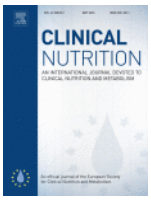

Sarcopenic obesity research perspectives outlined by the sarcopenic obesity global leadership initiative (SOGLI) – Proceedings from the SOGLI consortium meeting in rome November 2022

Gortan Cappellari G, Guillet C, Poggiogalle E, Ballesteros Pomar MD, Batsis JA, Boirie Y, Breton I, Frara S, Genton L, Gepner Y, Gonzalez MC, Heymsfield SB, Kiesswetter E, Laviano A, Prado CM, Santini F, Serlie MJ, Siervo M, Villareal DT, Volkert D, Voortman T, Weijs PJ, Zamboni M, Bischoff SC, Busetto L, Cederholm T, Barazzoni R, Donini LM, Anja Bosy-Westphal, Amelia Brunani, Paolo Capodaglio, Dario Coletti, Elisabetta Ferretti, Francesco Frigerio, Andrea Giustina, Andrea Lenzi, Elisabetta Marini, Silvia Migliaccio, Marianna Minnetti, Edoardo Mocini, Tatiana Moro, Maurizio Muscaritoli, Philippe Noirez, Antonio Paoli, Mariangela Rondanelli, Auralia Rughetti, Josje D Schoufour, Anna Skalska, Eva Topinkova, Hidekata Wakabayashi, Jianchun Yu

PII: S0261561423000547

DOI: https://doi.org/10.1016/j.clnu.2023.02.018

Published in: Clinical Nutrition

Received Date: 17 February 2023
Accepted Date: 17 February 2023
Available online: 24 February 2023

Please cite this article as: Gortan Cappellari, Gianluca et al. “Sarcopenic obesity research perspectives outlined by the sarcopenic obesity global leadership initiative (SOGLI) - Proceedings from the SOGLI consortium meeting in Rome November 2022.” *Clinical nutrition (Edinburgh, Scotland)* vol. 42,5 (2023): 687-699.

Clinical Nutrition

Sarcopenic obesity research perspectives outlined by the Sarcopenic Obesity Global Leadership Initiative (SOGLI) – proceedings from the SOGLI Consortium meeting in Rome November 2022

--Manuscript Draft--

Manuscript Number:	YCLNU-D-23-00353
Article Type:	Opinion Paper
Keywords:	sarcopenic obesity; obesity; sarcopenia; consensus
Corresponding Author:	Lorenzo M Donini Roma, Italy Italy
First Author:	Gianluca Gortan Cappellari
Order of Authors:	Gianluca Gortan Cappellari
	Christelle Guillet
	Eleonora Poggiogalle
	Maria D. Ballesteros Pomar
	John A. Bastsis
	Yves Boirie
	Irene Breton
	Stefano Frara
	Laurence Genton
	Yftach Gepner
	Maria Cristina Gonzalez
	Steven Heymsfield
	Eva Kiesswetter
	Alessandro Laviano
	Carla M. Prado
	Ferruccio Santini
	Mireille J. Serlie
	Mario Siervo
	Dennis T. Villareal
	Dorothee Volkert
	Trudy Voortman
	Peter J.M. Weijs
	Mauro Zamboni
	Stephan C. Bischoff
	Luca Busetto
	Tommy Cederholm
	Rocco Barazzoni
	Lorenzo Donini

	Anja Bosy-Westphal
	Amelia Brunani
	Paolo Capodaglio
	Dario Coletti
	Elisabetta Ferretti
	Francesco Frigerio
	Andrea Giustina
	Andrea Lenzi
	Elisabetta Marini
	Silvia Migliaccio
	Marianna Minnetti
	Edoardo Mocini
	Tatiana Moro
	Maurizio Muscaritoli
	Philippe Noirez
	Antonio Paoli
	Mariangela Rondanelli
	Aurelia Rughetti
	Josje D. Schoufour
	Anna Skalska
	Eva Topinkova
	Hidekata Wakabayashi
	Jianchun Yu
Abstract:	The European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of Obesity (EASO) launched the Sarcopenic Obesity Global Leadership Initiative (SOGLI) to reach expert consensus on a definition and diagnostic criteria for Sarcopenic Obesity (SO).The present paper de scribes the proceeding of the Sarcopenic Obesity Global Leadership Initiative (SOGLI) meeting that was held on November 25th and 26th, 2022 in Rome, Italy. This consortium involved the participation of 50 researchers from different geographic regions and countries. The document outlines an agenda advocated by the SOGLI expert panel regarding the pathophysiology, screening, diagnosis, staging and treatment of SO that needs to be prioritized for future research in the field.
Opposed Reviewers:	

Sarcopenic obesity research perspectives outlined by the Sarcopenic Obesity Global Leadership Initiative (SOGLI) – proceedings from the SOGLI Consortium meeting in Rome November 2022

Gianluca Gortan Cappellari [1]*, Christelle Guillet [2]*, Eleonora Poggiogalle [3]*, Maria D. Ballesteros Pomar [4], John A Batsis [5], Yves Boirie [2], Irene Breton [6], Stefano Frara [7], Laurence Genton [8], Yftach Gepner [9], Maria Cristina Gonzalez [10], Steven B Heymsfield [11], Eva Kiesswetter [12], Alessandro Laviano [3], Carla M. Prado [13], Ferruccio Santini [14], Mireille J Serlie [15], Mario Siervo [16], Dennis T Villareal [17], Dorothee Volkert [18], Trudy Voortman [19], Peter JM Weijs [15, 20], Mauro Zamboni [21], Stephan C. Bischoff [22], Luca Busetto [23], Tommy Cederholm [24], Rocco Barazzoni [1], Lorenzo M. Donini [3], and the SOGLI Expert Panel**

* equal contribution

** SOGLI Expert panel: Anja Bosy-Westphal [25], Amelia Brunani [26], Paolo Capodaglio [26], Dario Coletti [3], Elisabetta Ferretti [3], Francesco Frigerio [3], Andrea Giustina [7], Andrea Lenzi [3], Elisabetta Marini [28], Silvia Migliaccio [29], Marianna Minnetti [3], Edoardo Mocini [3], Tatiana Moro [23], Maurizio Muscaritoli [3], Philippe Noirez [30], Antonio Paoli [23], Mariangela Rondanelli [31], Auralia Rughetti [3], Josje D Schoufour [20], Anna Skalska [32], Eva Topinkova [33], Hidekata Wakabayashi [34], Jianchun Yu [35]

1 Department of Medical Sciences, University of Trieste, Trieste, Italy

2 University of Clermont Auvergne, INRA, CRNH, CHU Clermont-Ferrand, Clermont-Ferrand, France

3 Sapienza University, Rome, Italy

4 Complejo Asistencial Universitario de León, León, Spain

5 University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

6 Hospital General Universitario Gregorio Marañón, Madrid, Spain

7 Università Vita-Salute, IRCCS Ospedale San Raffaele, Milan, Italy

8 University Hospitals of Geneva, Switzerland

9 Tel-Aviv University, Tel-Aviv, Israel

10 Catholic University of Pelotas (UCPEL), Pelotas, RS, Brazil

11 Pennington Biomedical Research Center, Baton Rouge, LA, USA

12 Institute for Evidence in Medicine, Medical Center & Faculty of Medicine, University of Freiburg, Freiburg, Germany

13 University of Alberta, Edmonton, AB, Canada

14 University of Pisa, Pisa, Italy

15 Amsterdam University Medical Centers, Amsterdam, The Netherlands

16 Curtin University, Perth, Australia

17 Baylor College of Medicine, Houston, TX, USA

18 Friedrich-Alexander-Universität Erlangen-Nürnberg, Nuremberg, Germany

19 Erasmus University Medical Center, Rotterdam, the Netherlands

20 Amsterdam University of Applied Sciences, Amsterdam, Netherlands

21 University of Verona, Verona, Italy

22 University of Hohenheim, Stuttgart, Germany

23 University of Padua, Italy

24 Uppsala University and Karolinska University Hospital, Stockholm, Sweden

25 Institute of Human Nutrition and Food Science, Kiel University, 24105 Kiel, Germany

26 IRCCS, Istituto Auxologico Italiano, Piancavallo Verbania, Italy

27 University of Turin, Italy

28 University of Cagliari, Cagliari, Italy

29 Foro Italico University, Rome, Italy

30 University of Reims Champagne-Ardenne, Reims, France

31 University of Pavia, 27100 Pavia, Italy

32 Jagiellonian University Medical College, Kraków, Poland

33 Charles University, Prague and University of South Bohemia, Ceske Budejovice, Czech Republic

34 Tokyo Women's Medical University Hospital, Tokyo, Japan

35 Peking Union Medical College Hospital, Beijing, China

Corresponding author

Lorenzo M Donini,

Department of Experimental Medicine,

Sapienza University,

Ple Aldo Moro, 5, 00185, Rome, Italy

Lorenzomaria.donini@uniroma1.it

Summary

The European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of Obesity (EASO) launched the Sarcopenic Obesity Global Leadership Initiative (SOGLI) to reach expert consensus on a definition and diagnostic criteria for Sarcopenic Obesity (SO).

The present paper describes the proceeding of the Sarcopenic Obesity Global Leadership Initiative (SOGLI) meeting that was held on November 25th and 26th, 2022 in Rome, Italy. This consortium involved the participation of 50 researchers from different geographic regions and countries.

The document outlines an agenda advocated by the SOGLI expert panel regarding the pathophysiology, screening, diagnosis, staging and treatment of SO that needs to be prioritized for future research in the field.

Key words: sarcopenic obesity, obesity, sarcopenia, consensus

Introduction

The European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of Obesity (EASO) launched the Sarcopenic Obesity Global Leadership Initiative (SOGLI) to reach an expert consensus on the definition and the diagnostic criteria for Sarcopenic Obesity (SO) (1-3). The jointly appointed international expert panel proposed that SO is defined as the co-existence of excess adiposity and low muscle mass/function (4, 5). The diagnosis of SO should be considered in at-risk individuals who screen positive for co-existing surrogate markers of excess adiposity, such as elevated body mass index (BMI) or waist circumference (WC), and factors suggestive of low skeletal muscle mass and function (accepted risk factors, clinical symptoms, or validated questionnaires). Diagnostic procedures should initially include assessment of skeletal muscle function, followed by the assessment of body composition where the presence of excess adiposity and low skeletal muscle mass or related body compartments (fat-free mass, lean mass, appendicular lean mass) would confirm the diagnosis of SO. Individuals with SO should be further stratified into Stage I in the absence of clinical complications, or Stage II if SO is associated with complications linked to altered body composition or skeletal muscle dysfunction. To study the predictive value, treatment efficacy, and clinical impact of this new SO definition (4, 5) ESPEN and EASO encouraged prospective cohort studies and clinical trials in addition to secondary analysis of existing datasets. The aim of the present document is to outline future research agenda laid forth and advocated by the panel that should be prioritized in the SO field. The present paper represents the proceeding of the Sarcopenic Obesity Global Leadership Initiative (SOGLI) event that was held in November 2022 in Rome (Italy) and that involved 50 researchers from different research areas, coming from different geographic regions and countries.

a. Pathophysiology of sarcopenic obesity

SO is characterized by the combination of obesity, defined by high body fat percentage or fat mass index (FM in kg/m^2), and sarcopenia, defined as low muscle function accompanied by low skeletal muscle mass. In several conditions, including aging as well as chronic diseases across the lifespan, SO has been associated with poorer health outcomes than sarcopenia and obesity alone. SO therefore needs to be considered as a unique clinical condition, as its effect on clinical outcomes differ from those associated with obesity or sarcopenia per se. Early evidence suggests that SO can reduce a patient's quality of life to a larger extent than sarcopenia, obesity or even the sum of their separate effects (6). This is due to the existence of: 1) negative interaction and vicious cycling between body fat mass (FM) accumulation/dysfunction and the loss of skeletal muscle mass and function; and, 2) negative clinical interactions between obesity and sarcopenia, leading to synergistically higher risk for metabolic disease and functional impairment in SO compared to those caused by cumulative risk from each condition (7, 8). The consensus on SO (4, 5) supported that current definitions of obesity and sarcopenia should not be automatically applied to define SO. In

particular, sarcopenia has been defined as low skeletal muscle function and mass (appendicular lean mass in age related primary sarcopenia) (9), but muscle changes should be considered in the context of obesity and related to high fat and total body mass. Further research on the role of each factor and mechanism in SO, as well as on their interactions may lead to better understanding of the complex pathophysiology of this condition, with the potential to favour improved tools and define new targets for identifying and treating subjects at higher risk.

Suggestions for future research

1. The role of hormonal status on the pathogenesis and the pathophysiology of SO needs to be explored in detail. Hypercortisolism has been suggested as a clinical model for SO (10), testosterone deficiency contributes to loss of muscle and bone as well as fat accumulation (11); impairment of the GH/IGF-1 axis may be associated to the risk of the development of SO and ectopic fat deposition in the liver (12).
2. Definition and differentiation of primary from secondary SO should represent a topic for future research. Primary SO is related to aging as a cluster of risk factors for inevitable, progressive muscle loss with fat accumulation, or to sedentary lifestyle and poor dietary intake, or to direct negative impact of adipose tissue-induced inflammation on muscle mass. Secondary SO is due to the simultaneous presence of obesity as potential accelerating factor, and acute or chronic diseases which may provide the major pathophysiological background for the condition, with vicious cycling leading to muscle catabolism, low physical activity, poor dietary intake and gain of FM. The relevance of differentiating primary from secondary SO still needs to be assessed, and a clinical definition and approach could result from future research. The relevance of a healthy dietary pattern with adequate intake of proteins and other nutrients (e.g., vitamin D, magnesium), with probably different requirements for healthy aging or in the context of specific diseases, should however be considered as an urgent research goal. Moreover, as aging is also frequently associated with the onset and progression of chronic diseases (13), distinguishing the relative contribution of these two factors to SO may be challenging in older people. In this context, while differentiating chronological from biological age may be considered as a strategy to better identify primary vs. secondary SO, currently no cut-point values or universally accepted parameters are available to this aim. Nevertheless, robust evidence shows that senescent cells are associated to an aged-like inflamed niche that mirrors inflammation associated with ageing and delays regeneration (14). Furthermore, limiting senescence with senolytics ameliorates muscle wasting and strength in an experimental model of chronic disease (15).

3. Assessing metabolic perturbations in adipose tissue and skeletal muscle, as well as the interorgan crosstalk in patients with SO, is necessary to identify key pathways involved in the development of SO. Sarcopenia indeed contributes to lower physical activity and energy expenditure, possibly favouring increased adiposity with a resulting vicious cycle including muscle fat deposition. The specific role of muscle lipid deposition, both intramuscular and intramyocellular, in the onset and progression of SO should also be addressed, as it may promote lipotoxicity, with pro-inflammatory cascade and oxidative stress, altered mitophagy and mitochondrial dysfunction, impaired insulin signalling, and loss of muscle mass and function (16, 17). As several studies show that obesity is associated with muscle anabolic resistance (18, 19), further studies should also better clarify the potential relevance of these mechanisms in SO development.
4. Evidence shows that weight loss induced by several causes, including hypocaloric diets, bariatric surgery, medications, and chronic diseases involve the loss of both fat and muscle mass~~es~~, as well as muscle function. Subsequent weight regain may result in an unfavourable shift in body composition with relatively larger increases in fat mass compared to lean mass (20). Further research should focus on the identification of effective strategies, including combinations of exercise and nutrition interventions, to counteract muscle mass loss during weight loss and to prevent excessive FM weight gain or prevent the development of SO during weight regain. The preservation of muscle mass and function during weight loss is particularly relevant, since muscle is needed to adopt and implement exercise as an intervention against fat regain, such as in the case of visceral fat accumulation after bariatric surgery.
5. Derangements in neuromuscular junction (NMJ) efficiency have been previously demonstrated in obesity-independent, age-related sarcopenia (21). Whether NMJ alterations contribute mechanistically to SO needs to be elucidated in future research. Age-related loss of innervation, contributing to sarcopenia (22) and obesity-related defects at NMJ (23) have been indeed reported, but no studies are currently available on the nerve-muscle crosstalk in SO. Recently, denervation has been spotlighted to occur in inflammatory-based muscle wasting conditions such as cancer cachexia (24, 25), where fat has been shown to contribute to the chronic inflammation (26) similarly to what observed in SO (27).
6. The emerging role of potential negative interactions and cross-talk between bone and muscle and adipose tissue should be further analysed. Osteopenia-osteoporosis, sarcopenia and fat accumulation with overweight or obesity are commonly associated in the aging process. Furthermore, recent evidence suggests interconnection of these syndromes, with overlapping pathophysiological features (28).

7. The role of the variations in daily energy expenditure (EE) in the pathogenesis of SO should be better analysed. Fat-free mass accounts for up to ~70% of inter-individual variance in daily EE in non-exercise conditions; any sarcopenia-related changes in lean mass may induce changes in the rate of energy expenditure. It has been shown that reduced daily EE predicts future weight gain (29), indicating the relevance of EE in body weight homeostasis. The rate of whole-body EE can be accurately and continuously measured over 24 hours inside the metabolic chamber.
8. Sex differences must be considered while investigating the pathophysiology of SO, since further insights on this issue will certainly impact on the screening and diagnosis of SO in the future. Sex differences in body fat distribution are well established (30). These determine differences in responses to diet (31), metabolism (32), and disease states (33). At the same time, men have larger muscle mass and more glycolytic muscle fibers than women. Sex differences are reported in the development of muscle atrophy: men are more prone to inflammation-mediated atrophy, such as in cachexia, while women are more sensitive to disuse atrophy (34). The fast, glycolytic fibers undergo more pronounced atrophy in cachexia, while the slow, oxidative fibers undergo more pronounced atrophy in disuse. This indicates sex-dependent differences in the onset and development of fiber atrophy (34, 35).

b. Screening for sarcopenic obesity

Screening for SO is based on concomitant presence of high BMI or WC with ethnicity-specific cut-points (36-44) (table 1) and surrogate indicators potential sarcopenia indicators (e.g., clinical symptoms, existing risk factors or validated questionnaires (such as SARC-F in older subjects) (45, 46). The panel proposes adopting cut-points provided by WHO for BMI (38, 44) and the references given by National Institute of Health and Misra et al. for WC, respectively for Caucasian and Asian populations respectively (36, 41, 47). The panel strongly supports the idea that SO screening should be differentiated from diagnosis. Screening should ideally be simple, relying only on easily available instruments that are routinely available in primary care settings. Screening might be setting-specific (e.g., geriatric clinics, oncology departments, etc). Moreover, it should be adopted by health care professionals and patients and be cost-effective (48). The aim of SO screening entails to refer individuals identified at potential risk for further assessment and diagnosing. Rising awareness on the importance of SO in both professionals and the population at large is essential for effective population screening.

Suggestions for future research

1. <u>Waist circumference</u>
    a. Definitions of obesity that are based on BMI cut-points (table 1) are the most widely accepted. However, given the relevance of FM distribution on clinical outcome, additional

evidence should be gathered on the role and relevance of WC, and its relationship with BMI, with respect to SO screening. Further investigation could also assess whether WC could be used to identify a higher risk of SO in subjects with overweight/normal BMI (49, 50).

b. The validity of simple anthropometric equations including WC [e.g., relative fat mass – RFM = 64 - (20 × height/waist circumference) + (12 × sex)] may be evaluated. RFM has been shown to better predict whole-body fat percentage, measured by DXA, among women and men of different ethnicities (51).

c. The ability of WC to differentiate subcutaneous from visceral fat deposition and depots should be improved. WC shows a stronger association with Subcutaneous Adipose Tissue (SAT) than with Visceral Adipose Tissue (VAT), which is more strongly linked to metabolic abnormalities (52). Adjustment of WC to subcutaneous fat thickness (in relation to age) may contribute to reliable estimate of VAT (53). Sagittal abdominal diameter may represent an option for WC that may better indicate visceral fat (54).

d. Normative sex-, ethnicity- and age-specific cut points for BMI and WC to better define visceral obesity should be selected (Table 1) with subsequent prospective cohort studies to test their validity.

e. Potential changes in predictive value from use of continuous vs broad categorical variables should be verified. The association between WC and adverse health risk varies across BMI categories, and using the same WC threshold values for all BMI categories may lead to the loss of important information that affects the ability of WC to predict morbidity and mortality (55).

f. Potential clinical value of adjusting WC for BMI or other factors in order to improve its association with morbidity and mortality should be analysed. In particular, waist-to height ratio may be a reliable and accurate screening tool, as it proved to be for cardiometabolic risk factors in adults (56). However, optimal biological/allometric scaling (the change in relation to proportional changes in body size) for WC in the context of SO remains undefined (57). In general, WC and derived indexes could be as important or even more informative than BMI in persons with lower BMI levels, where elevated WC is more likely to be directly associated with visceral adiposity and increased cardio-metabolic risk) (55).

g. The best protocol for measurement of WC [at the level of iliac crest (NIH) or midpoint between the last rib and iliac crest (WHO) or immediately below the lowest rib at the narrowest waist (ASM)] should be defined. Standardized and harmonized WC assessment protocols are needed given the large inter-assay variability (10–20% in females and 6–10% in males) (52).

2. Muscle function screening

a. Predictive value of SARC-F questionnaire (45, 46) for SO screening should be further assessed. All items included in SARC-F refer to disability potentially related to muscle function (strength, assistance walking, rise from a chair, climbing stairs and history of falls) and might therefore provide a screening tool for SO as well. However, whether SARC-F is a good screening test in persons younger than 65 years and in subjects with obesity is substantially less investigated. Studies have suggested that the sensitivity of SARC-F may be improved by adding calf-circumference (CC) and further validation is needed for this model (58).

Table 1 Cut-points of body mass index (BMI) and waist circumference (WC) for Sarcopenic Obesity screening (as proposed in different study populations)

Parameter	Cut-points	Methods	Sample characteristics	Sample size	References
BMI	≥30 Kg/m^2	Consensus statement based on association of BMI with mortality	/	/	(44)
	≥27.5 Kg/m^2	Consensus statement based on association of BMI with health risks, high risk of type 2 diabetes and cardiovascular disease in Asian population	Asian	/	(59)
	≥28 Kg/m^2 for M ≥24 Kg/m^2 for F	Predictive value (sensitivity and specificity) and ROC analysis to identify cut-points relative to percent body fat	Mixed ethnicity (White, Black, Hispanic, "Other"), M and F, ≥18y	1393	(42)
	≥25 Kg/m^2	Predictive value (sensitivity and specificity) and ROC analysis to identify cut-points relative to percent body fat	Mixed ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, and "Other"), M and F, ≥60y	4984	(37)
	≥25 Kg/m^2	Predictive value (sensitivity and specificity) and ROC analysis to detect subjects with multiple risk factors (hyperglycemia, dyslipidemia, hypertension)	Asians, M and F, 20–84y	1193	(39)

WC	≥102 cm for M ≥88 cm for F	Predictive value (sensitivity and specificity) and ROC analysis to detect subjects with BMI ≥30 kg/m^2	Caucasian, M and F, 25–74y	1918	(40)
	2 levels I: ≥90 cm for M ≥80 cm for F; II: ≥102 cm for M ≥88 cm for F	Consensus statement on sex-specific cut-points to identify increased relative risk for the development of obesity-associated risk factors in most adults with a BMI of 25 to 34.9 kg/m^2	/	/	(36)
	2 levels I: ≥78 cm for M ≥72 cm for F; II: ≥90 cm for M ≥80 cm for F	Predictive value (sensitivity and specificity) and ROC analysis to detect cut-points associated with the presence of at least one cardiovascular risk factor	Asian-Indian, M and F, >18y	2050	(41)
	Optimal thresholds: 97.6cm for M 87.4cm for F	Predictive value (sensitivity and specificity) and ROC analysis to identify cut points relative to percent body fat	Mixed ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, and Other), M and F, ≥60y	4984	(37)
	Optimal cut-points	Predictive value (sensitivity and specificity) and ROC analysis to identify cut points associated to	Mixed ethnicity (Caucasian, Asian, Asian-Indian, African-	61 studies	(43)

	ranged from: 72.5 to 103cm for M 65.5 to 101.2cm for F	health outcomes	American, White American, Hispanic, Other), M and F, ≥18y	reviewed	

4

c. Diagnosis of sarcopenic obesity

The diagnosis of SO will be performed, according to the consensus algorithm, in two steps by sequentially assessing:

1) Skeletal muscle functional parameters: the panel supports the use of skeletal muscle strength [e.g., hand-grip strength (HGS), or chair-stand test (5-time sit-to-stand test; 30s chair stand test)].

2) Body composition: the panel supports dual-energy x-ray absorptiometry (DXA) as first choice, or bioelectrical impedance analysis (BIA) as an alternative. Computerized tomography (CT) or magnetic resonance imaging (MRI) should be used when possible, e.g. in patients undergoing these diagnostic procedures for other diagnostic reasons.

The panel further supports the use of cut-points provided by Dodds et al. (60) and Auyeung et al. for HGS (61), respectively for Caucasian and Asian populations, with reference ranges provided by Gallagher et al. for FM (62), by Janssen et al. for SMM/W (63) and by Levine et al. for ALM/W (64).

Suggestions for future research

1. <u>Skeletal muscle functional parameters:</u>
    a. Further definition of normative sex-, ethnicity- and age-specific cut points are needed (table 2) (47, 60-96). In particular, since sarcopenic obesity may be present also in younger people, age-specific cut-off points should be investigated and established for this age group (96).

       The use of an approach based on the concept of the minimum clinically important difference (MCID) on outcomes (97, 98), could be used as a criterion to aid cut-points definition. This represents the smallest improvement considered worthwhile for a patient.
    b. Evaluating whether hand-grip strength (HGS) and other functional parameters should be adjusted to body weight, height or BMI is also relevant. In previous studies, HGS per se was not associated with features of the metabolic syndrome, in contrast to HGS/body weight and HGS/BMI which showed a significant association. This suggests that adjusted parameters may be better suitable to identify the presence of metabolic complications of sarcopenia in SO (99, 100). Similar to WC, the best allometric scaling (considering how morphological/physiological traits or processes scale with one another) for HGS in the presence of SO needs to be thoroughly clarified (101). Finally studies on ALM/BMI suggest that body size and potentially fatness influence the association between lean mass and weakness as it happens in SO (102).
    c. The opportunity to refer to lower as opposed to upper limb strength for the diagnostic procedure should be considered. A greater decline in lower compared to upper limb

strength is commonly observed (103), suggesting potential higher sensitivity. Importantly, its specificity may be limited by potential confounding factors and comorbidities that may affect test results, such as osteoarthritis of the knee which is frequently observed in patients with obesity (104). Cognitive impairment as well as social and psychological limitations could also interfere. Moreover, among lower limb strength tests, some, such as the knee extension strength test, are not easily available in non-specialized centres. Gait speed or chair to stand tests could provide a simpler alternative. Walking speed is reported to be a valid, reliable, sensitive measure appropriate for assessing and monitoring functional status and overall health in a wide range of cohorts (105). Differences have been outlined by some authors who distinguish the chair stand test (along with HGS) as an indicator of skeletal muscle strength from gait speed as an indicator of physical performance (used to determine severity of sarcopenia) (106).

d. Potential use/preference of specific functional tests for selected patient groups should be addressed. It may also be relevant to validate, by correlation with biochemical or clinical parameters specific for SO, the best fit of different types of functional tests (e.g., HGS vs gait speed) with the clinical outcomes. Studies should aim at selecting tests that best represent muscle-specific functional deficiencies of SO or of specific groups of SO patients.

e. Possible continuous variable risk assessment values, not based on cut-points, should be identified and evaluated. Z-score or percentiles distribution for individual strength (or other measurements) compared to the reference population, could allow attribution of specific risk scores for SO. This approach would also allow quantitative monitoring of SO risk in the same individual over time, thus potentially contributing to the identification of individuals with fast progression. This can help to better prioritize treatments to patients at higher risk for negative outcomes.

f. A more complete assessment of mobility should also be considered, with combined composite scores integrating functional parameters, lifestyle assessment [Instrumental Activities of Daily Living questionnaire, naturalistic real-life measurements (e.g., actigraphy of physical activity level], mood and social aspects and other parameters that could influence mobility. The possibility to increase the relative importance of tests related to quality of life (due to reduced mobility) compared to purely functional tests (such as the measure of muscle force) should be finally considered.

2. <u>Body composition</u>

a. Further definition of normative sex-, ethnicity-, and age-specific cut-points is needed.

b. Despite pathophysiological interactions that lead to vicious cycles with potential mutual synergistic worsening of obesity and sarcopenia, there is currently insufficient clinical data

to suggest and support an integrated index for SO definition that simultaneously accounts for body fat and muscle mass. The definition of a single composite criterion for SO diagnosis including both FM and muscle measurements (e.g., VAT/ALM) should however be sought and validated (107).

c. The validity of absolute vs relative reduction of muscle mass (fat mass and lean mass or skeletal muscle mass normalized by height^2) (108) should be verified. In absolute terms, high body fat in obesity may result in a relative reduction of skeletal muscle mass (% skeletal muscle mass/body weight), also in the absence of absolute skeletal muscle loss. A relative reduction in skeletal muscle mass could therefore merely result from higher body fat. Individuals with obesity may conversely have comparable or even higher absolute skeletal muscle mass relative to non-obese counterparts, due to higher overall body mass and potentially higher related muscle workload in daily physical activity (109, 110). Moreover, a relative reduction of muscle mass in the presence of high total body mass and FM may have relevant clinical and functional impact even in the absence of absolute muscle mass loss (44, 111).

d. The clinical impact of lower or inadequate muscle strength and performance in individuals with normal or near-normal muscle mass should be assessed (112).

e. Segmental body composition analysis has provided reliable information about body composition in different studies (113). The validity of specific muscle areas, as surrogate of whole body muscle mass for prediction of clinical outcomes, should be further analysed and validated (114, 115).

f. The validity of specific muscle anthropometric measurements as surrogate of muscle mass for prediction of clinical outcomes in persons with obesity should be defined. Limited data is currently available on use of calf circumference (CC) in SO, mainly highlighting the need to standardize the procedure (116). Whether CC in SO is a muscle mass index, or a subcutaneous fat index or both should be better clarified. A Potentially improved predictive value of surrogate muscle measurements for clinical outcomes has however been reported when simple adjustment factors have been used (117-122), for example for BMI or other adiposity proxies, which deserves further investigation.

g. Specific standard procedures for surrogate measurements should be better defined (including patient position, dominant side evaluation, measurement site, number of repeated measures, use of mean or maximum of measurements).

h. The opportunity to use specific cut-points values for specific conditions, such as aging or chronic diseases and their validation vs. outcomes, is a potentially important issue that should be further evaluated.

i. Skeletal muscle quality should be considered. Skeletal muscle quality may be profoundly altered in people with obesity, particularly in terms of ectopic fat deposition (e.g., myosteatosis) which may be highly prevalent in the presence of excess body fat. Myosteatosis is indeed recognized to be negatively associated with skeletal muscle mass and strength (muscle quality), as well as with mobility and systemic metabolic derangements, including insulin resistance and type 2 diabetes, thereby being of prognostic relevance (27, 123, 124). Moreover, under conditions of oxidative stress and chronic inflammation, myoblasts with muscle regenerative function may transdifferentiate into myofibroblasts, which secrete a large amount of extracellular matrix components such as collagen to promote skeletal muscle fibrosis (125). Definition and tools to assess muscle quality in clinical practice remain however elusive and should represent an open research topic.

The role of changes in body fluids (dehydration and edema) in hampering the assessment of muscle mass should be considered. Studies performed in subjects with BMI ≥35 kg/m^2 revealed conflicting results, with ~~an~~ overestimation of body fat or fat-free mass using BIA methodology due, in particular, to modifications of hydration status; changes in plasma sodium concentrations after variable water intake may also conversely affect BIA measurements whereas hyper-hydration may cause underestimation of total body water (TBW) (126-128).

j. Obesity-specific adjustments in BIA equations may improve the accuracy of body composition estimation in these patients (129). Similarly, acute water ingestion before a DXA analysis (500 ml) significantly influences body composition (by inflating expanding fat free mass and reducing percent body fat) (130).

k. Upper sex-specific cut-points of 40% for female and 30% for male have been proposed as best predictors of mortality with regards to body fat in the NHANES sample (American population) using DXA (95). Woolcott et al. (51) developed a calculated % FM parameter defined as relative FM based not on body composition assessment, but rather calculated using height and waist circumference. These proposed parameters and values need to be validated in populations with different ethnicities and using different methods for % FM assessment.

l. Specific equations for the assessment of SMM/W (total skeletal muscle mass adjusted by weight) using BIA especially in individuals with BMI > 34 kg/m^2 (129) should be validated, also considering the potential need for age or disease specific BIA equations (131). Potential use of BIA electrical output values should be evaluated since they can potentially allow for better data comparison and help reduce complexity and variability related to the

use of different equations. Phase angle, a variable directly available from BIA electrical measurements that is independent from equation-related output, is a validated proxy for muscle mass and function (132, 133). Moreover different studies have highlighted the potential of bioelectrical impedance vector analysis (BIVA) in the analysis of body composition and in particular in subjects with SO (134, 135).

m. Selected modified or relatively new methodologies (e.g., segmental BIA; iDXA and visceral fat DXA-analyser; MRI and D3-creatine dilution (136), ultrasound (137, 138) should be validated for the assessment of body composition in particular in subjects with SO.

n. The potential relevance for clinical use of data from easily available, patient-operated devices, including for example smartphone apps for body scanning and anthropometric measurements and home scales with BIA capabilities should also be assessed.

Table 2. Cut-points values for Sarcopenic Obesity diagnosis (as proposed in various studies)

Parameter	Cut-points	Method	Sample characteristics	Sample size	References
Skeletal muscle function					
HGS	< 27 Kg for M < 16 Kg for F	HGS ≤ 2.5 SD below the gender-specific peak mean	Caucasian, M and F ≥ 5y	49964 (data from 12 studies)	(60)
	< 35,5 Kg for M < 20,0 Kg for F	CART and ROC/AUC models to identify cut points associated with adverse clinical outcomes such as mortality, falls, self-reported mobility limitation, and hip fracture	Mixed ethnicity, M and F ≥ 65y	12984	(66,67)
	<30 Kg for M <20 Kg for F	2 SD below the mean of the healthy young-adults group functional outcomes (walking speed ≤ 0.8 m/s; self-reported inability to walk for 1 km)	Caucasian , M and F, 20-102y (RG 20-29y)	1030 (RG 47)	(47)
	<26 Kg for M < 16 Kg for F	Consensus statement identifying cut-points corresponding to a mobility impairment expressed by physical performance tests such as slow walking (gait speed ≤ 0.8 m/s)	Mixed ethnicity, M and F, ≥65y	26625 (data from 9 studies)	(65)
	<28 Kg for M <18 Kg for F	Lowest quintile of the general Asian older population	Asian, M and F, ≥65y	26344 (data from 8	(61)

				cohorts)	
	Normative values based on gender, age, height, right/left side	<5th percentile of the general population aged between 39 and 73 years in 2006 to 2010 from across the United Kingdom	Caucasian, M and F, 39-73y	224830 (r) 224852 (l)	(79)
	26.6 ± 8.3 kg (low LMI) 34.6 ± 13.7 kg (normal LMI)	< LMI 17 kg/m^2 for men and 15 kg/m^2 for women	Caucasian, M and F, 48.8±9.6 y	817 (364 M, 453 F)	(96)
Knee extension strength test	<18 Kg for M <16 Kg for F	Predictive value (sensitivity and specificity) and ROC analysis to identify cut points based on percentage of normalized gain of mobility index (MI) derived from a questionnaire about activity of daily living	Asian, M and F ≥60y	950	(68)
	Strength/W (Kg/Kg) <0.40 for M <0.31 for F	Predictive value (sensitivity and specificity) and ROC analysis to identify cut points relative to the presence of functional limitation	Caucasian, M and F, ≥60y	947	(75)
	< 390.9 N/dm for M <266.4 N/dm for F	2 SD below the mean for the sex-specific RG (healthy young adults)	Caucasian, M and F, 20-102y (RG 20-29y)	1030 (RG 27)	(47)
5 times Sit-to-Stand Chair test	≥17 s	< 21.3 percentile of well-functioning older persons population	Mixed ethnicity, M and F, 70-79y	3024	(71)

30 s Chair Stand Test	60-64y: 15 for F, 17 for M; 65-69y: 15 for F, 16 for M; 70-74y: 14 for F, 15 for M; 75-79y: 13 for F, 14 for M; 80-84y: 12 for F, 13 for M; 85-89y: 11 for F and M; 90-94y: 9 for F and M	normative values across 5 years age ranges (outcomes: moderate functional ability as defined by CPF scale questionnaire and % of decline in physical performance)	Caucasian, M and F, ≥60y	2140	(77)
Body composition					
FM%	20-39y: >39% for F, >26% for M (Caucasians); >40% for F, >28% for M (Asians); >38% for F, >26% for M (African-Americans) 40-59 y: >41% for F, >29% for M (Caucasians); >41% for F, >29% for M (Asians);	Multiple regression model considering FM as outcome variable and BMI, sex, age and ethnicity as predictor variables	Asian, African-American, Caucasian, M and F, Adults	1626	(62)

	>39% for F, >27% for M (African-Americans); 60-79y: >43% for F, >31% for M (Caucasians); >41% for F, >29% for M (Asians); >41% for F, >29% for M (African-Americans);				
	>38% for F >27% for M	Percentage of body fat greater than the sex-specific median	Hispanic and non-Hispanic white, M and F, older people	808	(70)
	>37.2%for F >29.7% for M	Highest sex-specific quintile	Asian, M and F, ≥65y	1731	(72)
	>40.7% for F >27.3% for M	> 60th percentile of body fat of the study population	Caucasian, M and F, ≥60y	992	(69)
	>42.9% for F	2 highest quintiles of the study population	Caucasian, F, 67-78y	167	(80)
	>40.9% for F >30.33% for M	2 highest quintiles of the study population	Caucasian, M and F, 65-92y	2747	(76)
	>20.21% for M	2 highest quintiles of the young RG	Asian, M and F, 20-88y	591	(73)

	>31.71% for F		(RG 20-40)	(145 RG)	
	>25.8% for M >36.5% for F	2 highest quintiles of the study population	Asian, M and F, ≥40y	309	(74)
	>25% for M >32% for F	Expert opinion of the American Society of Bariatric Surgery	/	/	(78)
	RFM (derived from the ratio of h to WC) ≥40% for F ≥30% for M	Multiple regression model considering FM as outcome variable and BMI, education level, smoking status, sex and ethnicity as predictor variables	Mixed ethnicity, M and F, ≥20y	31008	(95)
	Highest two quintiles: 36.2 ± 3.8% for F 20.5 ± 3.3% for M	Highest two quintiles of FM% estimated using predictive equation including WC, hip circumference, triceps skinfold and gender [51]	Mixed ethnicity (non-Hispanic whites, non-Hispanic blacks, Mexican Americans), M and F, ≥70y	2917	(85)
SMM/W (BIA or DXA)	CLASS I of Sarcopenia (1-2 SD): 31.5-37% for M 22.1-27.6% for F; CLASS II of Sarcopenia (< 2 SD):	Class I: SMM/W within -1 to -2 SD of young adult values Class II: SMM/W -2 SD of young adult values	Mixed ethnicity, M and F, 18-39y	6414	(63)

	<31.5% for M <22.1% for F				
	CLASS I of Sarcopenia (1-2 SD): 42.9-38.2% for M 35.6-32.2% for F; CLASS II of Sarcopenia (< 2 SD): <38.2% for M <32.2% for F	Class I: SMM/W within -1 to -2 SD of young adult values Class II: SMM/W -2 SD of young adult values.	Asian, M and F, ≥40y (RG 18-40y)	309 (273 RG)	(74)
	CLASS I of Sarcopenia (1-2 SD): 27-23% for F CLASS II of Sarcopenia (< 2 SD): <23% for F	Class I: SMM/W within -1 to -2 SD of young adult values Class II: SMM/W -2 SD of young adult values	Caucasian, F, 20-50y (RG)	120 (RG)	(80)
ALM/W (DXA)	<29.9% for M <25.1% for F	1 SD below the sex specific mean for young adults	Asian, M and F, mean age 28.4 ± 3.1 and 26.3 ± 2.6	70 (RG)	(92)
	<30.1% M <21.2% F	1 SD below the mean of a young population RG	Asian, M and F, ≥ 40y (RG 20-39y)	10118 (5944 RG)	(81)
	<30.65% for M <23.9% for F	1 SD below the mean of a healthy young RG	Asian, M and F, ≥ 65y (RG 20-39y)	3483 (4192 RG)	(82)

< 25.7% for M < 19.4% for F	2 SD below the mean of a healthy young RG	Mixed ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, "other"), M and F, ≥ 60y (RG 18-59y)	4984 (10877 RG)	(64)
<30.3% for M <23.8% for F	1 SD below the mean of a healthy young RG	Asian, M and F, ≥ 20y (RG 20-39y)	11521 (4987 RG)	(83)
< 32.5% for M < 25.7% for F	1 SD below the mean of a healthy young RG	Asian, M and F, ≥ 60y (RG 20-39y)	2943 (2781 RG)	(84)
< 29.53% for M < 23.2% for F	2 SD below the mean of a healthy young RG	Asian, M and F, ≥60y (RG 20-39y)	2221 (2269 RG)	(86)
<31.3% for M <24.76% for F	1 SD below the mean of a healthy young RG	Asian, M and F, ≥40y (RG 20-39y)	3320	(87)
<32.2% for M <25.6% for F	Class I: within -1 to -2 SD of the healthy young adult values Class II: 2 SD below the mean of the healthy young adult values	Asian, M and F, ≥20y (RG 20-39y)	10485 (2513 RG)	(89)
<29.5% for M < 23.2% for F	2 SD below the mean of a healthy young RG	Asian, M and F, ≥50y (RG 20-40y)	3169 (2392 RG)	(88)
< 26.8% for M	2 SD below the mean of the young RG	Asian, M and F, ≥50y (20-40y	2893	(90)

	< 21% for F		RG)	(2113 RG)	
	< 32.2 for M < 25.5% for F	2 SD below the mean of the young RG	Asian, M and F, ≥20y (RG 20-30y)	15132 (2200 RG)	(91)
	< 44% for M < 52 % for F	1 SD below the mean of the young RG	Asian, M and F, ≥60y (RG 20-39y)	1433 (1746 RG)	(93)
	< 28.27% for M < 23.47% for F	2 SD below the mean of the young RG	Caucasian, M and F, 18-65y (RG 20-39y)	727 (222 RG)	(94)

Legend: 6MWT 6 minutes walking test, **ALM** appendicular lean mass**, AUC** area under the curve, **BIA**, bioelectrical impedance analyses, **BMI** body mass index, **CART** Classification and Regression Tree model, **CPF** Composite Physical Function, **DXA,** dual-energy X-ray absorptiometry, **FM** fat mass, **HGS** hand grip strength, **LMI** lean mass index, **mPPT** modified physical performance test, **RFM** relative fat mass, **RG** reference group, **ROC** Receiver operating characteristic, **SD** standard deviation, **SMM** skeletal muscle mass, **TMSE** Thai mental state examination, **W** weight, **WC** waist circumference,

d. Staging and overall structure of the algorithm

When the diagnosis of SO is established, a two-level staging is proposed, based on the presence or absence of complications (e.g., metabolic cardiovascular and respiratory diseases, or disabilities resulting from high FM and-or low muscle mass). This will aim at stratifying patients based on SO severity. SO stages were defined as follows (4, 5):

STAGE I: No complications attributable to altered body composition and skeletal muscle functional parameters;

STAGE II: Presence of at least one complication attributable to altered body composition and skeletal muscle functional parameters.

Suggestions for future research

1. The predictive value of the proposed algorithm in younger subjects should be directly assessed. Younger persons with SO may have a relative low muscle mass for their age but still relatively preserved muscle function. Moreover, in younger persons functional parameters may not be the primary clinical outcome of interest, particularly in secondary sarcopenia (e.g., patients with cancer or other chronic conditions, or hospitalised), and it is unknown whether temporary SO in younger individuals impacts long-term clinical outcomes and recovery.
2. The possibility to consider global as opposed to muscle-specific outcomes (e.g., lower quality of life related to impaired mobility, institutionalization, disability) as markers of severity of SO, and their inclusion in SO staging needs to be carefully evaluated since they may not be necessarily associated with (or only with) SO, but they may be clinically most relevant SO outcomes in older adults (139).
3. Use of big data analysis and artificial intelligence to aid the identification of other potential important parameters associated with SO, and to contribute to better define cut-points for SO diagnosis and identification of patients at higher risk of poor outcome, may represent a relevant topic for future research.

e. Prevention and treatment strategies for sarcopenic obesity

Treatment of SO is an important clinical challenge due, in particular, to the different phenotypic characteristics and to the different etiopathogenetic pathways leading to SO. Lifestyle interventions, including dietary intervention and optimal protein intake, as well as physical activity/exercise, are hallmarks in the treatment of SO (6). Because of the many pathological and clinical interactions between sarcopenia and obesity, as outlined above, treatment and prevention strategies may also not simply be a combination of known strategies to treat obesity and/or sarcopenia alone. Furthermore, certain treatment strategies for obesity may even be harmful for sarcopenia or vice-versa: intentional weight loss in older adults with obesity has been shown to improve morbidity and physical function (140), but weight loss may also lead to loss of muscle mass, which may worsen sarcopenia and hamper physical function. Although few clinical trials specifically focused on SO (141-144) have been performed, a personalized multidisciplinary approach combining nutritional, physical, psychological, pharmacological and surgical components seems to represent the best treatment of SO. Finally, the panel of experts underlined and agreed on the need to correctly define and diagnose SO before treatment.

Suggestions for future research

1. How clinical stratification proposed in the Consensus algorithm may influence the treatment of subjects with SO and the potential benefits of a more aggressive approach in subjects with higher clinical severity and risk for poor outcomes should be evaluated.
2. Primary and secondary SO may have different clinical and functional characteristics that should be independently investigated and better defined. Specific treatment strategies to address underlying pathophysiological mechanisms may be eventually needed.
3. Several endocrine disorders [hypercortisolism (10), testosterone deficiency, impairment of GH/IGF-1 axis, adult GH deficiency] including the endocrine consequences of various diseases (e.g., cirrhosis, COPD) are associated with SO. Treatment of SO in these conditions requires further specific investigation that may potentially lead to specific recommendations (145-147).
4. How functional characteristics of subjects with SO may influence treatment protocols (in particular the intensity and volume of physical exercise), and how aerobic and resistance treatment approaches can be combined need to be assessed. The evaluation of the efficacy of single and combined treatment options in different age groups or in patient groups with different levels of fitness may help identify the best strategies that can be used to optimise outcomes.
5. The efficacy of previously proposed approaches to treat obesity (notably caloric restriction, physical activity, pharmacological and psychological protocols, bariatric surgery) and sarcopenia [exercise and functional rehabilitation, adequate protein intake (including the most appropriate amount, timing and type of protein in the diet and its interactions with exercise), nutrient supplementation

(e.g. Vitamin D, whey protein, branched chain amino acids), pharmacological treatment] need to be validated and confirmed in subjects with SO. In particular, strategies to better preserve muscle mass during weight loss need to be identified. Both aerobic and resistance exercise, separately, or in combination, have been shown to improve functional status with concomitant caloric restriction in older adults with obesity, while synergistic improvements in physical function has been observed with both types of exercise (148). However, the potential combined role of other factors and treatments, including dietary aspects, still need to be fully addressed. In particular, more emphasis should be placed on studying forms of personalized physical exercise, which should take into account not only the different roles it plays in the treatment of SO (i.e. increase energy expenditure, maintain muscle mass) but also its coordination with other therapeutic strategies.

6. Novel medications (GLP-1, GIP, glucagon agonists) hold great promise for the treatment of obesity by allowing weight reductions above 15% (149). Assessment on the effects of these emerging treatments on lean mass changes as well as other specific components of the SO phenotype will likely become an important priority in order to allow for safe utilization in persons with, or at risk for SO.
7. Treatment of obesity by nutritional, pharmacological or surgical intervention leading to a reduction in fat mass and in fat free mass will also induce changes in energy metabolism (i.e., adaptive thermogenesis), thereby influencing daily energy balance (energy intake and energy expenditure) and future changes in body composition (150). A better understanding of the interplay between energy intake and energy expenditure will help to identify the best therapies aimed at preserving muscle mass over time.
8. Medications or nutritional formulations recommended to counteract sarcopenia may also be effective in the context of increased adiposity and SO, in terms of pharmacological lipophilic behaviour and compartment distribution, but this hypothesis should be directly tested in future clinical studies. In particular, muscle-anabolic therapeutic approaches considering nutritional supplementation (e.g., aminoacids, isoflavones), pharmacological/hormonal treatment (e.g., oestrogen, testosterone, selective androgen receptor modulators, recombinant human growth hormone (151), anamorelin, myostatin inhibitors, vitamin K), senolytic agents (152) or mesenchymal stem cells provided conflicting results and require further research. Finally, the efficacy of new treatments focused on muscle [e.g., antibody blockade of activin type II receptor (ActRII) signaling, which stimulates skeletal muscle growth] potentially leading to improvements in fat mass reduction and metabolic markers should be verified in the management of SO (153).

Conclusion

This document summarizes the result of the work carried out in recent years, in the context of the EASO ESPEN initiatives, by the SOGLI expert panel, leading to a meeting that took place in Rome in November 2022. In the context of other recently-published documents (systematic review of literature concerning SO, and ESPEN-EASO consensus on definition and diagnostic criteria) it proposes a starting point for research aimed at improving knowledge and clinical practice in SO.

At the moment the validation of the ESPEN-EASO criteria for SO screening and diagnosis using already available data from merging datasets (from Italy, Czech Republic, Finland, Poland) and from different epidemiological studies [Sarcopenia & Physical fRailty IN older people (SPRINTT), National Health and Nutrition Examination Survey (NHANES), National Health and Aging Trends Study (NHATS), Baltimore Longitudinal Study of Aging (BLSA)] is ongoing. We aim at producing results to be presented and discussed at the next SOGLI meeting that we are planning for fall 2023 where the many researchers interested in SO will be able to discuss their ideas and data, and kick off new initiatives.

References

1. Barazzoni R, Bischoff S, Boirie Y, Busetto L, Cederholm T, Dicker D, et al. Sarcopenic Obesity: Time to Meet the Challenge. Obesity facts. 2018;11(4):294-305. doi:10.1159/000490361
2. Barazzoni R, Bischoff SC, Boirie Y, Busetto L, Cederholm T, Dicker D, et al. Sarcopenic obesity: Time to meet the challenge. Clinical nutrition. 2018;37(6 Pt A):1787-93. doi:10.1016/j.clnu.2018.04.018
3. Donini LM, Busetto L, Bauer JM, Bischoff S, Boirie Y, Cederholm T, et al. Critical appraisal of definitions and diagnostic criteria for sarcopenic obesity based on a systematic review. Clinical nutrition. 2020;39(8):2368-88. doi:10.1016/j.clnu.2019.11.024
4. Donini LM, Busetto L, Bischoff SC, Cederholm T, Ballesteros-Pomar MD, Batsis JA, et al. Definition and diagnostic criteria for sarcopenic obesity: ESPEN and EASO consensus statement. Clinical nutrition. 2022;41(4):990-1000. doi:10.1016/j.clnu.2021.11.014
5. Donini LM, Busetto L, Bischoff SC, Cederholm T, Ballesteros-Pomar MD, Batsis JA, et al. Definition and Diagnostic Criteria for Sarcopenic Obesity: ESPEN and EASO Consensus Statement. Obesity facts. 2022;15(3):321-35. doi:10.1159/000521241
6. Baumgartner RN, Wayne SJ, Waters DL, Janssen I, Gallagher D, Morley JE. Sarcopenic obesity predicts instrumental activities of daily living disability in the elderly. Obesity research. 2004;12(12):1995-2004. doi:10.1038/oby.2004.250
7. Batsis JA, Villareal DT. Sarcopenic obesity in older adults: aetiology, epidemiology and treatment strategies. Nature reviews Endocrinology. 2018;14(9):513-37. doi:10.1038/s41574-018-0062-9
8. Koliaki C, Liatis S, Dalamaga M, Kokkinos A. Sarcopenic Obesity: Epidemiologic Evidence, Pathophysiology, and Therapeutic Perspectives. Current obesity reports. 2019;8(4):458-71. doi:10.1007/s13679-019-00359-9
9. Cruz-Jentoft AJ, Sayer AA. Sarcopenia. Lancet. 2019;393(10191):2636-46. doi:10.1016/S0140-6736(19)31138-9
10. Drey M, Berr CM, Reincke M, Fazel J, Seissler J, Schopohl J, et al. Cushing's syndrome: a model for sarcopenic obesity. Endocrine. 2017;57(3):481-5. doi:10.1007/s12020-017-1370-x
11. Saad F, Rohrig G, von Haehling S, Traish A. Testosterone Deficiency and Testosterone Treatment in Older Men. Gerontology. 2017;63(2):144-56. doi:10.1159/000452499
12. Poggiogalle E, Lubrano C, Gnessi L, Mariani S, Lenzi A, Donini LM. Fatty Liver Index Associates with Relative Sarcopenia and GH/ IGF- 1 Status in Obese Subjects. PloS one. 2016;11(1):e0145811. doi:10.1371/journal.pone.0145811
13. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet. 2012;380(9836):37-43. doi:10.1016/S0140-6736(12)60240-2
14. Moiseeva V, Cisneros A, Sica V, Deryagin O, Lai Y, Jung S, et al. Senescence atlas reveals an aged-like inflamed niche that blunts muscle regeneration. Nature. 2023;613(7942):169-78. doi:10.1038/s41586-022-05535-x
15. Huang Y, Wang B, Hassounah F, Price SR, Klein J, Mohamed TMA, et al. The impact of senescence on muscle wasting in chronic kidney disease. Journal of cachexia, sarcopenia and muscle. 2023;14(1):126-41. doi:10.1002/jcsm.13112
16. Dantas WS, Zunica ERM, Heintz EC, Vandanmagsar B, Floyd ZE, Yu Y, et al. Mitochondrial uncoupling attenuates sarcopenic obesity by enhancing skeletal muscle mitophagy and quality control. Journal of cachexia, sarcopenia and muscle. 2022;13(3):1821-36. doi:10.1002/jcsm.12982
17. Hong SH, Choi KM. Sarcopenic Obesity, Insulin Resistance, and Their Implications in Cardiovascular and Metabolic Consequences. International journal of molecular sciences. 2020;21(2). doi:10.3390/ijms21020494
18. Beals JW, Skinner SK, McKenna CF, Poozhikunnel EG, Farooqi SA, van Vliet S, et al. Altered anabolic signalling and reduced stimulation of myofibrillar protein synthesis after feeding and resistance exercise in people with obesity. The Journal of physiology. 2018;596(21):5119-33. doi:10.1113/JP276210
19. Guillet C, Delcourt I, Rance M, Giraudet C, Walrand S, Bedu M, et al. Changes in basal and insulin and amino acid response of whole body and skeletal muscle proteins in obese men. The Journal of clinical endocrinology and metabolism. 2009;94(8):3044-50. doi:10.1210/jc.2008-2216
20. Beavers KM, Lyles MF, Davis CC, Wang X, Beavers DP, Nicklas BJ. Is lost lean mass from intentional weight loss recovered during weight regain in postmenopausal women? The American journal of clinical nutrition. 2011;94(3):767-74. doi:10.3945/ajcn.110.004895
21. Deschenes M.R. OJ, Tufts H. The role of the neuromuscular junction in sarcopenia. In: Sakuma K., editor. Sarcopenia. Elsevier; Amsterdam, The Netherlands: 2021. pp. 59–80.
22. Gonzalez-Freire M, de Cabo R, Studenski SA, Ferrucci L. The Neuromuscular Junction: Aging at the Crossroad between Nerves and Muscle. Frontiers in aging neuroscience. 2014;6:208. doi:10.3389/fnagi.2014.00208

23. Yadav RL, Sharma D, Yadav PK, Shah DK, Agrawal K, Khadka R, et al. Somatic neural alterations in non-diabetic obesity: a cross-sectional study. BMC obesity. 2016;3:50. doi:10.1186/s40608-016-0131-3
24. Daou N, Hassani M, Matos E, De Castro GS, Costa RGF, Seelaender M, et al. Displaced Myonuclei in Cancer Cachexia Suggest Altered Innervation. International journal of molecular sciences. 2020;21(3). doi:10.3390/ijms21031092
25. Sartori R, Hagg A, Zampieri S, Armani A, Winbanks CE, Viana LR, et al. Perturbed BMP signaling and denervation promote muscle wasting in cancer cachexia. Science translational medicine. 2021;13(605). doi:10.1126/scitranslmed.aay9592
26. Camargo RG, Riccardi DM, Ribeiro HQ, Carnevali LC, Jr., de Matos-Neto EM, Enjiu L, et al. NF-kappaBp65 and Expression of Its Pro-Inflammatory Target Genes Are Upregulated in the Subcutaneous Adipose Tissue of Cachectic Cancer Patients. Nutrients. 2015;7(6):4465-79. doi:10.3390/nu7064465
27. Kalinkovich A, Livshits G. Sarcopenic obesity or obese sarcopenia: A cross talk between age-associated adipose tissue and skeletal muscle inflammation as a main mechanism of the pathogenesis. Ageing research reviews. 2017;35:200-21. doi:10.1016/j.arr.2016.09.008
28. Ormsbee MJ, Prado CM, Ilich JZ, Purcell S, Siervo M, Folsom A, et al. Osteosarcopenic obesity: the role of bone, muscle, and fat on health. Journal of cachexia, sarcopenia and muscle. 2014;5(3):183-92. doi:10.1007/s13539-014-0146-x
29. Ravussin E, Lillioja S, Knowler WC, Christin L, Freymond D, Abbott WG, et al. Reduced rate of energy expenditure as a risk factor for body-weight gain. The New England journal of medicine. 1988;318(8):467-72. doi:10.1056/NEJM198802253180802
30. Christen T, Trompet S, Noordam R, van Klinken JB, van Dijk KW, Lamb HJ, et al. Sex differences in body fat distribution are related to sex differences in serum leptin and adiponectin. Peptides. 2018;107:25-31. doi:10.1016/j.peptides.2018.07.008
31. Huang KP, Ronveaux CC, Knotts TA, Rutkowsky JR, Ramsey JJ, Raybould HE. Sex differences in response to short-term high fat diet in mice. Physiology & behavior. 2020;221:112894. doi:10.1016/j.physbeh.2020.112894
32. Wang C, Xu Y. Mechanisms for Sex Differences in Energy Homeostasis. Journal of molecular endocrinology. 2019;62(2):R129-R43. doi:10.1530/JME-18-0165
33. Li H, Konja D, Wang L, Wang Y. Sex Differences in Adiposity and Cardiovascular Diseases. International journal of molecular sciences. 2022;23(16). doi:10.3390/ijms23169338
34. Rosa-Caldwell ME, Greene NP. Muscle metabolism and atrophy: let's talk about sex. Biology of sex differences. 2019;10(1):43. doi:10.1186/s13293-019-0257-3
35. Carson JA, Hardee JP, VanderVeen BN. The emerging role of skeletal muscle oxidative metabolism as a biological target and cellular regulator of cancer-induced muscle wasting. Seminars in cell & developmental biology. 2016;54:53-67. doi:10.1016/j.semcdb.2015.11.005
36. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. Obesity research. 1998;6 Suppl 2:51S-209S.
37. Batsis JA, Mackenzie TA, Bartels SJ, Sahakyan KR, Somers VK, Lopez-Jimenez F. Diagnostic accuracy of body mass index to identify obesity in older adults: NHANES 1999-2004. International journal of obesity. 2016;40(5):761-7. doi:10.1038/ijo.2015.243
38. WHO. Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 2004;363(9403):157-63. doi:10.1016/S0140-6736(03)15268-3
39. Examination Committee of Criteria for 'Obesity Disease' in Japan, Japan Society for the Study of Obesity, New criteria for 'obesity disease' in Japan. Circulation journal : official journal of the Japanese Circulation Society. 2002;66(11):987-92. doi:10.1253/circj.66.987
40. Lean ME, Han TS, Morrison CE. Waist circumference as a measure for indicating need for weight management. Bmj. 1995;311(6998):158-61. doi:10.1136/bmj.311.6998.158
41. Misra A, Vikram NK, Gupta R, Pandey RM, Wasir JS, Gupta VP. Waist circumference cutoff points and action levels for Asian Indians for identification of abdominal obesity. International journal of obesity. 2006;30(1):106-11. doi:10.1038/sj.ijo.0803111
42. Shah NR, Braverman ER. Measuring adiposity in patients: the utility of body mass index (BMI), percent body fat, and leptin. PloS one. 2012;7(4):e33308. doi:10.1371/journal.pone.0033308
43. Wang Z, Ma J, Si D. Optimal cut-off values and population means of waist circumference in different populations. Nutrition research reviews. 2010;23(2):191-9. doi:10.1017/S0954422410000120
44. WHO. Obesity: preventing and managing the global epidemic. Report on a WHO Consultation on Obesity, Geneva, 3–5 June, 1997. WHO/NUT/NCD/98.1. Technical Report Series Number 894.Geneva: World Health Organization, 2000.

45. Malmstrom TK, Morley JE. SARC-F: a simple questionnaire to rapidly diagnose sarcopenia. Journal of the American Medical Directors Association. 2013;14(8):531-2. doi:10.1016/j.jamda.2013.05.018
46. Woo J, Leung J, Morley JE. Validating the SARC-F: a suitable community screening tool for sarcopenia? Journal of the American Medical Directors Association. 2014;15(9):630-4. doi:10.1016/j.jamda.2014.04.021
47. Studenski SA, Peters KW, Alley DE, Cawthon PM, McLean RR, Harris TB, et al. The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. The journals of gerontology Series A, Biological sciences and medical sciences. 2014;69(5):547-58. doi:10.1093/gerona/glu010
48. Wilson JMGJ, G. & World Health Organization (1968). . Principles and practice of screening for disease / J. M. G. Wilson, G. Jungner. World Health Organization. https://apps.who.int/iris/handle/10665/37650.
49. Batsis JA, Germain CM, Vasquez E, Lopez-Jimenez F, Bartels SJ. Waist Circumference, Physical Activity, and Functional Impairments in Older U.S. Adults: Results from the NHANES 2005-2010. Journal of aging and physical activity. 2015;23(3):369-76. doi:10.1123/japa.2014-0007
50. Germain CM, Vasquez E, Batsis JA. Physical Activity, Central Adiposity, and Functional Limitations in Community-Dwelling Older Adults. Journal of geriatric physical therapy. 2016;39(2):71-6. doi:10.1519/JPT.0000000000000051
51. Woolcott OO, Bergman RN. Relative fat mass (RFM) as a new estimator of whole-body fat percentage horizontal line A cross-sectional study in American adult individuals. Scientific reports. 2018;8(1):10980. doi:10.1038/s41598-018-29362-1
52. Bosy-Westphal A, Booke CA, Blocker T, Kossel E, Goele K, Later W, et al. Measurement site for waist circumference affects its accuracy as an index of visceral and abdominal subcutaneous fat in a Caucasian population. The Journal of nutrition. 2010;140(5):954-61. doi:10.3945/jn.109.118737
53. Chen CH, Chen YY, Chuang CL, Chiang LM, Chiao SM, Hsieh KC. The study of anthropometric estimates in the visceral fat of healthy individuals. Nutrition journal. 2014;13:46. doi:10.1186/1475-2891-13-46
54. Riserus U, de Faire U, Berglund L, Hellenius ML. Sagittal abdominal diameter as a screening tool in clinical research: cutoffs for cardiometabolic risk. Journal of obesity. 2010;2010. doi:10.1155/2010/757939
55. Ross R, Neeland IJ, Yamashita S, Shai I, Seidell J, Magni P, et al. Waist circumference as a vital sign in clinical practice: a Consensus Statement from the IAS and ICCR Working Group on Visceral Obesity. Nature reviews Endocrinology. 2020;16(3):177-89. doi:10.1038/s41574-019-0310-7
56. Ashwell M, Gunn P, Gibson S. Waist-to-height ratio is a better screening tool than waist circumference and BMI for adult cardiometabolic risk factors: systematic review and meta-analysis. Obesity reviews : an official journal of the International Association for the Study of Obesity. 2012;13(3):275-86. doi:10.1111/j.1467-789X.2011.00952.x
57. Churilla JR. Anthropometrics and Allometry: Beyond Body Mass Index. Metabolic syndrome and related disorders. 2018;16(4):159. doi:10.1089/met.2018.0031
58. Barbosa-Silva TG, Menezes AM, Bielemann RM, Malmstrom TK, Gonzalez MC, Grupo de Estudos em Composicao Corporal e N. Enhancing SARC-F: Improving Sarcopenia Screening in the Clinical Practice. Journal of the American Medical Directors Association. 2016;17(12):1136-41. doi:10.1016/j.jamda.2016.08.004
59. Consultation WHOE. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 2004;363(9403):157-63. doi:10.1016/S0140-6736(03)15268-3
60. Dodds RM, Syddall HE, Cooper R, Benzeval M, Deary IJ, Dennison EM, et al. Grip strength across the life course: normative data from twelve British studies. PloS one. 2014;9(12):e113637. doi:10.1371/journal.pone.0113637
61. Auyeung TW, Arai H, Chen LK, Woo J. Letter to the editor: Normative data of handgrip strength in 26344 older adults - a pooled dataset from eight cohorts in Asia. The journal of nutrition, health & aging. 2020;24(1):125-6. doi:10.1007/s12603-019-1287-6
62. Gallagher D, Heymsfield SB, Heo M, Jebb SA, Murgatroyd PR, Sakamoto Y. Healthy percentage body fat ranges: an approach for developing guidelines based on body mass index. The American journal of clinical nutrition. 2000;72(3):694-701. doi:10.1093/ajcn/72.3.694
63. Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. Journal of the American Geriatrics Society. 2002;50(5):889-96. doi:10.1046/j.1532-5415.2002.50216.x
64. Levine ME, Crimmins EM. The impact of insulin resistance and inflammation on the association between sarcopenic obesity and physical functioning. Obesity. 2012;20(10):2101-6. doi:10.1038/oby.2012.20
65. Chen LK, Woo J, Assantachai P, Auyeung TW, Chou MY, Iijima K, et al. Asian Working Group for Sarcopenia: 2019 Consensus Update on Sarcopenia Diagnosis and Treatment. Journal of the American Medical Directors Association. 2020;21(3):300-7 e2. doi:10.1016/j.jamda.2019.12.012
66. Lauretani F, Russo CR, Bandinelli S, Bartali B, Cavazzini C, Di Iorio A, et al. Age-associated changes in skeletal muscles and their effect on mobility: an operational diagnosis of sarcopenia. Journal of applied physiology. 2003;95(5):1851-60. doi:10.1152/japplphysiol.00246.2003

67. Patel SM, Duchowny KA, Kiel DP, Correa-de-Araujo R, Fielding RA, Travison T, et al. Sarcopenia Definition & Outcomes Consortium Defined Low Grip Strength in Two Cross-Sectional, Population-Based Cohorts. Journal of the American Geriatrics Society. 2020;68(7):1438-44. doi:10.1111/jgs.16419
68. Assantachai P, Muangpaisan W, Intalapaporn S, Sitthichai K, Udompunturak S. Cut-off points of quadriceps strength, declines and relationships of sarcopenia-related variables among Thai community-dwelling older adults. Geriatrics & gerontology international. 2014;14 Suppl 1:61-8. doi:10.1111/ggi.12207
69. Bahat G, Kilic C, Topcu Y, Aydin K, Karan MA. Fat percentage cutoff values to define obesity and prevalence of sarcopenic obesity in community-dwelling older adults in Turkey. The aging male : the official journal of the International Society for the Study of the Aging Male. 2020;23(5):477-82. doi:10.1080/13685538.2018.1530208
70. Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, et al. Epidemiology of sarcopenia among the elderly in New Mexico. American journal of epidemiology. 1998;147(8):755-63. doi:10.1093/oxfordjournals.aje.a009520
71. Cesari M, Kritchevsky SB, Newman AB, Simonsick EM, Harris TB, Penninx BW, et al. Added value of physical performance measures in predicting adverse health-related events: results from the Health, Aging And Body Composition Study. Journal of the American Geriatrics Society. 2009;57(2):251-9. doi:10.1111/j.1532-5415.2008.02126.x
72. Ishii S, Chang C, Tanaka T, Kuroda A, Tsuji T, Akishita M, et al. The Association between Sarcopenic Obesity and Depressive Symptoms in Older Japanese Adults. PloS one. 2016;11(9):e0162898. doi:10.1371/journal.pone.0162898
73. Kim TN, Yang SJ, Yoo HJ, Lim KI, Kang HJ, Song W, et al. Prevalence of sarcopenia and sarcopenic obesity in Korean adults: the Korean sarcopenic obesity study. International journal of obesity. 2009;33(8):885-92. doi:10.1038/ijo.2009.130
74. Lee J, Hong YP, Shin HJ, Lee W. Associations of Sarcopenia and Sarcopenic Obesity With Metabolic Syndrome Considering Both Muscle Mass and Muscle Strength. Journal of preventive medicine and public health = Yebang Uihakhoe chi. 2016;49(1):35-44. doi:10.3961/jpmph.15.055
75. Martien S, Delecluse C, Boen F, Seghers J, Pelssers J, Van Hoecke AS, et al. Is knee extension strength a better predictor of functional performance than handgrip strength among older adults in three different settings? Archives of gerontology and geriatrics. 2015;60(2):252-8. doi:10.1016/j.archger.2014.11.010
76. Pedrero-Chamizo R, Gomez-Cabello A, Melendez A, Vila-Maldonado S, Espino L, Gusi N, et al. Higher levels of physical fitness are associated with a reduced risk of suffering sarcopenic obesity and better perceived health among the elderly: the EXERNET multi-center study. The journal of nutrition, health & aging. 2015;19(2):211-7. doi:10.1007/s12603-014-0530-4
77. Rikli RE, Jones CJ. Development and validation of criterion-referenced clinically relevant fitness standards for maintaining physical independence in later years. The Gerontologist. 2013;53(2):255-67. doi:10.1093/geront/gns071
78. Seger JCH, D. B.; Westman, E. C.; Lindquist, R.; Scinta, W.; Richardson, L. A. et al. American Society of Bariatric Physicians Obesity Algorithm: Adult Adiposity Evaluation and Treatment 2013. www.obesityalgorithm.org (Accessed = 20.10.2021]).
79. Spruit MA, Sillen MJ, Groenen MT, Wouters EF, Franssen FM. New normative values for handgrip strength: results from the UK Biobank. Journal of the American Medical Directors Association. 2013;14(10):775 e5-11. doi:10.1016/j.jamda.2013.06.013
80. Zoico E, Di Francesco V, Guralnik JM, Mazzali G, Bortolani A, Guariento S, et al. Physical disability and muscular strength in relation to obesity and different body composition indexes in a sample of healthy elderly women. International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity. 2004;28(2):234-41. doi:10.1038/sj.ijo.0802552
81. An KO, Kim J. Association of Sarcopenia and Obesity With Multimorbidity in Korean Adults: A Nationwide Cross-Sectional Study. Journal of the American Medical Directors Association. 2016;17(10):960 e1-7. doi:10.1016/j.jamda.2016.07.005
82. Baek SJ, Nam GE, Han KD, Choi SW, Jung SW, Bok AR, et al. Sarcopenia and sarcopenic obesity and their association with dyslipidemia in Korean elderly men: the 2008-2010 Korea National Health and Nutrition Examination Survey. Journal of endocrinological investigation. 2014;37(3):247-60. doi:10.1007/s40618-013-0011-3
83. Cho Y, Shin SY, Shin MJ. Sarcopenic obesity is associated with lower indicators of psychological health and quality of life in Koreans. Nutrition research. 2015;35(5):384-92. doi:10.1016/j.nutres.2015.04.002
84. Chung JY, Kang HT, Lee DC, Lee HR, Lee YJ. Body composition and its association with cardiometabolic risk factors in the elderly: a focus on sarcopenic obesity. Archives of gerontology and geriatrics. 2013;56(1):270-8. doi:10.1016/j.archger.2012.09.007
85. Davison KK, Ford ES, Cogswell ME, Dietz WH. Percentage of body fat and body mass index are associated with mobility limitations in people aged 70 and older from NHANES III. Journal of the American Geriatrics Society. 2002;50(11):1802-9. doi:10.1046/j.1532-5415.2002.50508.x

86. Hwang B, Lim JY, Lee J, Choi NK, Ahn YO, Park BJ. Prevalence rate and associated factors of sarcopenic obesity in korean elderly population. Journal of Korean medical science. 2012;27(7):748-55. doi:10.3346/jkms.2012.27.7.748
87. Kim JH, Cho JJ, Park YS. Relationship between sarcopenic obesity and cardiovascular disease risk as estimated by the Framingham risk score. Journal of Korean medical science. 2015;30(3):264-71. doi:10.3346/jkms.2015.30.3.264
88. Kim MK, Baek KH, Song KH, Il Kang M, Park CY, Lee WY, et al. Vitamin D deficiency is associated with sarcopenia in older Koreans, regardless of obesity: the Fourth Korea National Health and Nutrition Examination Surveys (KNHANES IV) 2009. The Journal of clinical endocrinology and metabolism. 2011;96(10):3250-6. doi:10.1210/jc.2011-1602
89. Kim YS, Lee Y, Chung YS, Lee DJ, Joo NS, Hong D, et al. Prevalence of sarcopenia and sarcopenic obesity in the Korean population based on the Fourth Korean National Health and Nutritional Examination Surveys. The journals of gerontology Series A, Biological sciences and medical sciences. 2012;67(10):1107-13. doi:10.1093/gerona/gls071
90. Lee S, Kim TN, Kim SH. Sarcopenic obesity is more closely associated with knee osteoarthritis than is nonsarcopenic obesity: a cross-sectional study. Arthritis and rheumatism. 2012;64(12):3947-54. doi:10.1002/art.37696
91. Lee YH, Jung KS, Kim SU, Yoon HJ, Yun YJ, Lee BW, et al. Sarcopaenia is associated with NAFLD independently of obesity and insulin resistance: Nationwide surveys (KNHANES 2008-2011). Journal of hepatology. 2015;63(2):486-93. doi:10.1016/j.jhep.2015.02.051
92. Lim S, Kim JH, Yoon JW, Kang SM, Choi SH, Park YJ, et al. Sarcopenic obesity: prevalence and association with metabolic syndrome in the Korean Longitudinal Study on Health and Aging (KLoSHA). Diabetes care. 2010;33(7):1652-4. doi:10.2337/dc10-0107
93. Oh C, Jho S, No JK, Kim HS. Body composition changes were related to nutrient intakes in elderly men but elderly women had a higher prevalence of sarcopenic obesity in a population of Korean adults. Nutrition research. 2015;35(1):1-6. doi:10.1016/j.nutres.2014.07.018
94. Poggiogalle E, Lubrano C, Sergi G, Coin A, Gnessi L, Mariani S, et al. Sarcopenic Obesity and Metabolic Syndrome in Adult Caucasian Subjects. The journal of nutrition, health & aging. 2016;20(9):958-63. doi:10.1007/s12603-015-0638-1
95. Woolcott OO, Bergman RN. Defining cutoffs to diagnose obesity using the relative fat mass (RFM): Association with mortality in NHANES 1999-2014. International journal of obesity. 2020;44(6):1301-10. doi:10.1038/s41366-019-0516-8
96. Sanchez Torralvo FJ, Porras N, Abuin Fernandez J, Garcia Torres F, Tapia MJ, Lima F, et al. Normative reference values for hand grip dynamometry in Spain. Association with lean mass. Nutricion hospitalaria. 2018;35(1):98-103. doi:10.20960/nh.1052
97. Copay AG, Subach BR, Glassman SD, Polly DW, Jr., Schuler TC. Understanding the minimum clinically important difference: a review of concepts and methods. The spine journal : official journal of the North American Spine Society. 2007;7(5):541-6. doi:10.1016/j.spinee.2007.01.008
98. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. Controlled clinical trials. 1989;10(4):407-15. doi:10.1016/0197-2456(89)90005-6
99. Chon D, Shin J, Kim JH. Consideration of body mass index (BMI) in the association between hand grip strength and hypertension: Korean Longitudinal Study of Ageing (KLoSA). PloS one. 2020;15(10):e0241360. doi:10.1371/journal.pone.0241360
100. Chun SW, Kim W, Choi KH. Comparison between grip strength and grip strength divided by body weight in their relationship with metabolic syndrome and quality of life in the elderly. PloS one. 2019;14(9):e0222040. doi:10.1371/journal.pone.0222040
101. Folland JP, Mc Cauley TM, Williams AG. Allometric scaling of strength measurements to body size. European journal of applied physiology. 2008;102(6):739-45. doi:10.1007/s00421-007-0654-x
102. Cawthon PM, Peters KW, Shardell MD, McLean RR, Dam TT, Kenny AM, et al. Cutpoints for low appendicular lean mass that identify older adults with clinically significant weakness. The journals of gerontology Series A, Biological sciences and medical sciences. 2014;69(5):567-75. doi:10.1093/gerona/glu023
103. Candow DG, Chilibeck PD. Differences in size, strength, and power of upper and lower body muscle groups in young and older men. The journals of gerontology Series A, Biological sciences and medical sciences. 2005;60(2):148-56. doi:10.1093/gerona/60.2.148
104. Wang T, He C. Pro-inflammatory cytokines: The link between obesity and osteoarthritis. Cytokine & growth factor reviews. 2018;44:38-50. doi:10.1016/j.cytogfr.2018.10.002
105. Middleton A, Fritz SL, Lusardi M. Walking speed: the functional vital sign. Journal of aging and physical activity. 2015;23(2):314-22. doi:10.1123/japa.2013-0236
106. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyere O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age and ageing. 2019;48(1):16-31. doi:10.1093/ageing/afy169

107. Xiao J, Purcell SA, Prado CM, Gonzalez MC. Fat mass to fat-free mass ratio reference values from NHANES III using bioelectrical impedance analysis. Clinical nutrition. 2018;37(6 Pt A):2284-7. doi:10.1016/j.clnu.2017.09.021
108. Genton L, Mareschal J, Karsegard VL, Achamrah N, Delsoglio M, Pichard C, et al. An Increase in Fat Mass Index Predicts a Deterioration of Running Speed. Nutrients. 2019;11(3). doi:10.3390/nu11030701
109. Tomlinson DJ, Erskine RM, Morse CI, Winwood K, Onambele-Pearson G. The impact of obesity on skeletal muscle strength and structure through adolescence to old age. Biogerontology. 2016;17(3):467-83. doi:10.1007/s10522-015-9626-4
110. Villareal DT, Banks M, Siener C, Sinacore DR, Klein S. Physical frailty and body composition in obese elderly men and women. Obesity research. 2004;12(6):913-20. doi:10.1038/oby.2004.111
111. Chen LK, Lee WJ, Peng LN, Liu LK, Arai H, Akishita M, et al. Recent Advances in Sarcopenia Research in Asia: 2016 Update From the Asian Working Group for Sarcopenia. Journal of the American Medical Directors Association. 2016;17(8):767 e1-7. doi:10.1016/j.jamda.2016.05.016
112. Walowski CO, Braun W, Maisch MJ, Jensen B, Peine S, Norman K, et al. Reference Values for Skeletal Muscle Mass - Current Concepts and Methodological Considerations. Nutrients. 2020;12(3). doi:10.3390/nu12030755
113. Mereu E, Succa V, Buffa R, Sanna C, Mereu RM, Catte O, et al. Total body and arm bioimpedance in patients with Alzheimer's disease. Experimental gerontology. 2018;102:145-8. doi:10.1016/j.exger.2017.11.011
114. MacDonald AJ, Greig CA, Baracos V. The advantages and limitations of cross-sectional body composition analysis. Current opinion in supportive and palliative care. 2011;5(4):342-9. doi:10.1097/SPC.0b013e32834c49eb
115. Prado CM, Heymsfield SB. Lean tissue imaging: a new era for nutritional assessment and intervention. JPEN Journal of parenteral and enteral nutrition. 2014;38(8):940-53. doi:10.1177/0148607114550189
116. Kawakami R, Miyachi M, Sawada SS, Torii S, Midorikawa T, Tanisawa K, et al. Cut-offs for calf circumference as a screening tool for low muscle mass: WASEDA'S Health Study. Geriatrics & gerontology international. 2020;20(10):943-50. doi:10.1111/ggi.14025
117. Gonzalez MC, Mehrnezhad A, Razaviarab N, Barbosa-Silva TG, Heymsfield SB. Calf circumference: cutoff values from the NHANES 1999-2006. The American journal of clinical nutrition. 2021;113(6):1679-87. doi:10.1093/ajcn/nqab029
118. Kim M, Won CW. Sarcopenia in Korean Community-Dwelling Adults Aged 70 Years and Older: Application of Screening and Diagnostic Tools From the Asian Working Group for Sarcopenia 2019 Update. Journal of the American Medical Directors Association. 2020;21(6):752-8. doi:10.1016/j.jamda.2020.03.018
119. Li R, Hu X, Tan L, Xie L, Zhang L, Zhou J, et al. Screening for Sarcopenia with a Self-Reported Cartoon Questionnaire: Combining SARC-F with Finger-Ring Test. The journal of nutrition, health & aging. 2020;24(10):1100-6. doi:10.1007/s12603-020-1445-x
120. Lim WS, Lim JP, Chew J, Tan AWK. Calf Circumference as a Case-Finding Tool for Sarcopenia: Influence of Obesity on Diagnostic Performance. Journal of the American Medical Directors Association. 2020;21(9):1359-61. doi:10.1016/j.jamda.2020.03.033
121. Mo YH, Zhong J, Dong X, Su YD, Deng WY, Yao XM, et al. Comparison of Three Screening Methods for Sarcopenia in Community-Dwelling Older Persons. Journal of the American Medical Directors Association. 2021;22(4):746-50 e1. doi:10.1016/j.jamda.2020.05.041
122. Santos LP, Gonzalez MC, Orlandi SP, Bielemann RM, Barbosa-Silva TG, Heymsfield SB, et al. New Prediction Equations to Estimate Appendicular Skeletal Muscle Mass Using Calf Circumference: Results From NHANES 1999-2006. JPEN Journal of parenteral and enteral nutrition. 2019;43(8):998-1007. doi:10.1002/jpen.1605
123. Correa-de-Araujo R, Addison O, Miljkovic I, Goodpaster BH, Bergman BC, Clark RV, et al. Myosteatosis in the Context of Skeletal Muscle Function Deficit: An Interdisciplinary Workshop at the National Institute on Aging. Frontiers in physiology. 2020;11:963. doi:10.3389/fphys.2020.00963
124. Tardif N, Salles J, Guillet C, Tordjman J, Reggio S, Landrier JF, et al. Muscle ectopic fat deposition contributes to anabolic resistance in obese sarcopenic old rats through eIF2alpha activation. Aging cell. 2014;13(6):1001-11. doi:10.1111/acel.12263
125. Chen Q-N, Fan Z, Lyu A-K, Wu J, Guo A, Yang Y-F, et al. Effect of sarcolipin-mediated cell transdifferentiation in sarcopenia-associated skeletal muscle fibrosis. Experimental Cell Research. 2020;389(1):111890. doi:10.1016/j.yexcr.2020.111890
126. Ugras S. Evaluating of altered hydration status on effectiveness of body composition analysis using bioelectric impedance analysis. The Libyan journal of medicine. 2020;15(1):1741904. doi:10.1080/19932820.2020.1741904
127. Ballesteros-Pomar MD, Gonzalez-Arnaiz E, Pintor-de-la Maza B, Barajas-Galindo D, Ariadel-Cobo D, Gonzalez-Roza L, et al. Bioelectrical impedance analysis as an alternative to dual-energy x-ray absorptiometry in the assessment of fat mass and appendicular lean mass in patients with obesity. Nutrition. 2022;93:111442. doi:10.1016/j.nut.2021.111442

128. Johnson Stoklossa CA, Forhan M, Padwal RS, Gonzalez MC, Prado CM. Practical Considerations for Body Composition Assessment of Adults with Class II/III Obesity Using Bioelectrical Impedance Analysis or Dual-Energy X-Ray Absorptiometry. Current obesity reports. 2016;5(4):389-96. doi:10.1007/s13679-016-0228-5
129. Becroft L, Ooi G, Forsyth A, King S, Tierney A. Validity of multi-frequency bioelectric impedance methods to measure body composition in obese patients: a systematic review. International journal of obesity. 2019;43(8):1497-507. doi:10.1038/s41366-018-0285-9
130. Barreira TV, Tseh W. The effects of acute water ingestion on body composition analyses via Dual-Energy X-Ray Absorptiometry. Clinical nutrition. 2020;39(12):3836-8. doi:10.1016/j.clnu.2020.03.037
131. Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Gomez JM, et al. Bioelectrical impedance analysis--part I: review of principles and methods. Clinical nutrition. 2004;23(5):1226-43. doi:10.1016/j.clnu.2004.06.004
132. Di Vincenzo O, Marra M, Di Gregorio A, Pasanisi F, Scalfi L. Bioelectrical impedance analysis (BIA) -derived phase angle in sarcopenia: A systematic review. Clinical nutrition. 2021;40(5):3052-61. doi:10.1016/j.clnu.2020.10.048
133. Wu H, Ding P, Wu J, Yang P, Tian Y, Zhao Q. Phase angle derived from bioelectrical impedance analysis as a marker for predicting sarcopenia. Frontiers in nutrition. 2022;9:1060224. doi:10.3389/fnut.2022.1060224
134. Buffa R, Saragat B, Cabras S, Rinaldi AC, Marini E. Accuracy of specific BIVA for the assessment of body composition in the United States population. PloS one. 2013;8(3):e58533. doi:10.1371/journal.pone.0058533
135. Marini E, Buffa R, Saragat B, Coin A, Toffanello ED, Berton L, et al. The potential of classic and specific bioelectrical impedance vector analysis for the assessment of sarcopenia and sarcopenic obesity. Clinical interventions in aging. 2012;7:585-91. doi:10.2147/CIA.S38488
136. Cawthon PM, Blackwell T, Cummings SR, Orwoll ES, Duchowny KA, Kado DM, et al. Muscle Mass Assessed by the D3-Creatine Dilution Method and Incident Self-reported Disability and Mortality in a Prospective Observational Study of Community-Dwelling Older Men. The journals of gerontology Series A, Biological sciences and medical sciences. 2021;76(1):123-30. doi:10.1093/gerona/glaa111
137. Heymsfield SB, Gonzalez MC, Lu J, Jia G, Zheng J. Skeletal muscle mass and quality: evolution of modern measurement concepts in the context of sarcopenia. The Proceedings of the Nutrition Society. 2015;74(4):355-66. doi:10.1017/S0029665115000129
138. Simo-Servat A, Ibarra M, Libran M, Rodriguez S, Perea V, Quiros C, et al. Usefulness of Muscle Ultrasound to Study Sarcopenic Obesity: A Pilot Case-Control Study. Journal of clinical medicine. 2022;11(10). doi:10.3390/jcm11102886
139. Roh E, Choi KM. Health Consequences of Sarcopenic Obesity: A Narrative Review. Frontiers in endocrinology. 2020;11:332. doi:10.3389/fendo.2020.00332
140. Petroni ML, Caletti MT, Dalle Grave R, Bazzocchi A, Aparisi Gomez MP, Marchesini G. Prevention and Treatment of Sarcopenic Obesity in Women. Nutrients. 2019;11(6). doi:10.3390/nu11061302
141. Kritchevsky SB, Beavers KM, Miller ME, Shea MK, Houston DK, Kitzman DW, et al. Intentional weight loss and all-cause mortality: a meta-analysis of randomized clinical trials. PloS one. 2015;10(3):e0121993. doi:10.1371/journal.pone.0121993
142. Poggiogalle E, Migliaccio S, Lenzi A, Donini LM. Treatment of body composition changes in obese and overweight older adults: insight into the phenotype of sarcopenic obesity. Endocrine. 2014;47(3):699-716. doi:10.1007/s12020-014-0315-x
143. Poggiogalle E, Parrinello E, Barazzoni R, Busetto L, Donini LM. Therapeutic strategies for sarcopenic obesity: a systematic review. Current opinion in clinical nutrition and metabolic care. 2021;24(1):33-41. doi:10.1097/MCO.0000000000000714
144. Eglseer D, Traxler M, Schoufour J, Weijs P, Voortman T, Boirie Y, et al. Effectiveness of nutritional and exercise interventions in individuals with sarcopenic obesity around retirement age: A systematic review and meta-analysis. Nutr Rev. IN PRESS.
145. Hoffman DM, O'Sullivan AJ, Freund J, Ho KK. Adults with growth hormone deficiency have abnormal body composition but normal energy metabolism. The Journal of clinical endocrinology and metabolism. 1995;80(1):72-7. doi:10.1210/jcem.80.1.7829643
146. Sinclair M, Grossmann M, Hoermann R, Angus PW, Gow PJ. Testosterone therapy increases muscle mass in men with cirrhosis and low testosterone: A randomised controlled trial. Journal of hepatology. 2016;65(5):906-13. doi:10.1016/j.jhep.2016.06.007
147. Baillargeon J, Urban RJ, Zhang W, Zaiden MF, Javed Z, Sheffield-Moore M, et al. Testosterone replacement therapy and hospitalization rates in men with COPD. Chronic respiratory disease. 2019;16:1479972318793004. doi:10.1177/1479972318793004
148. Villareal DT, Aguirre L, Gurney AB, Waters DL, Sinacore DR, Colombo E, et al. Aerobic or Resistance Exercise, or Both, in Dieting Obese Older Adults. The New England journal of medicine. 2017;376(20):1943-55. doi:10.1056/NEJMoa1616338

149. Hope DCD, Vincent ML, Tan TMM. Striking the Balance: GLP-1/Glucagon Co-Agonism as a Treatment Strategy for Obesity. Frontiers in endocrinology. 2021;12:735019. doi:10.3389/fendo.2021.735019
150. Piaggi P, Vinales KL, Basolo A, Santini F, Krakoff J. Energy expenditure in the etiology of human obesity: spendthrift and thrifty metabolic phenotypes and energy-sensing mechanisms. Journal of endocrinological investigation. 2018;41(1):83-9. doi:10.1007/s40618-017-0732-9
151. Rossini A, Lanzi R, Galeone C, Pelucchi C, Pennacchioni M, Perticone F, et al. Bone and body composition analyses by DXA in adults with GH deficiency: effects of long-term replacement therapy. Endocrine. 2021;74(3):666-75. doi:10.1007/s12020-021-02835-6
152. Kirkland JL, Tchkonia T. Senolytic drugs: from discovery to translation. Journal of internal medicine. 2020;288(5):518-36. doi:10.1111/joim.13141
153. Heymsfield SB, Coleman LA, Miller R, Rooks DS, Laurent D, Petricoul O, et al. Effect of Bimagrumab vs Placebo on Body Fat Mass Among Adults With Type 2 Diabetes and Obesity: A Phase 2 Randomized Clinical Trial. JAMA network open. 2021;4(1):e2033457. doi:10.1001/jamanetworkopen.2020.33457