sup>19</sup>Department of Translational and Precision Medicine, Sapienza University, Rome, Italy, <sup>20</sup>Department of Clinical and Experimental Medicine, Neurological Institute, University of Pisa, Pisa, Italy, <sup>21</sup>Human Nutrition Research Unit, Department of Agricultural, Food and Nutritional Science, University of Alberta, Edmonton, AB, Canada, <sup>22</sup>Department of Medical Oncology and Hematology, Cantonal Hospital, St. Gallen, Switzerland, <sup>23</sup>Department of Cardiology and Pneumology, University Medicine Goettingen (UMG), Goettingen, Germany, <sup>24</sup>German Center for Cardiovascular Research (DZHK), partner site Göttingen, Germany, <sup>25</sup>Department of Cardiology, IRCCS San Raffaele Pisana, Rome, Italy

## Abstract

The term sarcopenia was introduced in 1988. The original definition was a “muscle loss” of the appendicular muscle mass in the older people as measured by dual energy x-ray absorptiometry (DXA). In 2010, the definition was altered to be low muscle mass together with low muscle function and this was agreed upon as reported in a number of consensus papers. The Society of Sarcopenia, Cachexia and Wasting Disorders supports the recommendations of more recent consensus conferences, i.e. that rapid screening, such as with the SARC-F questionnaire, should be utilized with a formal diagnosis being made by measuring grip strength or chair stand together with DXA estimation of appendicular muscle mass (indexed for height<sup>2</sup>). Assessments of the utility of ultrasound and creatine dilution techniques are ongoing. Use of ultrasound may not be easily reproducible. Primary sarcopenia is aging associated (mediated) loss of muscle mass. Secondary sarcopenia (or disease-related sarcopenia) has predominantly focused on loss of muscle mass without the emphasis on muscle function. Diseases that can cause muscle wasting (i.e. secondary sarcopenia) include malignant cancer, COPD, heart failure, and renal failure and others. Management of sarcopenia should consist of resistance exercise in combination with a protein intake of 1 to 1.5 g/kg/day. There is insufficient evidence that vitamin D and anabolic steroids are beneficial. These recommendations apply to both primary (age-related) sarcopenia and secondary (disease related) sarcopenia. Secondary sarcopenia also needs appropriate treatment of the underlying disease. It is important that primary care health professionals become aware of and make the diagnosis of age-related and disease-related sarcopenia. It is important to address the risk factors for sarcopenia, particularly low physical activity and sedentary behavior in the general population, using a life-long approach. There is a need for more clinical research into the appropriate measurement for muscle mass and the management of sarcopenia. Accordingly, this position statement provides recommendations on the management of sarcopenia and how to progress the knowledge and recognition of sarcopenia.

**Keywords** Sarcopenia; Cachexia; Geriatric assessment; Muscle; Skeletal; Muscle strength

\*Correspondence to: John E. Morley, Division of Geriatric Medicine, Saint Louis University School of Medicine, 1402 S. Grand Blvd., M238. St. Louis, MO 63104, USA. Email: john.morley@health.slu.edu

The term, sarcopenia, was coined in 1988 by Irwin Rosenberg at a meeting in Albuquerque, New Mexico, to refer to muscle wasting of the older people<sup>1</sup>. Its etymological origins are two

Greek words: *sarx* for flesh and *penia* for reduced or deficiency. Baumgartner *et al.*<sup>2</sup> proposed an operational definition of sarcopenia in 1998. Utilizing dual energy X-ray

absorptiometry (DXA) to measure lean soft tissue, the authors defined sarcopenia as being  $<2$  SDs of appendicular muscle mass (ASM, kg) per height squared ( $m^2$ ) below the mean of a young reference group. Using this criterion, Baumgartner *et al.* showed that the prevalence and the severity of sarcopenia significantly increased with age and that it was associated with physical disability. In 2002, Janssen *et al.*,<sup>3</sup> using bioelectrical impedance analysis (BIA), showed that in the Third National Health and Nutrition Examination Survey (NHANES III), functional impairment was three times as likely in persons with an estimated lean mass below 2 SDs of the mean. Baumgartner *et al.*<sup>4</sup> found that in older persons with obesity, those who had lost muscle mass had worse outcomes than those who had maintained their muscle mass. They coined the term ‘sarcopenic obesity’ for this condition. By the early 2000s, it was recognized that there are numerous causes of age-related sarcopenia, including loss of motor units innervating muscle, systemic inflammation, oxidative stress, decline in anabolic hormones, and the ‘anorexia of aging’ coupled with a decrease in physical activity<sup>5,6</sup> (Figure 1). At this stage, it was recognized that there were both primary sarcopenia (age related) and secondary sarcopenia (disease related, as with diabetes mellitus, cancer, chronic obstructive pulmonary disease, or heart failure).

## Evolving definition of sarcopenia

### Primary sarcopenia (sarcopenia of aging)

In 2010, the European Working Group on Sarcopenia for Older Persons<sup>7</sup> recommended a new operational definition of sarcopenia of aging, i.e. the presence of low muscle mass together with low muscle function (strength or performance). Over the last decade, numerous other consensus groups have agreed to this revision to the meaning of sarcopenia of aging.<sup>8–12</sup> However, these groups all used different cut-offs to

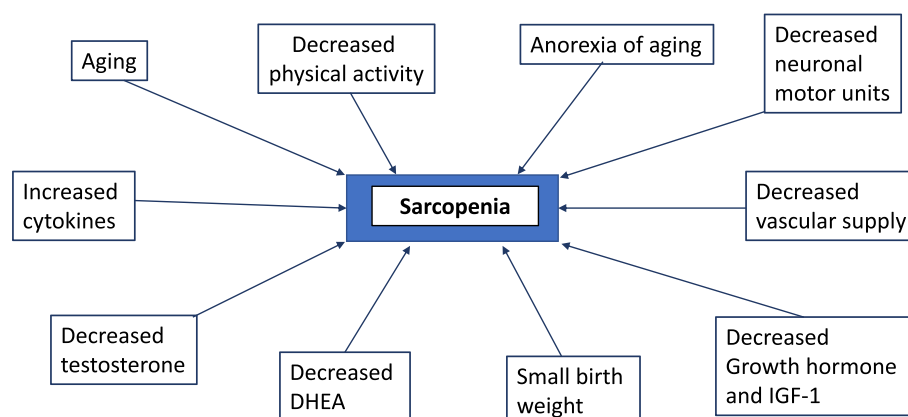
define sarcopenia of aging, highlighting the fact that different cut-offs are necessary for different ethnic groups.<sup>12</sup>

Towards the end of last year, two consensus articles on sarcopenia of aging were published. One was an update by the European Working Group on Sarcopenia (EWGSOP2),<sup>13</sup> and the other was on the management of sarcopenia of aging by the International Clinical Practice Guidelines for Sarcopenia (ICFSR).<sup>14</sup> The EWGSOP2 requires low muscle strength as a key characteristic of low muscle quality and the presence of low muscle quantity to confirm the diagnosis. If a person also has functional impairment, confirmed with a physical performance measure,<sup>15</sup> this is characterized as severe sarcopenia. The authors recommended measuring muscle strength with either grip strength or the chair stand test. Muscle mass can be measured by DXA, magnetic resonance imaging, or computed tomography. Either gait speed, the short physical performance battery (SPPB), the Timed Up and Go test, or the 400-m-walk can be used for the assessment of physical performance.

Recognizing the limited time available during a typical visit to a health care professional, the EWGSOP2 also suggested that case finding should be used to identify older persons at risk for sarcopenia. They recommended the use of clinical symptoms usually associated with sarcopenia or the SARC-F (Figure 2), a questionnaire with five questions, which has high specificity, albeit low sensitivity, to identify persons with sarcopenia.<sup>16–20</sup> The SARC-F has been translated into multiple languages. The SARC-F is also recommended by the ICFSR for screening.<sup>14</sup> The specificity of the SARC-F can be improved by measuring calf circumference as well.<sup>21</sup> The Ishii screening test (age, grip strength, and calf circumference) is recommended as an alternative screening test.<sup>22,23</sup> However, this already includes grip strength, which is a core measure of sarcopenia.

While BIA was not strongly supported by the EWGSOP2, to measure muscle mass, they recognize that its portability, affordability, and availability make BIA a feasible tool to estimate muscle mass in many care settings. Ultrasound of

**Figure 1** The factors involved in the pathogenesis of primary (age related) sarcopenia.



**Figure 2** SARC-F questionnaire (includes scoring).

Component	Question	Scoring
Strength	How much difficulty do you have in lifting and carrying 10 pounds?	None = 0 Some = 1 A lot or unable = 2
Assistance in walking	How much difficulty do you have walking across a room?	None = 0 Some = 1 A lot, use aids, or unable = 2
Rise from a chair	How much difficulty do you have transferring from a chair or bed?	None = 0 Some = 1 A lot or unable without help = 2
Climb stairs	How much difficulty do you have climbing a flight of 10 stairs?	None = 0 Some = 1 A lot or unable = 2
Falls	How many times have you fallen in the past year?	None = 0 1 – 3 falls = 1 ≥ 4 falls = 2

muscle such as the quadriceps is emerging as a potential tool to measure muscle quantity and, because it excludes intermuscular adipose tissue from the measurement, also muscle quality<sup>24,25</sup>; a protocol for using ultrasounds in sarcopenia has recently been proposed by the European Geriatric Medicine Society.<sup>26</sup>

There is increasing evidence that creatine dilution, implemented by ingesting a dose of the deuterium labelled isotope, may also offer an accurate approach for measuring muscle mass.<sup>27,28</sup> Studies so far suggest creatine dilution estimates of muscle mass may have good correlations with functional outcomes.<sup>27,28</sup> Nonetheless, its relevance and practicality in clinical settings remain to be determined.

The ICFSR consensus made similar conditional recommendations utilizing the SARC-F for screening and applying either the original EWGSOP or Foundation for NIH (FNIH) diagnostic criteria.<sup>14</sup>

### Secondary sarcopenia

Malignant disease has been the most studied secondary sarcopenia, and international consensus definitions specific to cancer sarcopenia<sup>29</sup> are predicated on disease specific outcomes: mortality, complications of cancer surgery, and chemotherapy toxicity. Whether this secondary sarcopenia should be considered early cachexia or sarcopenia remains controversial,<sup>30</sup> but it is becoming clearer that sarcopenia is only one of the different features of muscle changes during cancer cachexia. Owing to the prevalent use of computed tomography imaging in cancer diagnosis and follow-up, secondary analysis of oncologic imaging for skeletal muscle cross-sectional areas or volumes is the current standard for the quantification of muscle mass in this domain.

There are several points of relevance regarding age-related and disease-related loss of muscle mass. Loss of muscle mass with age occurs in a continuous fashion after reaching peak

muscle mass in young adulthood (at about 30 years of age). A variety of longitudinal observational studies provide information on the rate of muscle loss per decade. The percentage loss of ASM per 10 years is of the order of ~5% in men and is usually reported to be somewhat lower in women. Chronic illness-related muscle loss is also progressive; however, these are non-linear and of a considerably greater magnitude than the values seen in aging. For example, cancers of advanced stage induce muscle loss over time that take an exponential course<sup>31,32</sup> with increasing intensity according to the disease progression, varying from 2% per 100 days to 15% per 100 days. Total cumulative loss in 12 months in colon cancer patients was 15.6%, equivalent to circa 30 years of aging<sup>31</sup>; this is partially disease-related but also in part a consequence of cancer surgery or systemic antineoplastic therapies which induce punctate short-term losses. Acute illness requiring hospitalization is associated with even higher intensity of muscle loss than in cancer. In elective hip replacement surgery during an average of  $5.6 \pm 0.3$  days of hospitalization, associated with significant decline in quadriceps ( $-3.4 \pm 1.0\%$ ) and thigh muscle cross-sectional area (CSA) ( $-4.2 \pm 1.1\%$ ) in the non-operated leg ( $P < 0.05$ ) aging.<sup>33,34</sup> This could be in part due to bed rest as 5 days of one-legged knee immobilization using a full leg cast resulted in decline of quadriceps muscle CSA from baseline of  $3.5 \pm 0.5\%$  ( $P < 0.0001$ ). Acute sarcopenia secondary to hospitalization or chronic disease exacerbations may be partially recoverable or may lead to heightened risk of developing sarcopenia at a young age.<sup>35</sup>

## Management of sarcopenia

For the management of sarcopenia, there is a strong recommendation that individuals with sarcopenia should be enrolled in a resistance exercise programme. There is a reasonable

amount of evidence that resistance exercise will increase both muscle mass and strength.<sup>36–38</sup> The use of a protein rich diet (1 to 1.5 g/day) or protein supplementation received a conditional recommendation based on a small amount of evidence and a previous consensus conference.<sup>39–41</sup> Higher doses of protein (up to 2 g/day) may be appropriate in persons with severe illness or injury or when there is evidence of a pro-inflammatory/catabolic state.<sup>39,40</sup>  $\beta$ -hydroxy  $\beta$ -methylbutyrate (HMB) has been shown to improve muscle mass and to preserve muscle strength and function in older people with sarcopenia or frailty.<sup>42</sup> Vitamin D supplementation specifically for sarcopenia was found to have insufficient evidence, though there is evidence that persons with low vitamin D levels may improve their strength with vitamin D supplementation.<sup>43</sup> Similarly, while testosterone can increase muscle mass and strength in older individuals and a meta-analysis has confirmed its safety,<sup>44–47</sup> the lack of evidence in persons with sarcopenia did not lead to its integration into these recommendations. Preliminary data with anamorelin, a growth hormone secretagogue receptor type 1 (ghrelin receptor) agonist that increases muscle mass but not strength,<sup>48,49</sup> and anti-myostatin antibodies<sup>49–53</sup> were considered insufficient to make recommendations in favour of their use.

## Recommendations

Recently, an ICD-10-CM code for sarcopenia as a disease has become available allowing physicians to formally include sarcopenia in the list of diagnosis that can be used and funded.<sup>54–56</sup> Based on the available evidence and the two recent consensus recommendations, the task force of the Society for Sarcopenia, Cachexia and Wasting Disorders recommends for clinical application the following:

- 1 Health care professionals are encouraged to screen for sarcopenia using simple screening tools such as the SARC-F.
- 2 Where available and feasible, physicians should make a formal diagnosis of sarcopenia utilizing grip strength or chair stand and—if available—a measurement of fat-free mass. At present, we recommend ASM per height squared estimated by DXA, but recognize CT, BIA, ultrasound, or creatine dilution techniques may be as good or more accurate approaches for estimating muscle mass in the future.
- 3 Resistance exercise should be prescribed for any older person suspected of having sarcopenia both for secondary prevention and/or treatment.
- 4 A protein intake of 1 to 1.5 g/kg/day in conjunction with physical exercise seems reasonable for a person with sarcopenia.
- 5 At present, there is insufficient evidence that vitamin D, anabolic steroids, or newer pharmacological agents should be used to treat sarcopenia.

- 6 These recommendations apply to both primary (age related) sarcopenia and secondary (disease related) sarcopenia. In the second, treating the disease(s) related to sarcopenia is also essential.

Consensus documents on sarcopenia in older persons (EWGSOP and ICSFR) as well as those for sarcopenia in chronic disease<sup>29</sup> have something in common: they intend to put sarcopenia in the clinical frontline. It is time that health professionals are educated in the diagnosis and management of sarcopenia and are encouraged to screen for sarcopenia and educate their patients on primary and secondary prevention of sarcopenia.

To progress the knowledge and recognition of sarcopenia, the task force recommends the following actions:

- 1 promotion of sarcopenia measurement in epidemiological studies of older adults, including in studies of chronic disease, and also in other disease or organ oriented specialties;
- 2 collaboration with health care policy makers and health care providers regarding medical claims using the ICD diagnosis code for sarcopenia;
- 3 development and assessment of new treatments for sarcopenia in individuals with either primary or secondary sarcopenia;
- 4 advocating common standards in the quality of clinical trials for sarcopenia, including consistent outcome measurements and recognition of such measures by regulatory agencies;
- 5 address the risk factors for sarcopenia, particularly low physical activity and sedentary behaviour in the general population, using a life-long approach;
- 6 explore the impact of targeted nutritional approaches to countermeasure muscle loss alone and in a multimodal approach to maximize anabolic potential (e.g. exercise and anabolic therapy); and
- 7 identify the pathophysiological pathways leading to sarcopenia.

## Acknowledgements

The authors of this manuscript certify that they comply with the ethical guidelines for editorship and publishing in the *Journal of Cachexia, Sarcopenia and Muscle*.<sup>57</sup>

## Conflict of interest

A.J.S.C. has received speaker fees and/or honoraria from Astra Zeneca, Menarini, Novartis, Nutricia, Servier, Vifor,

Actimed, CVRx, Enopace, Faraday, Gore, Respicardia, Stealth Peptides, and V-Wave. A.J.C.-J. has received speaker fees from Abbott Nutrition, Fresenius, Nestlé, Nutricia, and Sanofi-Aventis; is a member of advisory boards for Abbott Nutrition, Nestlé, and Pfizer; and has worked on research projects with Abbott Nutrition and Nutricia. J.C. discloses the following: consultant/independent contractor: Amgen, AstraZeneca, Coherus, Enzychem, Merck, and Pfizer;

grant/research support: AstraZeneca, Genentech, and Helsinn; Chair/DSMB member: Beyond Spring. S.H. serves in Tanita and Medifast Medical Advisory Boards. A.L. has received honoraria for independent lectures at educational events organized by nutrition industry. He is a member of the scientific advisory board of Smartfish.

## References

- Rosenberg IH. Sarcopenia: origins and clinical relevance. *J Nutr* 1997;**127**( Suppl):990S–991S.
- Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, et al. Epidemiology of sarcopenia among the elderly in New Mexico. *Am J Epidemiol* 1998;**147**:755–763.
- Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. *J Am Geriatr Soc* 2002;**50**:889–896.
- Baumgartner RN, Wayne SJ, Waters DL, Janssen I, Gallagher D, Morley JE. Sarcopenic obesity predicts instrumental activities of daily living disability in the elderly. *Obes Res* 2004;**12**:1995–2004.
- Morley JE, Baumgartner RN, Roubenoff R, Mayer J, Nair KS. Sarcopenia. *J Lab Clin Med* 2001;**137**:231–243.
- Clark BC, Manini TM. Sarcopenia ≠ dynapenia. *J Gerontol A Biol Sci Med Sci* 2008;**63**:829–834.
- Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. *Age Ageing* 2010;**39**:412–423.
- Morley JE, Abbatecola AM, Argiles JM, Baracos V, Bauer J, Bhasin S, et al. Sarcopenia with limited mobility: an international consensus. *J Am Med Dir Assoc* 2011;**12**:403–409.
- Fielding RA, Vellas B, Evans WJ, Bhasin S, Morley JE, Newman AB, et al. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. *J Am Med Dir Assoc* 2011;**12**:249–256.
- Muscaritoli M, Anker SD, Argiles J, Aversa Z, Bauer JM, Biolo G, et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) “cachexia-anorexia in chronic wasting diseases” and “nutrition in geriatrics”. *Clin Nutr* 2010;**29**:154–159.
- Dam TT, Peters KW, Fragala M, Cawthon PM, Harris TB, McLean R, et al. An evidence-based comparison of operational criteria for the presence of sarcopenia. *J Gerontol A Biol Sci Med Sci* 2014;**69**:584–590.
- Chen LK, Liu LK, Woo J, Assantachai P, Auyeung TW, Bahyah KS, et al. Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. *J Am Med Dir Assoc* 2014;**15**:95–101.
- Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyere O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* 2019;**48**:16–31.
- Dent E, Morley JE, Cruz-Jentoft AJ, Arai H, Kritchevsky SB, Guralnik J, et al. International Clinical Practice Guidelines for Sarcopenia (ICFSR): screening, diagnosis and management. *J Nutr Health Aging* 2018;**22**:1148–1161.
- Cawthon PM. Assessment of lean mass and physical performance in sarcopenia. *J Clin Densitom* 2015;**18**:467–471.
- Malmstrom TK, Miller DK, Simonsick EM, Ferrucci L, Morley JE. SARC-F: a symptom score to predict persons with sarcopenia at risk for poor functional outcomes. *J Cachexia Sarcopenia Muscle* 2016;**7**:28–36.
- Woo J, Leung J, Morley JE. Defining sarcopenia in terms of incident adverse outcomes. *J Am Med Dir Assoc* 2015;**16**:247–252.
- Bahat G, Yilmaz O, Kiliç C, Oren MM, Karan MA. Performance of SARC-F in regard to sarcopenia definitions, muscle mass and functional measures. *J Nutr Health Aging* 2018;**22**:898–903.
- Ida S, Kaneko R, Murata K. SARC-F for screening among older adults: a meta-analysis of screening test accuracy. *J Am Med Dir Assoc* 2018;**19**:685–689.
- Kim S, Kim M, Won CW. Validation of the Korean version of the SARC-F questionnaire to assess sarcopenia: Korean Frailty and Aging Cohort Study. *J Am Med Dir Assoc* 2018;**19**:40–45.e1.
- Barbosa-Silva TG, Menezes AM, Bielemann RM, Malmstrom TK, Gonzalez MC. Grupo de Estudos em Composicao corporal e Nutricao (COCONUT) Enhancing SARC-F: Improving sarcopenia screening in the clinical practice. *J Am Med Dir Assoc* 2016;**17**:1136–1141.
- Locquet M, Beaudart C, Reginster JY, Petermans J, Bruyere O. Comparison of the performance of five screening methods for sarcopenia. *Clin Epidemiol* 2017;**10**:71–82.
- Ishii S, Tanaka T, Shibasaki K, Ouchi Y, Kikutani T, Higashiguchi T, et al. Development of a simple screening test for sarcopenia in older adults. *Geriatr Gerontol Int* 2014;**14**:93–101.
- Ticinesi A, Meschi T, Narici MV, Lauretani F, Maggio M. Muscle ultrasound and sarcopenia in older individuals: a clinical perspective. *J Am Med Dir Assoc* 2017;**18**:290–300.
- Nijholt W, Scafoglieri A, Jager-Wittenaar H, Hobbelen JSM, van der Schans CP. The reliability and validity of ultrasound to quantify muscles in older adults: a systematic review. *J Cachexia Sarcopenia Muscle* 2017;**8**:702–712.
- Perkisas S, Baudry S, Bauer J, Beckwee D, De Cock A-M, Hobbelen H, et al. Application of ultrasound for muscle assessment in sarcopenia: towards standardized measurements. *Eur Geriatr Med* 2018;**9**:739–757.
- Shankaran M, Czerwieńiec G, Fessler C, Wong PA, Killion S, Turner SM, et al. Dilution of oral D3-creatine to measure creatine pool size and estimate skeletal muscle mass: development of a correction algorithm. *J Cachexia Sarcopenia Muscle* 2018;**9**:540–546.
- Cawthon PM, Orwoll ES, Peters KE, Ensrud KE, Cauley JA, Kado DM, et al. Strong relation between muscle mass determined by D3-creatine dilution. Physical performance and incidence of falls and mobility limitations I a prospective cohort of older men. *J Gerontol A Biol Sci Med Sci* 2018;Jun 12; <https://doi.org/10.1093/Gerona/gly129> Epub ahead of print.
- Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol* 2011;**12**:489–495.
- Anker SD, Coats AJ, Morley JE, Rosano G, Bernabei R, von Haehling S, et al. Muscle wasting disease: a proposal for a new disease classification. *J Cachexia Sarcopenia Muscle* 2014;**5**:1–3.
- Muscaritoli M, Lucia S, Molfino A, Cederholm T, Rossi Fanelli F. Muscle atrophy in aging and chronic diseases: is it sarcopenia or cachexia? *Intern Emerg Med* 2013;**8**:553–560.
- Lieffers JR, Mourtzakis M, Hall KD, McCargar LJ, Prado CM, Baracos VE. A



- viscerally driven cachexia syndrome in patients with advanced colorectal cancer: contributions of organ and tumor mass to whole-body energy demands. *Am J Clin Nutr* 2009;**89**:1173–1179.
33. Prado CM, Sawyer MB, Ghosh S, Lieffers JR, Esfandiari N, Antoun S, et al. Central tenet of cancer cachexia therapy: do patients with advanced cancer have exploitable anabolic potential? *Am J Clin Nutr* 2013;**98**:1012–1019.
  34. Kouw IWK, Groen BBL, Smeets JSJ, Kramer IF, van Kranenburg JMX, Nilwik R, et al. One week of hospitalization following elective hip surgery induces substantial muscle atrophy in older patients. *J Am Med Dir Assoc* 2019;**20**:35–42.
  35. Wall BT, Dirks ML, Snijders T, Senden JM, Dolmans J, van Loon LJ. Substantial skeletal muscle loss occurs during only 5 days of disuse. *Acta Physiol (Oxf)* 2014;**210**:600–611.
  36. Vlietstra L, Hendrickx W, Waters DL. Exercise interventions in healthy older adults with sarcopenia: a systematic review and meta-analysis. *Australas J Ageing* 2018;**37**:169–183.
  37. Csapo R, Alegre LM. Effects of resistance training with moderate vs heavy loads on muscle mass and strength in the elderly: a meta-analysis. *Scand J Med Sci Sports* 2016;**26**:995–1006.
  38. Roth SM, Ferrell RF, Hurley BF. Strength training for the prevention and treatment of sarcopenia. *J Nutr Health Aging* 2000;**4**:143–155.
  39. Bauer J, Biolo G, Cederholm T, Cesari M, Cruz-Jentoft AJ, Morley JE, et al. Evidence-based recommendations for optimal dietary protein intake in older people: a position paper from the PROT-AGE study group. *J Am Med Dir Assoc* 2013;**14**:542–559.
  40. Bauer JM, Verlaan S, Bautmans I, Brandt K, Donini LM, Maggio M, et al. Effects of a vitamin D and leucine-enriched whey protein nutritional supplement on measures of sarcopenia in older adults, the PROVIDE study: a randomized, double-blind, placebo-controlled trial. *J Am Med Dir Assoc* 2015;**16**:740–747.
  41. Liao CD, Tsauo JY, Wu YT, Cheng CP, Chen HC, Huang YC, et al. Effects of protein supplementation combined with resistance exercise on body composition and physical function in older adults: a systematic review and meta-analysis. *Am J Clin Nutr* 2017;**106**:1078–1091.
  42. Bear DE, Langan A, Dimidi E, Wandrag L, Harridge SDR, Hart N, et al.  $\beta$ -Hydroxy- $\beta$ -methylbutyrate and its impact on skeletal muscle mass and physical function in clinical practice: a systematic review and meta-analysis. *Am J Nutr* 2019;**109**:119–1132.
  43. Beaudart C, Buckinx F, Rabenda V, Gillain S, Cavalier E, Slomian J, et al. The effects of vitamin D on skeletal muscle strength, muscle mass, and muscle power: a systematic review and meta-analysis of randomized controlled trials. *J Clin Endocrinol Metab* 2014;**99**:4336–4345.
  44. Skinner JW, Otsel DM, Bowser A, Nargi D, Agarwal S, Peterson MD, et al. Muscular responses to testosterone replacement vary by administration route: a systematic review and meta-analysis. *J Cachexia Sarcopenia Muscle* 2018;**9**:465–481.
  45. Ottenbacher KJ, Ottenbacher ME, Ottenbacher AJ, Acha aA, Ostir GV. Androgen treatment and muscle strength in elderly men: a meta-analysis. *J Am Geriatr Soc* 2006;**54**:1666–1673.
  46. Albert SG, Morley JE. Testosterone therapy, association with age, initiation and mode of therapy with cardiovascular events: a systematic review. *Clin Endocrinol (Oxf)* 2016;**85**:436–443.
  47. de Spiegeleer A, Beckwe D, Bautmans I, Petrovic M. Sarcopenia Guidelines Development Group for the Belgian Society of Gerontology and Geriatrics (BSGG). Pharmacological interventions to improve muscle mass, muscle strength and physical performance in older people: an umbrella review of systematic reviews and meta-analyses. *Drugs Aging* 2018;**35**:719–734.
  48. Temel JS, Abernethy AP, Currow DC, Friend J, Duus EM, Yan Y, et al. Anamorelin in patients with non-small-cell lung cancer and cachexia (ROMANA 1 and ROMANA 2): results from two randomised, double-blind, phase 3 trials. *Lancet Oncol* 2016;**17**:519–531.
  49. Anker SD, Coats AJ, Morley JE. Evidence for partial pharmaceutical reversal of the cancer anorexia-cachexia syndrome: the case of anamorelin. *J Cachexia Sarcopenia Muscle* 2015;**6**:275–277.
  50. Morley JE, von Haehling S, Anker SD. Are we closer to having drugs to treat muscle wasting disease? *J Cachexia Sarcopenia Muscle* 2014;**5**:83–87.
  51. Polkey MI, Praestgaard J, Berwick A, Franssen FME, Singh D, Steiner MD, et al. Activin type II receptor blockade for treatment of muscle depletion in COPD: a randomized trial. *Am J Respir Crit Care Med* 2018; Aug 10; <https://doi.org/10.1164/rccm.201802-0286OC> [Epub ahead of print].
  52. Morley JE. Pharmacologic options for the treatment of sarcopenia. *Calcif Tissue Int* 2016;**98**:319–333.
  53. Vellas B, Fielding R, Bhasin S, Cerreta F, Goodpaster B, Guralnik JM, et al. Sarcopenia trials in specific diseases: report by the International Conference on Frailty and Sarcopenia Research Task Force. *J Frailty Aging* 2016;**5**:194–200.
  54. Anker SD, Morley JE, von Haehling S. Welcome to the ICD-10 code for sarcopenia. *J Cachexia Sarcopenia Muscle* 2016;**7**:512–514.
  55. Cao L, Morley JE. Sarcopenia is recognized as an independent condition by an International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10-CM) code. *J Am Med Dir Assoc* 2016;**17**:675–677.
  56. Vellas B, Fielding RA, Bens C, Bernabei R, Cawthon PM, Cederholm T, et al. Implications of ICD-10 for sarcopenia clinical practice and clinical trials: report by the International Conference on Frailty and Sarcopenia Research Task Force. *J Frailty Aging* 2018;**7**:2–9.
  57. Von Haehling S, Morley JE, Coats AJS, Anker SD. Ethical guidelines for publishing in the *Journal of Cachexia, Sarcopenia and Muscle*; Update 2017. *J Cachexia Sarcopenia Muscle* 2017;**8**:1081–1083.