Clinical Nutrition 41 (2022) 2244–2263

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Narrative Review

Advances in muscle health and nutrition: A toolkit for healthcare professionals

Carla M. Prado [a, *], Francesco Landi [b], Samuel T.H. Chew [c], Philip J. Atherton [d], Jeroen Molinger [e, f], Tobias Ruck [g], Maria Cristina Gonzalez [h]

[a] Department of Agricultural, Food and Nutritional Science, University of Alberta, Edmonton, AB, Canada
[b] Fondazione Policlinico A. Gemelli IRCCS, Rome, Italy
[c] Department of Geriatric Medicine, Changi General Hospital, Singapore Health Services (Simei Campus), Singapore
[d] Centre of Metabolism, Ageing & Physiology (COMAP), Medical Research Council (MRC) Versus Arthritis Centre for Musculoskeletal Ageing Research (CMAR), and National Institution for Health Research (NIHR) Biomedical Research Centre (BRC), School of Medicine, University of Nottingham, Nottingham, UK
[e] Duke University Hospital, School of Medicine, Durham, NC, USA
[f] Erasmus Medical Center, University Rotterdam, Rotterdam, the Netherlands
[g] Department of Neurology, Medical Faculty, Heinrich Heine University Düsseldorf, Düsseldorf, Germany
[h] Post-graduate Program in Health and Behavior, Catholic University of Pelotas, and Post-graduate Program in Nutrition and Food, Federal University of Pelotas, Pelotas, Rio Grande do Sul, Brazil

ARTICLE INFO

Article history:
Received 18 February 2022
Accepted 31 July 2022

Keywords:
Muscle mass
Malnutrition
Body composition
Nutrition screening
Nutrition assessment
Nutrition interventions

SUMMARY

Low muscle mass and malnutrition are prevalent conditions among adults of all ages, with any body weight or body mass index, and with acute or chronic conditions, including COVID-19. This article synthesizes the latest research advancements in muscle health and malnutrition, and their impact on immune function, and clinical outcomes. We provide a toolkit of illustrations and scientific information that healthcare professionals can use for knowledge translation, educating patients about the importance of identifying and treating low muscle mass and malnutrition. We focus on the emerging evidence of mitochondrial dysfunction in the context of aging and disease, as well as the cross-talk between skeletal muscle and the immune system. We address the importance of myosteatosis as a component of muscle composition, and discuss direct, indirect and surrogate assessments of muscle mass including ultrasound, computerized tomography, deuterated creatine dilution, and calf circumference. Assessments of muscle function are also included (handgrip strength, and physical performance tests). Finally, we address nutrition interventions to support anabolism, reduce catabolism, and improve patient outcomes. These include protein and amino acids, branched-chain amino acids, with a focus on leucine; β-hydroxy-β-methylbutyrate (HMB), vitamin D; n-3 polyunsaturated fatty acids (n-3 PUFA), polyphenols, and oral nutritional supplements. We concluded with recommendations for clinical practice and a call for action on research focusing on evaluating the impact of body composition assessments on targeted nutrition interventions, and consequently their ability to improve patient outcomes.

1. Introduction

Low muscle mass and malnutrition impact the health and well-being of many individuals, especially older adults and patients with acute and chronic diseases. As such, early detection and intervention are essential to counteract the detrimental effects of these conditions. The advent of body composition assessment has allowed researchers to define important characteristics and consequences of low muscle mass (Fig. 1). Since low muscle and malnutrition are often hidden in patients with normal weight or in

Abbreviations: BIA, bioelectrical impedance analysis; BMI, body mass index; CRP, C-reactive protein; CT, computerized tomography; D_3Cr, deuterated creatine; DXA, dual-energy X-ray absorptiometry; EAA, essential amino acid; GLIM, Global Leadership Initiative in Malnutrition; HMB, β-hydroxy-β-methylbutyrate; HOMA-IR, homeostasis model assessment for insulin resistance; ICU, intensive care unit; MPB, muscle protein breakdown; MPS, muscle protein synthesis; MRI, magnetic resonance imaging; MST, Malnutrition Screening Tool; mTOR, mammalian target of rapamycin; MUST, Malnutrition Universal Screening Tool; n-3 PUFA, n-3 polyunsaturated fatty acids; NRS-2002, Nutrition Risk Screening 2002; ONS, oral nutritional supplement; PhA, phase angle; RCT, randomized controlled trial; SGA, Subjective Global Assessment; US, ultrasound.

* Corresponding author. 2-021 Li Ka Shing Centre for Health Innovation, University of Alberta, Edmonton, AB, T6G 2E1, Canada. Fax: +1780 492.9555.
E-mail address: Carla.prado@ualberta.ca (C.M. Prado).

https://doi.org/10.1016/j.clnu.2022.07.041

those with excess adiposity, these conditions are frequently overlooked; therefore, such techniques are of significant value [1,2]. In fact, both malnutrition and low muscle mass are prevalent among young and older adults of any body weight or body mass index (BMI) and in any clinical condition, including COVID-19 [2–4]. They can also occur regardless of weight change [5]. Finally, low muscle mass and malnutrition are associated with impaired immune function and are independent predictors of adverse clinical outcomes, such as the ones highlighted in Fig. 2 [2,3,6–14].

Integrating assessment of muscle mass and malnutrition into clinical practice across the continuum of care is challenging but required for early identification of at-risk patients [2]. This would also allow for appropriate and personalized nutrition and exercise interventions in the context of multimodal therapy (Fig. 1), which can be delivered by a multidisciplinary team [15,16]. Efforts to translate research-based evidence to daily clinical practice takes time but eventually becomes reality, improving patient care and clinical outcomes. For example, it took 50 years after the term "osteoporosis" was coined and defined for osteoporosis to be recognized as a condition that is readily assessed and treated [17]. (Fig. S1).

While our understanding of both the importance of poor muscle health and nutritional status as therapeutic target/approach has grown, these conditions are still underappreciated, with a wide gap between research findings and evidence-based clinical practice. To bridge this gap, or translate the knowledge from research into clinical practice, there is a need for more high-quality studies highlighting the value of assessing and treating these conditions; increased awareness; and a pathway for clinical practice implementation. Regarding increased awareness, common barriers are: limited access to information sources; high volumes of evidence but limited dedicated time to read; and limited research interpretation skills [18].

This article reports on the 119th Abbott Nutrition Research Conference held in June 2021. This is an annual global research conference on key topics in pediatric and adult nutrition. The objective of this edition was to bring together global experts to provide healthcare professionals with a summary of the latest advances in muscle mass and malnutrition research in the contexts of aging and disease. In addition to synthesizing and updating the scientific literature discussed at the meeting, our goal with this publication is to enable continued knowledge transfer beyond the conference by providing a resource that healthcare professionals can use as educational materials on this topic. As such, this article is a "toolkit" comprising scientific information and illustrations that can facilitate knowledge transfer on the identification, importance, and treatment of low muscle mass and malnutrition.

To improve understanding of the content hereby discussed, we first define some important concepts. For instance, several terms are commonly employed to describe muscle mass, such as lean soft tissue, fat-free mass, and skeletal muscle. Although these terms are often used interchangeably, they depict different body compartments containing skeletal muscle [19] and are specific to the techniques employed for body composition assessment. Here, we use precise terminology to describe body compartments containing skeletal muscle, and this may therefore differ from original studies. We also used the term "muscle mass" generically to describe lean soft tissue, fat-free mass, and skeletal muscle. To avoid the confusion between primary and secondary sarcopenia (terms defined elsewhere [20]), we will hereby use the term "muscle health" to depict adequate muscle mass, composition (i.e., no myosteatosis), and/or function (i.e., strength and physical performance). We will use the term "sarcopenia" to depict conditions of low muscle mass and function concurrently [21,22].

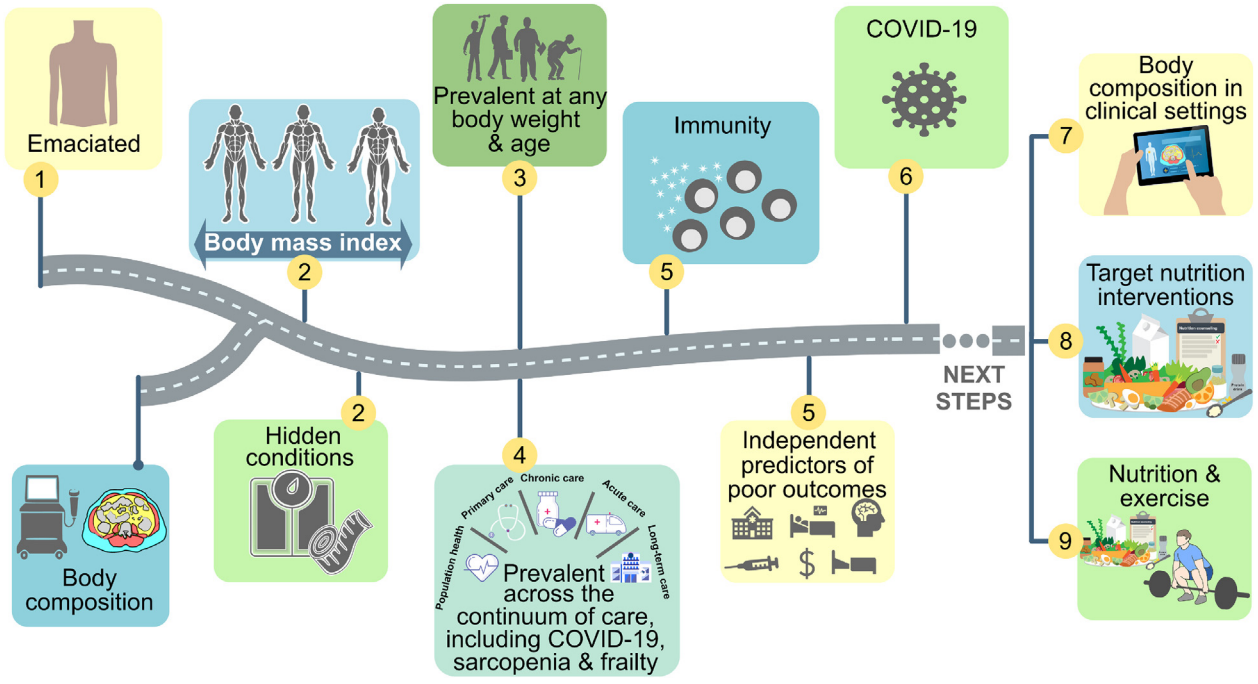

Fig. 1. Chronology of malnutrition, muscle, and body composition definitions. The advent of new technology to assess body composition has allowed us to understand that low muscle mass and malnutrition: (1) are not only observed in people who have an emaciated appearance; (2) may be hidden conditions; (3) are prevalent at any body weight and age; (4) are particularly prevalent in older adults and across the continuum of care; and (5) are associated with immunity, and are independent predictors of clinical outcomes. Also, (6) COVID-19 has capitalized the importance of low muscle mass. Future research is required to (7) implement body composition assessment in clinical settings, (8) explore the use of targeted nutrition interventions to prevent and treat low muscle mass and malnutrition, and (9) understand the effects of concurrent nutrition and exercise interventions to maximize anabolic potential.

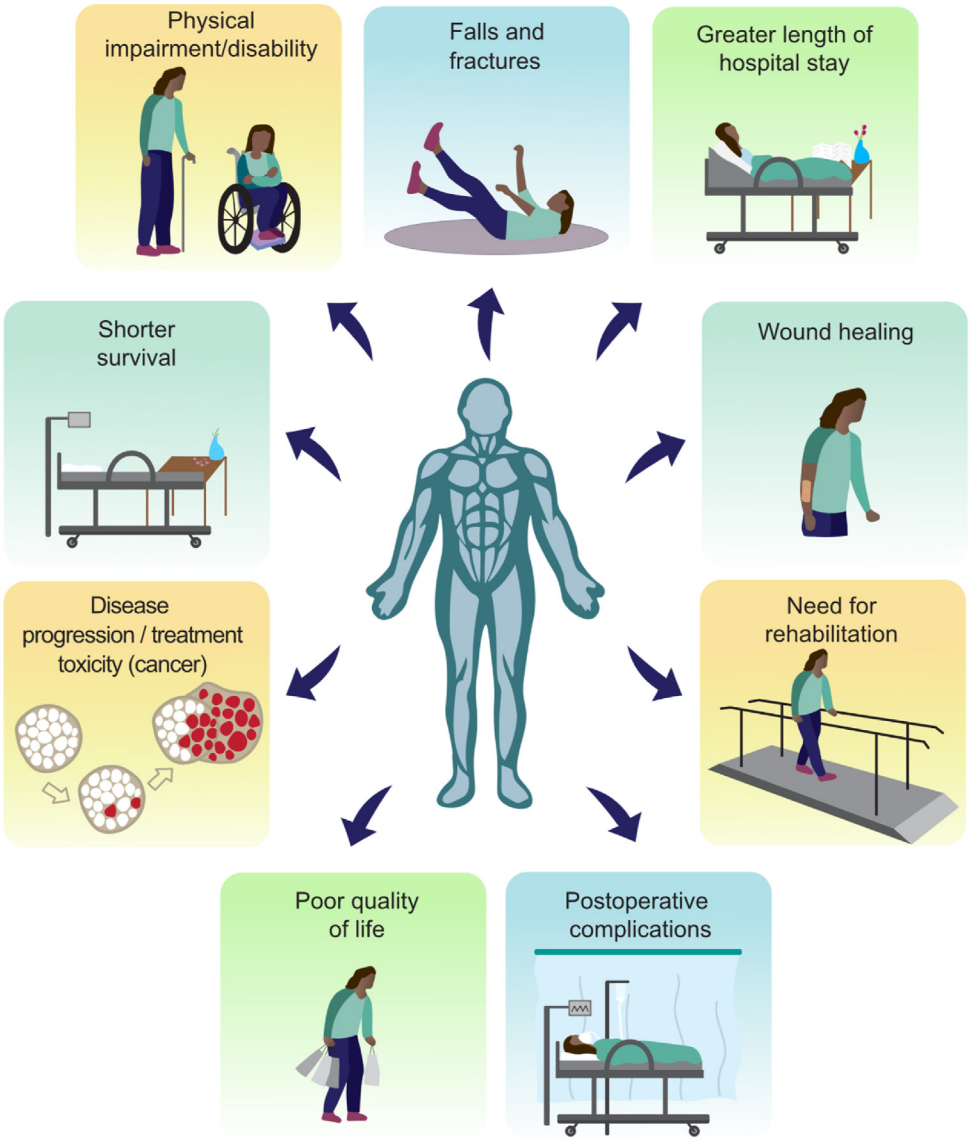

Fig. 2. Selected consequences of low muscle mass (or related conditions, such as sarcopenia, frailty, and cachexia) and malnutrition across aging and clinical populations. There is an extensive body of research reporting on the associations between low muscle mass and physical impairment or disability, falls and fractures, increased length of hospital stay, wound healing, need for rehabilitation, higher risk of post-operative complications, poor quality of life, tumor progression, increased treatment toxicity, and reduced survival.

2. Toward a better understanding of low muscle mass and malnutrition as overlapping conditions

Low muscle mass is a defining criterion for the diagnosis of malnutrition, sarcopenia, and cachexia, according to current consensus definitions [21–25]. Aside from the phenotype of low muscle mass, these conditions share common characteristics including etiological factors, such as aging, low physical activity, reduced nutrient intake and absorption, and systemic inflammation (Fig. 3). Given these similarities, malnutrition and muscle-related conditions (i.e., low muscle mass, myosteatosis [or fatty infiltration of muscle tissue], sarcopenia, cachexia, and frailty) should not be viewed as isolated entities but rather as conditions that can occur simultaneously or sequentially in some individuals. *Most patients with malnutrition have low muscle mass or sarcopenia, but people with malnutrition do not necessarily need to have low muscle mass or sarcopenia* [23,24]. *Likewise, not all patients with low muscle mass or sarcopenia are malnourished*. Malnutrition is often a precursor to sarcopenia as it leads to reduced physical function and unfavorable changes in body composition. For instance, malnutrition at baseline was associated with a four-fold increased risk of developing sarcopenia over a five-year period in community-dwelling older adults [26]. Consequently, sarcopenia can both precede frailty and be a component of frailty, which is a precursor to adverse outcomes; and both conditions often overlap with malnutrition [27,28].

Although low muscle mass and malnutrition can occur independently of each other, they frequently overlap, especially among hospitalized patients and those with chronic conditions such as cancer [1,29–31]. A recent systematic review and meta-analysis of 39 studies in older hospitalized patients (n = 8868) found that almost 50% of patients were simultaneously diagnosed with malnutrition and frailty, and 42% were diagnosed with malnutrition and sarcopenia, highlighting their concurrent presence [29]. Among patients with head and neck cancer (61% with advanced cancer) at diagnosis, malnutrition was found in 14% of those with

concurrent low muscle mass and myosteatosis; only 7% of patients presented with low muscle mass alone [30]. Furthermore, the prevalence of malnutrition, frailty, and sarcopenia ranged from 44% to 69% among patients with cachexia [31]. The overlap between conditions has also been described in a recent general population cohort study (n = 111 983); among individuals diagnosed with malnutrition, 68% also had cachexia, 91% had sarcopenia, and 92% had frailty [32]. The cumulative impact of having these conditions simultaneously remains to be established, but evidence suggests worse health outcomes. For instance, hospitalized older patients with concurrent malnutrition and sarcopenia had a greater hazard ratio for shorter survival than those with malnutrition alone [33].

3. Emerging evidence on the pathophysiology of low muscle mass

Low muscle mass is prevalent among older adults as a consequence of the aging process and can be exacerbated in patients (of any age) with chronic disease, acute illness, or injuries. As low muscle mass is a common component of malnutrition, sarcopenia, and cachexia, understanding its pathophysiology is relevant for advancing diagnosis and treatment. Immobility and catabolic conditions induce muscle loss when protein degradation pathways become active: the ubiquitin-proteasome system, which degrades most myofibrillar proteins; and the autophagy-lysosome system, which bulk degrades cellular components and organelles in the cytoplasm (e.g., mitochondria) [34,35]. Malnutrition and acute and chronic diseases are accelerators for muscle loss (Fig. 4). While the pathophysiology of muscle wasting is incompletely understood, factors contributing to muscle catabolism have been the focus of intensive research in the last decades, and these include abnormalities in muscle proteostasis, i.e., fasted/fed-state and disuse regulation of muscle protein synthesis (MPS) and muscle protein breakdown (MPB) [36,37], glucose and insulin homeostasis [38], inflammation [38,39], neuromuscular [40], and/or microvascular function [41,42]. These concepts can be further reviewed elsewhere [43,44].

In relation to emerging facets of muscle atrophy, mitochondrial dysfunction is increasingly recognized as an important metabolic regulator [45,46]. In the context of aging, several skeletal muscle mitochondrial processes are impaired, including mitochondrial bioenergetics, as well as mitochondrial synthesis and breakdown ("mitophagy") [47,48]. Mechanisms contributing to these mitochondrial modifications are reviewed elsewhere [49–51]. Notably, impaired mitochondrial function has been associated with both reduced muscle mass and strength. Although most of the evidence is based on animal experiments, there is a considerable body of research investigating alterations of mitochondrial processes in individuals with low muscle mass and/or function [49]. For instance, a recent study using genome-wide transcriptional profiling demonstrated that reduced mitochondrial bioenergetic capacity in muscle was the main factor distinguishing the presence of sarcopenia in older adults [52]. Moreover, differences in mitochondrial function of respiratory muscles were found across body composition phenotypes in patients undergoing lung resections: those with concurrent low muscle mass and high adiposity (i.e., sarcopenic obesity) had the lowest expression of markers for mitochondrial dynamics (i.e., biogenesis, fusion, and fission), compared to other phenotypes [53].

Mitochondrial dysfunction also exists in other acute and chronic conditions, such as cancer and sepsis [54]. The rapid muscle wasting in critical illness may also be partly due to inflammation-mediated mitochondrial dysfunction, with altered metabolism causing protein catabolism and suppressed lipid metabolism and therefore, myosteatosis [46]. With myosteatosis, blood flow to muscle is reduced giving rise to metabolic dysfunction, including insulin resistance, inflammation, and the loss of muscle mass and function [55].

3.1. Cross-talk between muscle and immune system

The cross-talk between skeletal muscle, as the largest organ in the body, and the immune system is also an emerging theme. Indeed, muscle is no longer seen as a passive target of the immune system but as an active player that regulates both innate and adaptive immune responses [56]. Three main mechanisms of interaction between skeletal muscle and immune cells have been discussed in the literature, including the release of myokines,

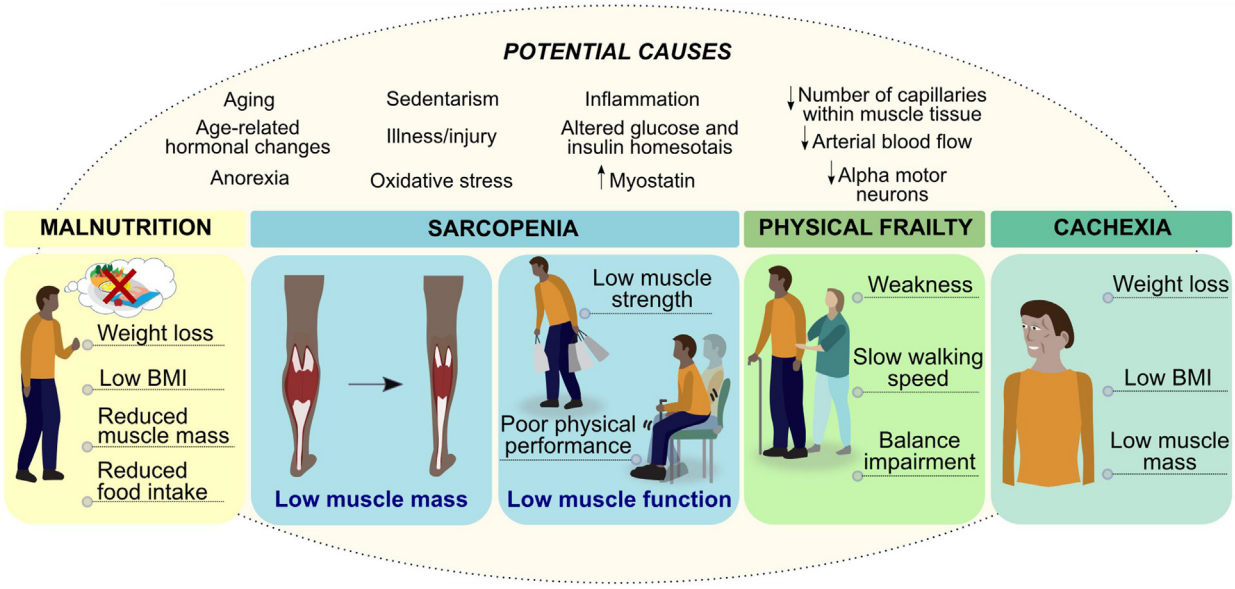

Fig. 3. Interplay among malnutrition, sarcopenia, physical frailty, and cachexia. Malnutrition is one of the factors that can lead to loss of muscle mass and function (i.e., sarcopenia), which may progress to physical frailty, with negative health outcomes such as mobility and disability. In contrast, malnutrition and low muscle mass may progress to cachexia in individuals with chronic diseases, such as cancer. Because excess adiposity may mask underlying malnutrition and/or low muscle mass, in depth assessments are essential for early identification of at-risk patients and targeted interventions.

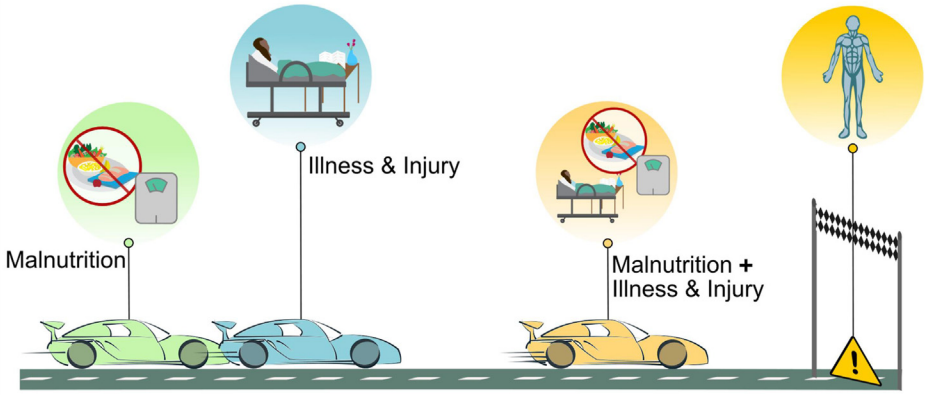

Fig. 4. Factors that accelerate muscle loss. Malnutrition, illness and injury are accelerators of muscle loss. However, the rate of muscle loss is greater (i.e., accelerated) when these factors are combined, leading to severe, more rapid muscle loss.

expression of cell surface molecules, and cell to cell interaction [56–58]. In addition to contributing to sarcopenia and mitochondrial dysfunction, aging also affects the immune system by impairing these mechanisms of interaction, therefore reducing the functionality of immune cells in a process known as "immunosenescence" [58].

Aging is associated with low levels of chronic inflammation – referred to as "inflammaging". In the presence of low-grade inflammation, myokines such as interleukin-6 and interleukin-15 activate pro-inflammatory programming leading to muscle catabolism [57]. The regenerative capacity and inflammatory responses in aged muscles are also affected due to impaired homeostasis of regulatory T cells [57]. Although these and other mechanisms explaining the interplay between skeletal muscle and immune cells have been proposed based on *in vitro* and animal experiments, evidence from clinical studies is limited to cross–sectional associations between inflammatory markers and body composition measures [57]. For example, a recent report from the Copenhagen Sarcopenia Study indicated that concentrations of pro-inflammatory cytokines (i.e., C-reactive protein [CRP], tumor necrosis factor-alpha, interleukin-4, and interferon-γ) increased with aging and were associated with poor physical function; however, only CRP was weakly associated with appendicular lean soft tissue index [59].

Few longitudinal studies with contradicting findings exist to date. In a small prospective cohort study, older adults with high circulating interleukin-6 and CRP levels at baseline had an increased risk of presenting with lower appendicular lean soft tissue after a 5-year follow-up [60]. Although another longitudinal study showed an age-related decline in muscle function, no difference in the incidence of sarcopenia among older adults with a "senescent-like phenotype" compared to a "less senescent-like phenotype" was found [61]. Despite these early clinical findings, immune function is highly relevant in the context of muscle loss, and future studies will confirm or refute these observations.

4. Who is at risk of malnutrition and muscle loss?

4.1. Aging

Poor musculoskeletal health and malnutrition are common among older adults and tied to declining function and the ability to live independently. After the third decade of life, individuals experience an approximately 3%–5% decline in skeletal muscle per decade that is associated with senescence (Fig. 5) [62–66]. Muscle composition also deteriorates with aging, with myosteatosis occurring independently of changes in body weight [67]. The incipient, age-related decline in muscle mass and composition can be accelerated by multiple factors as previously discussed in Sections 2 and 3. A major contributor to malnutrition and muscle loss is anorexia of aging, which is a common term to describe the unintentional decline in nutrient intake later in life [68]. Although adults experience gradual age-related muscle loss, there is some evidence of acute muscle wasting during immobilization even when healthy adults (independent of their age) are provided with adequate energy and protein intakes; but this has been shown to occur more rapidly in older adults [69–71].

4.2. Chronic diseases

Across the healthcare continuum, low muscle mass and malnutrition can overlap and occur as direct consequences of chronic disease or its treatment [3], as observed in renal disease and cancer. Between 11% and 54% of patients with chronic kidney disease are malnourished; the prevalence of sarcopenia has been shown to range between 4% and 42%, depending on the diagnostic criteria used and the patient population [72]. Among patients with cancer, approximately 40% may have low muscle mass, and on average 70% are malnourished [1,73,74]. Muscle loss in chronic illness is progressive over time, but the extent and rate of decline varies across conditions because of the multiple factors affecting the muscle (Fig. 5, Fig. 6) [20]. Furthermore, immobilization and bed rest contribute to an increased rate of muscle wasting among patients with chronic illness [75,76]. The burden of both low muscle mass and malnutrition is common in these patients, highlighting the importance of nutrition interventions to treat and maintain muscle and nutritional status, as both can impact outcomes.

4.3. Critical illness

Muscle loss and malnutrition are also highly prevalent features of critical illness, which is characterized by systemic inflammation [77,78]. Serial ultrasound measurements of cross-sectional area of a quadriceps muscle obtained during the first week of hospitalization in the intensive care unit (ICU) showed early and rapid muscle loss, which is quantitatively more substantial in severely ill patients (Fig. 5) [79]. Myosteatosis identified from computerized tomography (CT) scans upon admission is associated with mortality, independent of muscle mass, and is thus an important marker of muscle

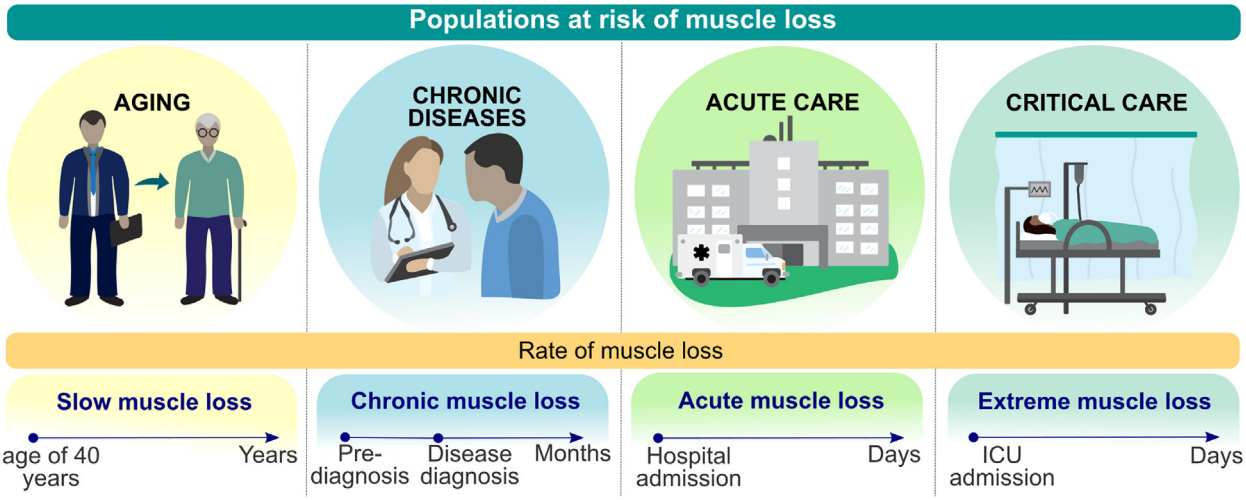

Fig. 5. Illustration showing populations at increased risk of muscle loss. The rate and extent of muscle loss vary across non-clinical and clinical conditions, ranging from gradual loss over years with advancing age to acute and extreme loss over a few days in hospitalized patients due to immobilization, negative caloric-protein balance, and disease-related factors. Abbreviation: ICU, intensive care unit.

composition [80]. Regarding malnutrition, between 38% and 78% of critically ill patients are malnourished, which is independently associated with poor clinical outcomes [81]. Muscle wasting, myosteatosis, and malnutrition impact survival and long-term recovery of critically ill patients, underscoring the importance of early and consistent nutrition interventions and monitoring.

4.4. COVID-19

As a new disease, COVID-19 has amplified the relevance of low muscle mass as never before; the loss is severe and may have long-term consequences (Fig. 7 and Fig. S2) [82,83]. In patients with COVID-19, the pooled prevalence of CT-assessed low skeletal muscle mass is 33.6% [84]. Although inconsistencies exist, preliminary results (article under review, personal communications Dr. C. Prado, PhD, RD) of a systematic review on the clinical impact of abnormal body composition in COVID-19 show low muscle mass as a strong predictor of mortality, hospitalization outcomes, mechanic ventilation, disease severity, and ICU admission [85]. The prevalence of abnormal muscle composition (i.e., low muscle radiodensity) ranged between 28.7% and 85.2%. In contrast to muscle quantity findings, low muscle radiodensity was consistently associated with adverse outcomes in these patients [85].

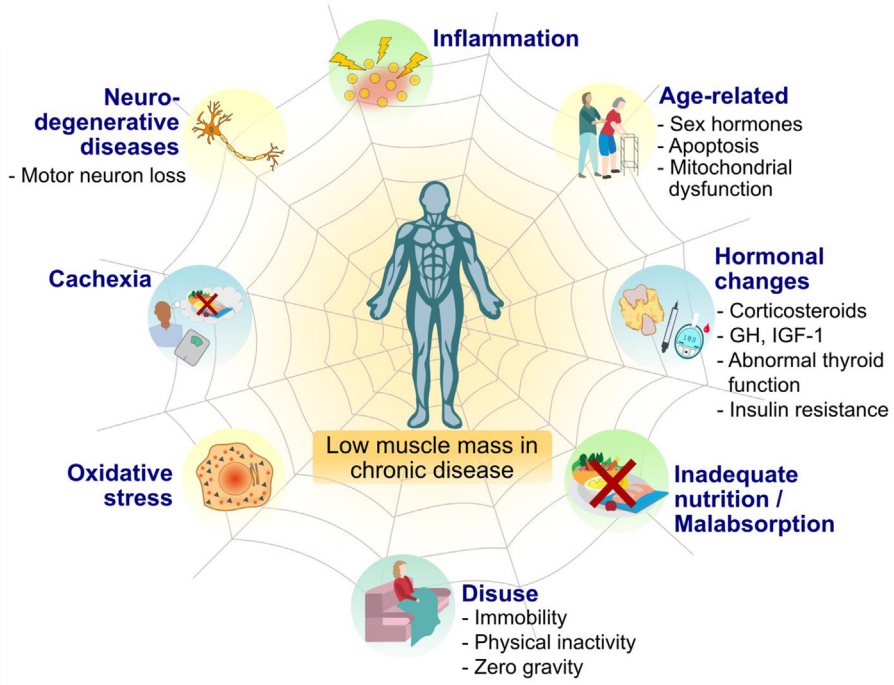

Fig. 6. Selected risk factors contributing to low muscle mass in people with chronic conditions. Abnormalities in muscle mass can emerge if at least one of these factors is present; however, multiple risk factors in chronic disease can lead to severe low muscle mass. Abbreviation: GH, growth hormone; IGF-1, insulin-like growth factor 1.

Malnutrition is also highly prevalent in patients with COVID-19, with up to 80% of hospitalized patients either at risk for malnutrition or malnourished and 67% of critically ill patients being malnourished [86,87]. The extended periods of reduced nutrient intake, bed rest, and systemic inflammation are common among patients and well-known factors that drive muscle loss and malnutrition in acute and critical illness, which now includes COVID-19. Another factor possibly contributing to malnutrition and muscle loss in this population is hypermetabolism. A recent study has shown that resting energy expenditure increased in critically ill patients with COVID-19 from week 1 to week 3 of mechanical ventilation, and it was maintained until week 7, suggesting specific caloric needs throughout ICU stay, particularly in patients without obesity [88]. Persistent hypermetabolism was also demonstrated in another study, with energy expenditure similarly varying across individuals with distinct BMI during ICU stay [89].

Importantly, patients can experience long COVID-19 syndrome, a situation where COVID-19-related symptoms extend into recovery [82]. These symptoms include fatigue, dyspnea, loss of smell and taste, lack of appetite, nausea, and diarrhea that negatively impact nutrient intake and increase the risk for or exacerbate muscle loss and malnutrition, therefore affecting recovery (Fig. S3) [90]. Moreover, patients with no pre-COVID-19 functional deficits experience significant losses in muscle strength and physical function that continue past the acute phase [91]. As such, the evidence highlights the importance of multimodal interventions during the acute phase and continuing throughout recovery.

5. Identify at-risk patients

5.1. Advances in malnutrition assessment

Diagnosing malnutrition remains a challenge despite various published diagnostic criteria. To address this issue, the Global Leadership Initiative in Malnutrition (GLIM) published a set of evidence-based, clinically relevant criteria to be used in conjunction with a comprehensive nutritional assessment or validated assessment tools, like the Subjective Global Assessment (SGA), to diagnose adult malnutrition in any healthcare setting [23,24]. Thus, GLIM criteria should not replace screening and nutritional assessment: they should be used alongside valid malnutrition risk screening and assessment tools. The working group further suggests practical approaches for the low muscle mass phenotypic criteria [92,93]. Figure 8 describes the framework, the phenotypic (non-volitional weight loss, low BMI, and reduced muscle mass) and etiologic (reduced food intake/assimilation and inflammation/disease burden) criteria for the diagnosis of malnutrition and the severity grading of malnutrition, which can be assessed by evaluating the degree of nonvolitional weight loss, BMI, or muscle mass reduction.

5.2. Advances in low muscle mass assessment

Assessing body composition is important for both clinical and research applications, in particular to identify patients with low muscle mass or muscle loss and assess treatment efficacy of anabolic interventions. As a common measure used in clinical settings, BMI is not an indicator of muscle health and therefore, not an appropriate proxy of body composition [94]. Several body composition techniques are available to measure or estimate muscle mass [92,93]. Each technique has its own advantages, limitations, and factors that need to be considered. Some of these factors include validity (e.g., the extent to which one technique produces comparable measures to the best reference technique), feasibility (e.g., availability, equipment and personnel costs, structure, portability for bedside evaluations), safety (e.g., radiation exposure), and practicality (including patient convenience and setting considerations) [95,96].

The overall performance of commonly used methods may differ between research and clinical (inpatient and outpatient) settings (Fig. 9). For example, magnetic resonance imaging (MRI) accurately measures muscle mass at the whole body level, and magnetic resonance-based approaches (e.g., spectroscopy) can be used to determine intramyocellular and extramyocellular lipid content as markers of muscle composition [97,98]. Although these methods are useful in research, they are not yet available in clinical settings; advances in data acquisition and analysis may allow their clinical application in the near future. Computerized tomography scans of selected sites are often used in research settings based on clinically obtained images (i.e., from patient's medical records); yet, prospectively collecting these images solely for muscle mass assessment is not indicated because of high radiation exposure. Notably, although dual-energy X-ray absorptiometry (DXA) does not assess muscle mass; it measures lean soft

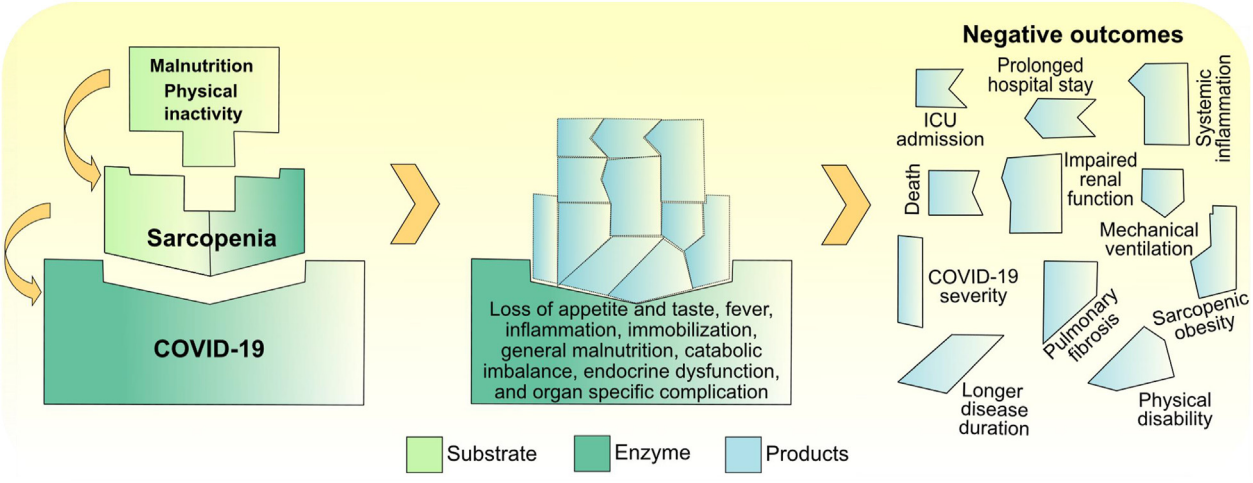

Fig. 7. Interplay of malnutrition, physical inactivity, sarcopenia, and COVID-19 using the substrate and enzyme analogy [83]. Malnutrition can be viewed as the substrate (foundation) for sarcopenia, which in turn serves as the substrate for COVID-19. COVID-19 symptoms and consequences can catalyze or worsen the occurrence of sarcopenia, leading to adverse heath outcomes. Abbreviation: ICU, intensive care unit.

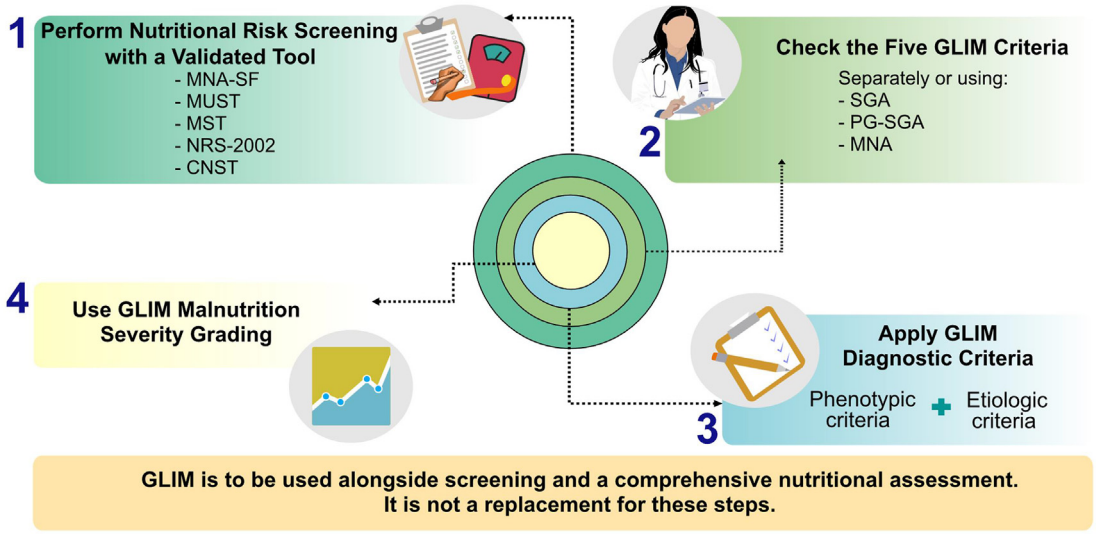

Fig. 8. Steps for diagnosing malnutrition The Global Leadership Initiative on Malnutrition (GLIM) framework is to be used alongside nutritional screening and assessment; it is not a replacement of these steps. Any healthcare professional should be able to assess all five GLIM criteria, not necessarily through a comprehensive nutritional assessment that is restricted to trained professionals. The five GLIM criteria involve the phenotypic criteria (non-volitional weight loss, low BMI, and reduced muscle mass) and the etiologic criteria (reduced food intake/assimilation and inflammation/disease burden). Adapted from Prado CM et al. [96] Abbreviation: CNST, Canadian Nutrition Screening Tool; MNA, Mini Nutrition Assessment; MNA-SF, Mini Nutrition Assessment – Short Form; MST, Malnutrition Screening Tool; MUST, Malnutrition Universal Screening Tool; NRS-2002, Nutritional Risk Screening-2002; PG-SGA, Patient-Generated Subjective Global Assessment; SGA, Subjective Global Assessment.

tissue mass, as further explained in Section 5.2.4. Finally, although anthropometry does not measure body composition, it can be considered useful in clinical settings as a marker of muscle mass. The availability and cost of anthropometric measurements are important considerations, yet the method has poor performance as a research tool.

5.2.1. Bioelectrical impedance analysis and phase angle

Bioelectrical impedance analysis (BIA) estimates muscle mass using population-, equation-, and device-specific prediction equations; these may be potential sources of error when used in individual patients [99,100]. An alternative approach is to use phase angle (PhA), a derived BIA value from resistance and reactance measures, which is becoming an emerging marker of abnormal body composition. Phase angle is an indicator of cell membrane health and integrity and has been used as a prognostic indicator in a variety of conditions, such as survival in patients with cancer [101]. Phase angle has also been associated with markers of inflammation and oxidative stress [102]. Because reactive oxygen species can disrupt cell membrane, there is a recent interest in using PhA as an alternative approach to blood biomarkers of oxidative stress. For example, low PhA predicted 60-day mortality in patients with COVID-19 [103], a condition marked by systemic inflammation and oxidative stress [104].

Research suggests PhA is correlated with muscle area, muscle composition, and associated with a higher risk of dysmobility syndrome, which is defined by a score consisting of six components (i.e., osteoporosis, low lean mass, history of falls, slow gait speed, low handgrip strength and high fat mass) [99,105]. Moreover, a systematic review found the prevalence of sarcopenia was higher in patients with low PhA [106]. Notably, the cut-off values for low PhA are not to be used interchangeably as they are population- and device-specific. Furthermore, factors affecting the ratio between extracellular and intracellular water (i.e., fluid balance) can influence PhA measures [107,108]. These include obesity, edema, physical activity, and other disease-related factors. This creates a challenge as low PhA may be due to modifications in cell mass and hydration, or to impaired cellular function related to disease (e.g. patients with a BMI >40 kg/m^2 showing lower PhA) [109].

5.2.2. Ultrasound

With the availability of portable measurement devices, ultrasound (US) is a promising tool for muscle mass assessment in clinical practice [110–112]. Research shows US-derived thicknesses of the upper arm and upper thigh were well correlated with measurements of muscle area using CT scans, suggesting it is a suitable, radiation-free alternative to CT [111]. As an example of clinical application, a recent study using US detected a 15% ± 13% reduction in quadriceps muscle thickness of critically ill patients over five days of ICU stay [113]. Ultrasound can also detect muscle echo intensity as a measure of muscle composition in terms of fatty infiltration and the presence of fibrous tissue [114].

Research using US has shown significant differences in muscle thickness and echo intensity in the upper leg and upper abdomen between younger and older adults but not in the upper arm, suggesting age-related changes in muscle are site-specific rather than similar for all muscle groups [112]. Assessing multiple sites may therefore capture changes in muscle parameters to a greater extent than using a single measurement site. However, using several sites may not be practical. As shown in a study of community-dwelling older adults, models including US-derived muscle thickness measured at two sites (i.e., arm and thigh) had sufficient predictive value for appendicular lean soft tissue [115].

Ultrasound technology has evolved in recent years and now includes pocket-sized devices that allow comparable measures of muscle thickness and architecture to those obtained using standard US devices [116]. Nevertheless, the current lack of standardized protocols and cut-off values to identify low muscle mass limit its widespread use in clinical practice. Another challenge is measuring muscle parameters in individuals with obesity or edema, as these conditions have been shown to influence muscle echo intensity [114]. Previous research recommends correcting muscle echo intensity for subcutaneous adipose tissue thickness using a

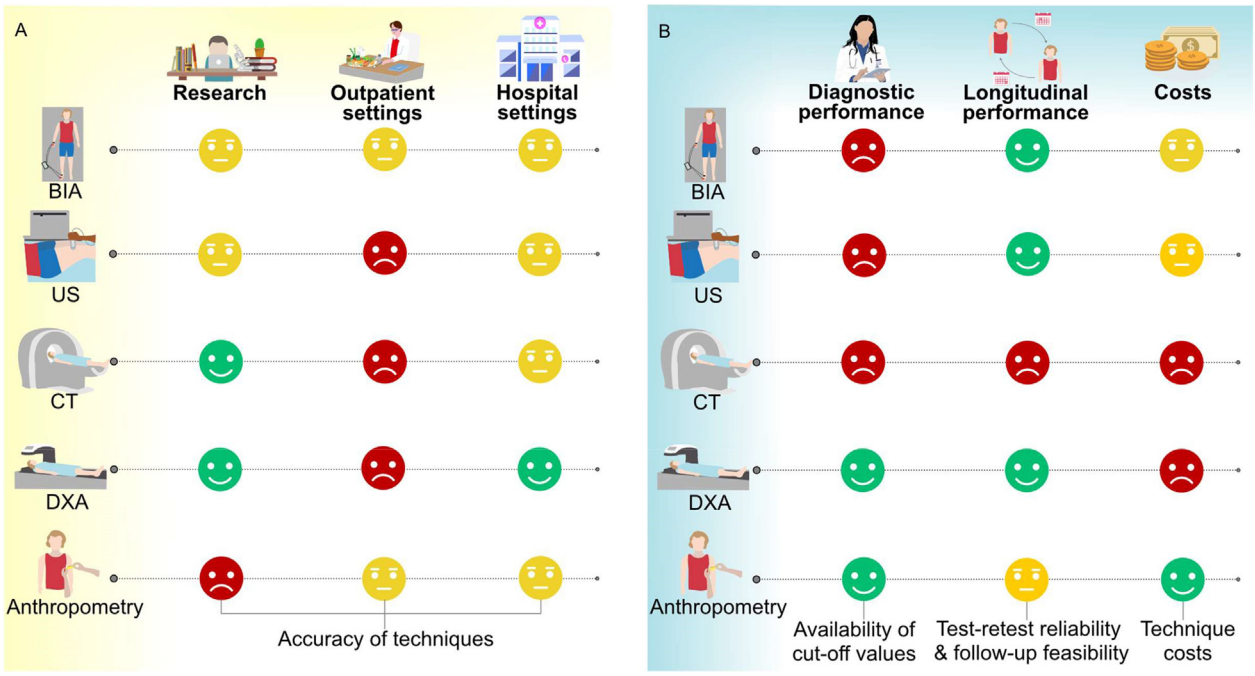

Fig. 9. Diagram summarizing the overall performance of currently available techniques based on their A) accuracy and B) availability of cut-off values for low muscle mass, reliability and feasibility of repeated measures for longitudinal assessments (muscle mass), and associated costs in assessing muscle mass in research, outpatient, and hospital settings. Performance is rated as poor (red face), moderate (yellow face), and sufficient (green face). Abbreviation: BIA, bioelectrical impedance analysis; CT, computerized tomography; DXA, dual-energy X-ray absorptiometry; US, ultrasound. Courtesy of Dr. M.C. Gonzalez. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

predefined calibration equation, but whether this equation is applicable to different populations and other US devices remains unclear [117].

5.2.3. Computerized tomography imaging

Using CT scan data to assess body composition has greatly expanded our understanding of the relationship between muscle mass and tolerance to anticancer treatment, complications, and survival, particularly in oncology. However, separating adipose and muscle tissues in a CT scan has historically relied on manual segmentation, which is labor and time intensive and subject to variability. Several software programs are now available for automated CT segmentation, with data showing strong agreement between automated and manual analysis [118]. In addition to being faster than manual segmentation, similar associations with mortality in patients with cancer have been reported [119]. Three-dimensional measurements of muscle, adipose tissue, as well as multiple other tissues and organs is the newest technology for the fully automated CT assessment of body composition [96]. As such, a number of two-dimensional cross-sectional areas (i.e., CT slices) can be quickly quantified with sufficient accuracy and precision [120]. This information can be used with other patient clinical data using artificial intelligence for predictive models of health outcomes [121].

In addition to semi- and fully automated segmentations, other advances have been made to explore the use of CT scans for body composition assessment. For example, regions of interest other than the third lumbar vertebra (the preferred level given its strongest correlations between single-slice areas and total-body muscle and adipose tissue volumes [122]) have been explored when CT scans at this vertebra level is not available [123]. Furthermore, skeletal muscle index reference values are being developed using data from healthy adults, which will improve comparison of prevalence and significance of low muscle mass across different populations [124–128]. Another important CT parameter is muscle radiodensity, a marker of muscle composition of increasing prognostic value [129]. In patients with colorectal cancer, low preoperative muscle radiodensity was associated with greater postoperative length of hospital stay, complication rates, and mortality [130,131]. A systematic review and meta-analysis of 40 studies in patients with cancer highlighted a 73% greater mortality risk in patients with myoesteatosis compared to their counterparts [110]. Computerized tomography scan data show myosteatosis has been associated with low muscle strength, poor preoperative physical fitness, muscle metabolic dysfunction, and mortality in different populations [110,132,133]. Myosteatosis has also been associated with greater risk of prediabetes and type 2 diabetes, increased homeostasis model assessment for insulin resistance (HOMA-IR), as well as circulating levels of glucose, insulin, CRP, and interleukin-6 [134]. Also importantly, patients with both myosteatosis and low muscle mass may present at greater risk for poorer outcomes, compared to each of these conditions alone [30,135].

5.2.4. Dual-energy x-ray absorptiometry

As a method to assess body composition, DXA has been widely used in research and clinical settings. This equipment can measure total-body lean soft tissue, fat-free mass (lean soft tissue plus bone mineral content), fat mass, and % fat. DXA has been endorsed for body composition assessment by the GLIM Body Composition Working Group [92,93], and European and Asian sarcopenia working groups [21,22].

As summarized elsewhere, DXA appendicular lean soft tissue has been correlated with MRI and CT measures of skeletal muscle volume [136]. DXA does not directly measure muscle mass; it rather measures lean soft tissue mass, which includes muscle mass but also other tissues and organs (the latter at the whole body level) [19]. Analysis from the Sarcopenia Definitions and Outcomes Consortium did not show consistent associations between DXA

measures of lean soft tissue and adverse outcomes in older adults [137,138]. Furthermore, DXA is a costly technique that is also influenced by body thickness, soft tissue hydration, and differences across devices and software versions [19,139,140]. Despite these limitations, DXA is a popular and useful technique as it measures three body compartments and emits low radiation doses. Clinically, DXA is recommended for fat mass assessment, but its validity for assessing lean soft tissue remains unknown [141].

5.2.5. Deuterated creatine dilution

Deuterated creatine (D_3Cr) is a novel measure of functional muscle mass – the functional contractile tissue independent of lipid and fibrotic tissue [142]. A single oral dose of D_3Cr is absorbed and diluted in the creatine pool in skeletal muscle. Metabolized, enriched D_3Cr is determined from a single spot urine collection to estimate muscle mass, i.e., creatine pool size. The method is well correlated with the state-of-the-art MRI; however, it is only moderately correlated with DXA among aging adults [143,144]. A prospective study based on the Osteoporotic Fractures in Men (MrOS) cohort showed strong associations between D_3Cr muscle mass (adjusted by body weight) and physical performance, fatigue, risk of injurious falls, mobility limitations, and all-cause mortality; whereas DXA appendicular lean soft tissue (adjusted by height squared) was only positively associated with handgrip strength [145,146]. In spite of being an indirect measure of muscle mass, the method is precise, non-invasive, and safe. However, this analysis relies on the use of high-performance liquid chromatography, a sophisticated analysis that limits its use in clinical practice [147].

5.2.6. Surrogate approaches for assessing muscle mass

Assessing muscle mass should be an integral part of the Nutrition Care Process. When body composition techniques are not available in clinical settings, surrogate approaches can be used, including physical examination for obvious muscle loss and anthropometry (e.g., mid-upper arm circumference and calf circumference) (Fig. 10). Surrogate approaches can help clinicians identify high-risk patients, potentially informing early interventional strategies to alleviate or prevent muscle loss. Handgrip strength and physical performance tests (e.g., sit-to-stand test and gait speed) are techniques commonly employed to assess muscle function in the diagnosis of sarcopenia and frailty; however, they should not be used as surrogate measures of muscle mass (i.e., quantity) [21,22,92,93].

5.2.6.1. Calf circumference. Calf circumference is an anthropometric measure highly correlated with direct and indirect measures of skeletal muscle mass, and therefore it is useful to assess the muscle mass component of the malnutrition and sarcopenia diagnosis [92,93,148–150]. Calf circumference can also be used as a screening tool for case-finding in different populations, when body composition techniques are not available, as endorsed by the 2019 Asian Working Group [22] and the GLIM Body Composition Working Group [92,93]. In addition, calf circumference appears to be more sensitive at identifying age-associated loss of muscle mass than are upper arm circumferences [149,150]. While measuring calf circumference is a valuable tool in inpatient and outpatient settings, a variety of confounding factors can affect measurement and its interpretation, such as age, BMI, ethnicity, and edema.

Adjustment factors for BMI have been published using North-American population representative data including Caucasian, Mexican-Americans, Non-Hispanic Black, and other races/ethnicities healthy adults (Fig. 11) [151]. Calf circumference can be used in adults by applying a simple adjustment factor before comparing it to sex-specific cut-off values [151]. Notably, the BMI-adjustment factor should not be applied to individuals with a BMI <18.5 kg/m^2 who have weight or muscle loss, particularly in aging and clinical populations. This is because adjustment factors for people with low BMI (i.e., BMI <18.5 kg/m^2) were derived from "healthy" individuals (population-based study) who represented only 2% of the total sample analyzed. As such, these individuals were healthy and young (median age of 27 years), distinguishing them from people in other BMI categories in their study [151], and underweight patients seen in clinical practice. The adjustment factor for this BMI category (rounded value: +4.0 cm) was therefore developed to prevent underestimation of calf muscle in healthy adults when using raw measurements, allowing a direct comparison with suggested cut-off values [151]. As such, no adjustment value should be applied for older adults and clinical populations presenting with a BMI <18.5 kg/m^2 who are suspected to have weight or muscle losses, as low muscle mass could be in fact hidden if the adjustment factor is applied. Notably, adjustment factors for lower extremity edema are also available [152]. Notwithstanding, calf circumference may not detect small changes in muscle mass when compared to other body composition techniques, precluding its use in short period of follow-up.

6. Can we prevent or revert muscle loss and malnutrition with nutrition interventions?

Nutrition is central to support muscle anabolism, reduce catabolism, and improve outcomes in patients with muscle loss and malnutrition [153,154]. Moreover, nutrition interventions are most beneficial when they are proactive, initiated early, and continued through recovery, preferably as part of multimodal interventions that also include exercise. Both nutrition and exercise interventions serve as anabolic stimulus to skeletal muscle; however, an additive effect on muscle mass is observed when these strategies are combined, particularly using protein supplementation and resistance exercise [155,156]. For instance, a 12-week multimodal intervention including supervised and home-based exercise programs, protein supplementation, and nurse-led support increased lean soft tissue (by 0.9 kg; standard error: 0.4 kg; $p = 0.03$) in older patients diagnosed with advanced pancreatic cancer, relative to controls [157].

Maintaining or building muscle mass requires an adequate provision of energy to spare muscle protein and provide adequate substrate for MPS [158]. Interventions in older adults, people with obesity, and patients with highly catabolic conditions, such as cancer cachexia and end-stage renal disease, are particularly challenging because they need to overcome anabolic resistance and disease trajectory to be effective [159]. As recently reviewed, differences in anabolic resistance exist across populations, and research has focused on dietary strategies addressing the post-prandial period to maximize anabolic potential [159]. Likewise, nutrients such as protein/amino acids, vitamin D, n-3 polyunsaturated fatty acids (n-3 PUFA), β-hydroxy-β-methylbutyrate (HMB), and polyphenols can support muscle health and recovery by affecting both muscle and immune function, demonstrating the interaction between muscle and immune systems. These and other nutritional strategies are actively being explored in nutrition intervention trials focusing on muscle mass, sarcopenia and cachexia [160]. Because achieving nutritional intake goals in older adults and clinical populations may be challenging, individualized nutritional counseling should be offered concurrent to nutrition therapy, as endorsed by nutrition care guidelines [161,162].

6.1. Protein and amino acids

Protein and amino acids support muscle by providing substrates for MPS and the immune system by converting pro-inflammatory M1 macrophages to the anti-inflammatory form, M2 [163]. The

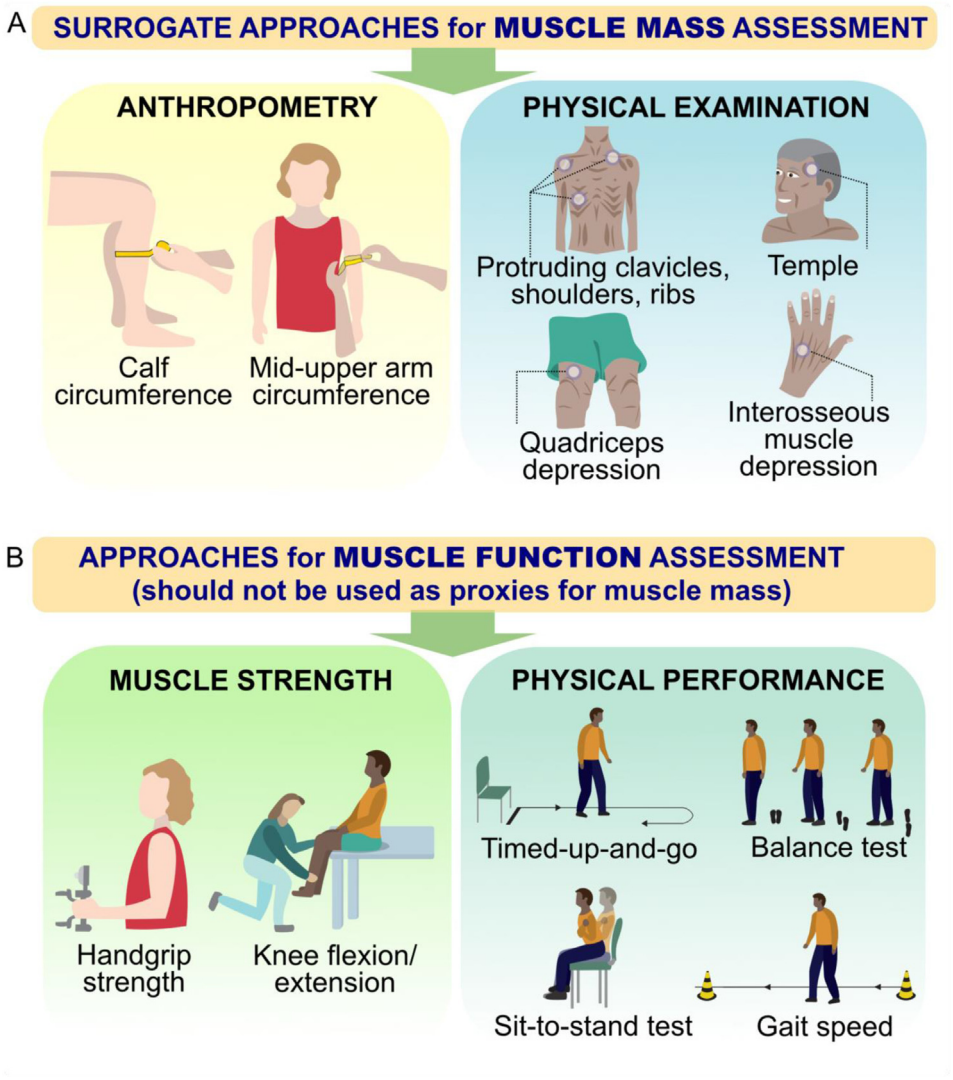

Fig. 10. Surrogate approaches for muscle mass assessment in clinical practice when valid body composition techniques are not available. A) Approaches include anthropometric measurements (i.e., calf circumference, mid-upper arm circumference) and visual examination of muscle loss in specific body sites (i.e., clavicles, shoulders, ribs, temples, thighs, and hands). B) Approaches for muscle function assessment should not be employed as surrogate measures of muscle mass.

ability of dietary proteins to stimulate MPS primarily depends on their essential amino acid (EAA) content and rate of protein digestion. Studies in humans show transient increases in MPS, peaking 45–90 min after ingestion of a bolus of protein high in EAAs, with excess amino acids remaining in the circulation [164,165]. This suggests muscle has an intrinsic capacity to recognize when it has taken in enough amino acids at a given period to replace those lost during the intervening fasting periods [164,165]. Interestingly, after 90–180 min, MPS returns to baseline, which indicates that muscle is only transiently responsive to the intake of dietary protein, particularly in relation to its EAA content [166].

Compared to plant sources of protein, animal-derived proteins have a higher digestibility and provide EAAs required for MPS (including a greater content of leucine) [167]. Consequently, studies have shown greater anabolic effect of animal-based protein on MPS than plant-based proteins at both rest and after exercise conditions [168–170]. For instance, soy protein was found to be less effective than whey protein in stimulating MPS and had no effect on MPS at rest with 40g of soy protein isolate in older men [170]. Blending plant- and animal-derived proteins may enhance the anabolic effect of plant proteins thereby increasing and extending MPS through correction of EAA deficiencies and the different rates of digestion between protein sources, suggesting any rate-limiting issues would be minimized [167].

In contrast to whey protein, collagen protein hydrolysate supplementation alone does not elicit an acute response on MPS as it is an incomplete protein [165,171–173]. A small crossover study testing the effects of supplementing the diet (0.8 g/kg body weight/d of protein) with either collagen or whey protein for 15 days reported no changes in lean soft tissue of older women; although nitrogen balance was maintained with collagen, nitrogen excretion was higher with whey protein supplementation [174]. Collagen is rich in non-EAAs, which may explain its positive effects on nitrogen balance [165]. Moreover, a mixed blend of collagen and milk protein induced MPS to a similar extent as milk protein alone, and also exhibited a greater increases in mammalian target of rapamycin (mTOR) signaling in spite of lower leucine content [175].

Finally, more research is needed to understand the proportion of animal- and plant-base protein sources that should make up protein recommendations in the malnutrition and muscle health contexts. An expert group paper discussing protein sources for patients with cancer has suggested that although both animal and

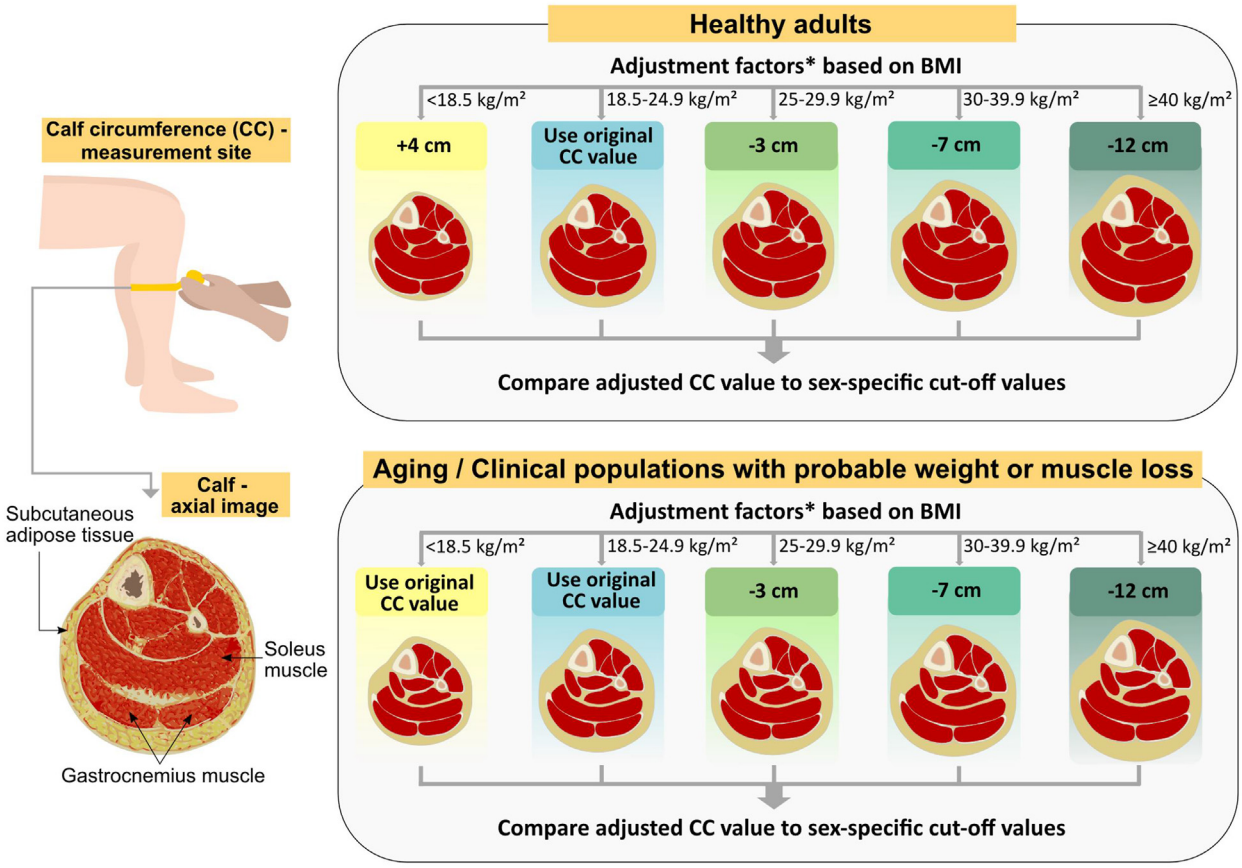

Fig. 11. Illustration depicting adjustment factors for measurements of calf circumference according to BMI categories as proposed by Gonzalez et al. [151] Before comparing calf circumference values to suggested sex-specific cut-off points, adjustment factors based on BMI categories should be applied (except for individuals with a BMI <18.5 kg/m^2 who have weight or muscle losses, particularly in aging and clinical populations (see text for details). Abbreviation: BMI, body mass index; CC, calf circumference. *Age-adjusted linear regression models. Courtesy of Dr. M.C. Gonzalez.

plant protein sources are needed, 65% or more of protein intake should come from animal sources during treatment for such a highly catabolic condition [176]. This remains to be investigated in this and other clinical scenarios.

6.2. Branched-chain amino acids: focus on leucine

Leucine is a branched-chain amino acid. Compared to other EAAs, leucine is perhaps the most potent anabolic one [177]. Feeding 3 g leucine daily to healthy young men is associated with a pronounced increase in MPS, even in the absence of other amino acids, suggesting a recognition system of leucine as a marker of protein intake [178]. Furthermore, results of a meta-analysis indicated that leucine supplementation was effective in increasing measures of muscle mass (assessed as lean soft tissue and fat-free mass) in older adults [179]. Despite these findings, supplementation with leucine or branched-chain amino acid alone may not stimulate the maximal response of MPS as they lack other EAA [155].

6.3. β-hydroxy- β-methylbutyrate (HMB)

β-hydroxy-β-methylbutyrate is a bioactive anabolic metabolite of leucine that is synthesized in muscle and found in small amounts in the diet. When orally consumed, HMB exerts similar anabolic effects on MPS as leucine. Interestingly, supplementation with HMB has been shown to suppress MPB to a greater degree than does leucine [178]. Although the impact of HMB supplementation on muscle mass and strength has not been positive in all studies [180], overall findings are promising. A systematic review and meta-analysis of 15 randomized controlled trials (RCTs) conducted in a variety of clinical conditions showed that HMB supplementation is associated with improved muscle mass and strength; however, the effect size was small [181]. In patients with cancer, higher quality studies also support a beneficial effect of HMB supplementation on improving muscle mass and function, decreasing hospitalization, and improving survival in patients with cancer, in spite of the limited evidence [182].

6.4. Vitamin D

Vitamin D is a fat-soluble vitamin well recognized for its role in bone and muscle health. Research has demonstrated the link between vitamin D deficiency and muscle dysfunction, possibly due to the loss of vitamin D receptor function, increased oxidative stress and impaired mitochondrial function [183]. There is also evidence of a longitudinal association between low vitamin D status and sarcopenia [184]. Moreover, vitamin D affects immunity, and it has been shown to downregulate the expression of pro-inflammatory cytokines, increase the proliferation, differentiation and growth of muscle, and increase naturally occurring regulatory T cells involved in modulating immune response [163,183,185,186]. Findings from

systematic reviews and a meta-analysis suggest beneficial effects of vitamin D supplementation on muscle strength and physical performance, but not on muscle mass in older adults [187–189].

6.5. Long chain n-3 polyunsaturated fatty acids (n-3 PUFA)

As a class of fatty acids, n-3 PUFA exert anti-inflammatory effects that strengthen crosstalk between skeletal muscle and immune system cells to promote muscle anabolism [163]. *In vitro* research shows n-3 PUFAs' anti-inflammatory effects reduce cytokine-mediated loss of specific muscle proteins and cell death to promote anabolism by inhibiting proteolysis [163]. Daily supplementation with n-3 PUFA is associated with improving muscle mass and physical performance in healthy aging adults [190]. Improvements in muscle composition have also been observed in patients with cancer receiving omega 3 supplementation [191,192]. A meta-analysis also reported a positive effect of n-3 PUFA supplementation on measures of muscle mass (i.e., lean soft tissue, fat-free mass, skeletal muscle) and lower-body strength (i.e., quadriceps maximum voluntary capacity) in healthy and clinical populations [193]. Nonetheless, in patients with cancer, another meta-analysis showed no effects of n-3 PUFA supplementation (alone or in oral nutritional supplements [ONS]) on improving muscle mass, body weight, and quality of life; however, the likelihood of developing chemotherapy-induced peripheral neuropathy was reduced in those who received n-3 PUFA supplements [194]. As studies included in both meta-analyses were substantially heterogeneous regarding population, supplement dosage/duration, and outcome assessment, future well-designed RCTs should be conducted to clarify the effects of n-3 PUFA supplementation in different populations.

6.6. Polyphenols

Similar to n-3 PUFA, polyphenols have anti-inflammatory properties that may modify the crosstalk between muscle and immune cells. In this sense, polyphenols reduce signaling by nuclear factor kappa B, thus diminishing the inflammatory response to improve muscle synthesis [163]. However, to date, the evidence on the effects of polyphenol supplements on muscle health in older adults and clinical populations is limited. For example, one small RCT showed no additional benefit of Montmorency cherry concentrate to resistance exercise combined with whey protein supplementation on MPS in healthy older men [195]. Furthermore, intervention with resveratrol led to increased mitochondria number and downregulation of genes associated with adverse mitochondrial bioenergetics in muscle samples from older adults, but did not improve glucose metabolism or insulin sensitivity in older adults with impaired glucose tolerance [196].

6.7. Oral nutritional supplements (ONS)

In addition to improving food intake, the use of ONS is a cornerstone for preventing and treating muscle loss and malnutrition; ONS contain additional protein, energy, and micronutrients and potentially other specialized nutrients or ingredients previously described to support muscle health and improve nutritional status. Research has shown that supplementation with ONS improves energy, protein, and micronutrient intakes beyond food alone [197,198].

Several RCTs have been performed to evaluate the effects of ONS on health outcomes of older adults and clinical populations [199–201]. For instance, one RCT compared the effect of dietary counseling with either an ONS containing HMB (ONS-HMB) or placebo beverage for six months on nutritional and functional outcomes in a large sample of community-dwelling older adults at risk for malnutrition (n = 811) [202]. The study showed the proportion of participants not admitted or readmitted to the hospital and those who gained at least 5% body weight at six months was greater in the ONS-HMB group versus placebo (33% vs 9%, $p < 0.001$), and consuming ONS-HMB was associated with greater improvements in serum 25-hydroxyvitamin D levels, leg strength, grip strength in women, and improved energy and protein intakes [202]. Another large RCT also indicated beneficial effects of a protocol-guided individualized nutrition support in hospitalized patients at risk of malnutrition, with 91% of patients in the intervention arm receiving ONS for 30 days [203]. The intervention was associated with a decreased risk of adverse clinical outcomes and all cause-mortality, and it also improved quality of life and functional status, compared to a placebo group receiving standard care (i.e., hospital food). Furthermore, findings from a narrative review support the efficacy of a whey protein ONS (enriched with leucine and vitamin D) for patients with or at risk of sarcopenia (i.e., community dwelling older adults, patients at rehabilitation units and care homes, and individuals with sarcopenic obesity) to increase skeletal muscle and related body compartments [204]. Studies in clinical settings have similarly supported the use of ONS in improving muscle mass or composition. For example, one RCT explored the impact of ONS with dietary advice in post-discharge patients at nutritional risk following cancer surgery [205]. After 3 months, the intervention group presented with a lower prevalence of low muscle mass, compared to the control group [205].

6.8. Nutraceuticals

Several nutraceuticals may exert positive effects on muscle anabolism, strength, and function. These include creatine, carnitine, and β-alanine to improve bioenergetics either at rest or under exercise conditions, nitrates to improve vascular function, and the biologics phosphatidic and ursolic acids, which have been shown to trigger growth pathways in muscle [206–209]. However, further research is required to evaluate these compounds and their efficacy on muscle health in individuals with or at risk for muscle loss either due to aging, malnutrition, or disease.

7. Adjuvant exercise interventions

It is important to acknowledge the significance of regular exercise, preferably in combination with nutrition interventions as a multimodal approach across the continuum of care. A systematic review of 37 RCTs compared the effect of nutrition combined with regular exercise vs exercise alone on muscle mass and function in healthy older adults [188]. Exercise was found to improve muscle mass, strength and physical performance; however, additional benefits of concurrent nutrition intervention are unclear [188]. A pooled analysis of studies offering protein supplements and/or higher protein diets to older adults revealed that only interventions combining nutrition and resistance exercise benefited appendicular lean soft tissue and handgrip strength [210]. For instance, a four-arm RCT has demonstrated the synergistic effect of combining resistance exercise training, protein, and vitamin D in older adults with sarcopenia or dynapenia (i.e., low muscle function alone) [211]. Participants receiving all three interventions showed greater improvements on muscle echo intensity, PhA, and knee extension torque, compared to each isolated intervention or no intervention [211]. In addition to its positive effects on muscle quantity and composition and cardiovascular function, regular exercise improves

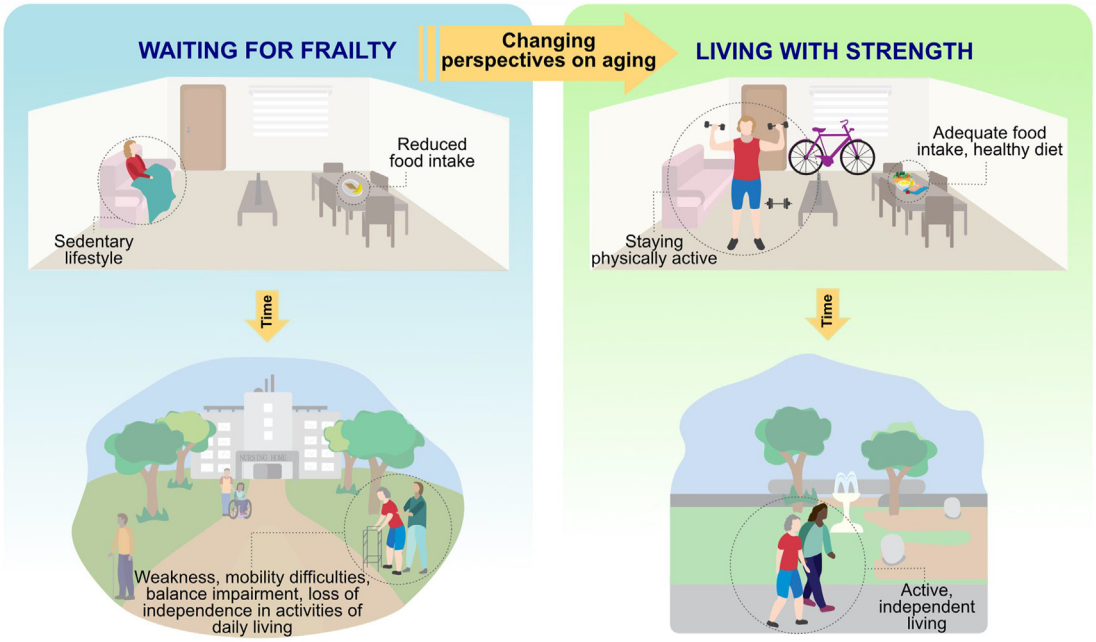

Fig. 12. Illustration highlighting the concept of "Waiting for Frailty" (i.e., frailty, disability, and loss of independence) versus "Living with Strength" (i.e., staying physically active and maintaining an adequate food/nutrient intake) for active, independent living in the community for as long as possible.

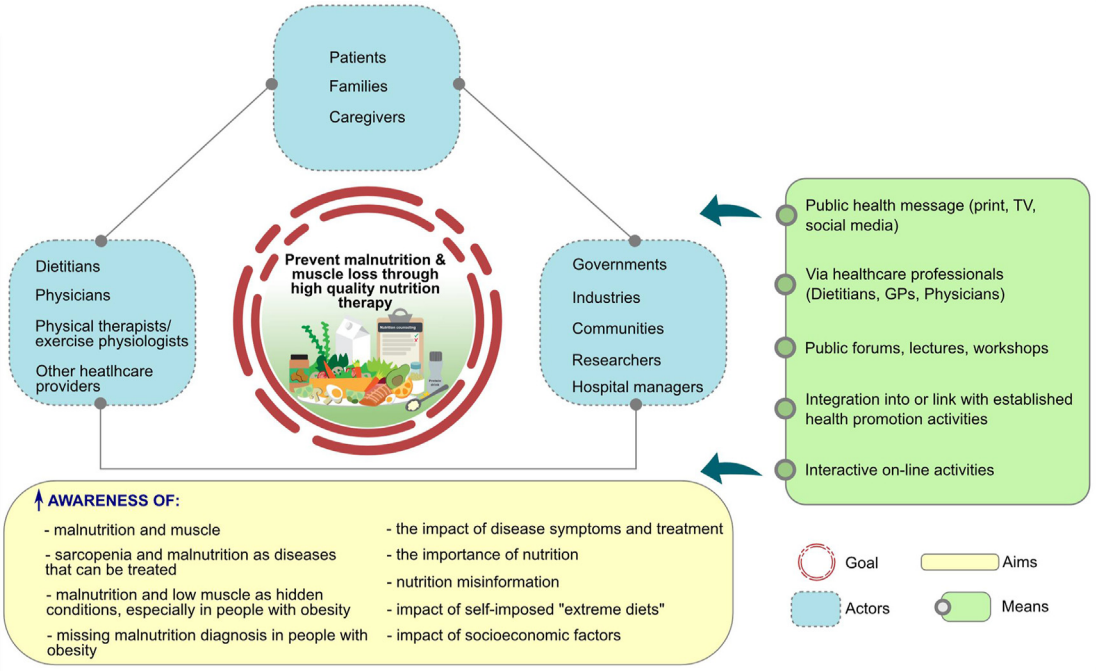

Fig. 13. An important aspect of preventing malnutrition and low muscle mass is to increase nutrition knowledge. Illustration depicting stakeholders (healthcare providers, patients, families, caregivers, etc.) and potential means of achieving the aim of providing high quality nutrition therapy.

immune function via myokines like interleukin-15 that also stimulates myogenesis and reduces adiposity, thereby affecting body composition [212,213].

Evidence suggests that both resistance and endurance-based exercises have a beneficial effect on mitochondrial health and function by reducing oxidative damage, improving oxidative coupling ability, increasing mitochondrial and mitochondrial protein genesis [214]. As such, exercise may play a key role in mediating the impact of mitochondrial dysfunction and poor muscle health. Fig. S4 depicts an analogy of the importance of both nutrition and exercise interventions to be used in patient educational materials.

8. Healthy aging: shifting the focus from waiting for frailty to living with strength

Not all older adults will develop frailty. The paradigm of healthy aging should focus on maintaining good health and the ability to live meaningful and independent lives for as long as possible (Fig. 12). This includes optimizing nutrition and exercise to avoid age-related muscle loss that can progress to frailty, dysmobility syndrome, and loss of independence. Studies suggest home-based interventions that combine exercise and nutrition can indeed improve frailty scores and physical performance and increase the number of days in a month in which physical and mental health are described as overall good [215–217]. In addition to health benefits, lifestyle programs in community-dwelling adults are also cost-effective interventions, emphasizing their economic impact to public health costs [217–219].

9. Recommendations for clinical practice

To ensure at-risk patients are consistently screened, assessed, treated, and monitored, we offer the following clinical practice recommendations:

- **Advance screening, assessment, and diagnostic practices for low muscle mass and malnutrition**– Screening helps to identify at-risk individuals who require further assessment and treatment for muscle loss and malnutrition. Assessing muscle mass should be an integral part of the Nutrition Care Process, and it starts with nutrition screening. The SARC-F and SARC-CalF tools can be used to screen for sarcopenia in older adults [220]. Several validated tools are available to screen for malnutrition risk, such as the Malnutrition Universal Screening Tool (MUST), the Malnutrition Screening Tool (MST), and the Nutrition Risk Screening 2002 (NRS-2002) [221–223]. Using validated assessment tools within the GLIM framework (Fig. 8) for malnutrition diagnoses and the proper use and interpretation of body composition assessment (to identify low muscle mass) should be reinforced in patient care pathways. Efforts from the GLIM Body Composition Working Group will facilitate the latter [92,93]. Additionally, the ongoing COVID-19 pandemic and the increased use of telehealth highlighted the relevance and need for digital tools such as the R-MAPP (Remote – Malnutrition APP) for screening, assessment, and monitoring patients remotely [224].
- **Use of surrogate tools to identify low muscle mass in the absence of body composition techniques** – As not all body composition assessment methods are available in all clinical settings, surrogate markers of muscle mass can be implemented (Fig. 10). As discussed previously, calf circumference is an anthropometric measure that correlates well with muscle mass, requires minimal training, and is a useful tool in clinical practice. Measuring calf circumference to identify low muscle mass can also be used in conjunction with validated assessment tools within the GLIM framework to help diagnose malnutrition.
- **Promote multimodal care** – The pathophysiology of muscle loss is multifactorial, and so is the need for a multidisciplinary approach to prevent/halt this condition. Physicians, dietitians, nurses, exercise physiologists and/or physical and occupational therapists all have a role to play.
- **Provide nutrition education for patients, families and caregivers** (Fig. 13) – Increasing awareness of low muscle and malnutrition and improving patients' knowledge on early signs of muscle loss and malnutrition are key. According to a survey, older adults with varied appetite and protein intake levels considered one meal containing a good protein source to be sufficient for achieving their daily protein needs, emphasizing the need for nutrition education [225]. Furthermore, older adults may be unaware of the importance of snacking and eating in the absence of hunger, as well as the consequences of weight and muscle losses [226,227]. Limited health care professional knowledge of the nutritional needs and concerns of older adults and clinical populations may also hinder adequate nutrition intervention [228]. Healthcare professionals should also be aware that muscle loss can occur in the absence of changes in body weight, particularly in older adults with obesity [229]. Institutions and healthcare professionals (supported by patients' families and caregivers) have a duty to implement educational strategies related to preventing malnutrition and muscle loss (Fig. 13). This includes but is not limited to verbal and/or written advice and plain-language resources on how to increase caloric and protein intakes, lectures, workshops, group discussions, and cooking courses [230]. Please refer to the **Supporting File** which contains a separate sets of figures clinicians can use to individualize educational booklets, presentations, and online resources.

10. Outlook on future research

Research is needed to understand the benefit of integrating body composition assessment into clinical practice, and the impact of using this information to personalize nutrition interventions to prevent and treat low muscle mass and malnutrition. Specific immunological and muscle-related targets should be explored, which may transform the understanding and treatment of low muscle mass. Furthermore, more research is required to explore the impact of nutrition and exercise interventions to maximize anabolic potential, physical performance, and outcomes in healthy aging, and acute and chronic disease, including acute conditions like COVID-19. Recommendations for future nutrition trials have been provided in order to rapidly advance knowledge translation of interventions addressing muscle, sarcopenia and cachexia to clinical practice [160].

11. Conclusion

Clinical practice is changing, and healthcare professionals are encouraged to implement many of the tools hereby discussed to assess muscle loss and malnutrition in their settings. Muscle loss and malnutrition can be hidden from view, yet screening is the only means of identifying at-risk individuals; assessment can diagnose the presence and severity of low muscle mass and/or malnutrition. Several nutrition interventions including individual nutrients or ingredients, bioactive ingredients, and ONS have been shown to improve muscle mass, composition, and function (muscle health) and can be important tools to addressing muscle loss [154]. Importantly, combining nutrition interventions with exercise as components of a multimodal approach is an important strategy to improving patient outcomes.

Author contribution

All authors were responsible for conceptualization, writing, review and editing.

Funding statement

Abbott Nutrition provided support and funding for the Abbott Nutrition Research Conference and this publication.

Conflict of interest

C.M.P. has previously received honoraria and/or paid consultancy from Abbott Nutrition, Nutricia, Nestlé Health Science, Fresenius Kabi, and Pfizer. T.R. reports grants from German Ministry of Education, Science, Research and Technology; grants and personal fees from Sanofi-Aventis and Alexion; personal fees from Abbott Nutrition, Argenx, Biogen, BMS, Roche, Novartis, and Teva; and personal fees and nonfinancial support from Merck Serono, outside the submitted work. S.T.H.C has previously received grant co-funding, travel grant and honoraria from Abbott Nutrition. M.C.G. has received paid consultancy from Abbott Nutrition and Nestlé Brazil. F.L., P.J.A, J.M., T.B. have previously received grant funding and paid consultancy from Abbott Nutrition.

Acknowledgments

We thank Carolyn Alish and Camila E Orsso who provided medical writing and illustration services in the development of this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2022.07.041.

References

[1] Bhuachalla Éb Ní, Daly LE, Power DG, Cushen SJ, MacEneaney P, Ryan AM. Computed tomography diagnosed cachexia and sarcopenia in 725 oncology patients: is nutritional screening capturing hidden malnutrition? J Cachexia Sarcopenia Muscle 2018;9:295–305.
[2] Deutz NEP, Ashurst I, Ballesteros MD, Bear DE, Cruz-Jentoft AJ, Genton L, et al. The underappreciated role of low muscle mass in the management of malnutrition. J Am Med Dir Assoc 2019;20(1):22–7.
[3] Prado CM, Purcell SA, Alish C, Pereira SL, Deutz NE, Heyland DK, et al. Implications of low muscle mass across the continuum of care: a narrative review. Ann Med 2018;50:675–93.
[4] Damanti S, Cristel G, Ramirez GA, Bozzolo EP, Da Prat V, Gobbi A, et al. Influence of reduced muscle mass and quality on ventilator weaning and complications during intensive care unit stay in COVID-19 patients. Clin Nutr 2021;S0261–5614(21):375–7.
[5] Brown JC, Caan BJ, Cespedes Feliciano EM, Xiao J, Weltzien E, Prado CM, et al. Weight stability masks changes in body composition in colorectal cancer: a retrospective cohort study. Am J Clin Nutr 2021;113(6):1482–9.
[6] Demling RH. Nutrition, anabolism, and the wound healing process: an overview. Eplasty 2009;9:e9.
[7] Landi F, Camprubi-Robles M, Bear DE, Cederholm T, Malafarina V, Welch AA, et al. Muscle loss: the new malnutrition challenge in clinical practice. Clin Nutr 2019;38:2113–20.
[8] Abugroun A, Nayyar A, Abdel-Rahman M, Patel P. Impact of malnutrition on hospitalization outcomes for older adults admitted for sepsis. Am J Med 2021;134:221–226.e1.
[9] Han TS, Yeong K, Lisk R, Fluck D, Fry CH. Prevalence and consequences of malnutrition and malnourishment in older individuals admitted to hospital with a hip fracture. Eur J Clin Nutr 2021;75(4):645–52.
[10] Lanctin DP, Merced-Nieves F, Mallett RM, Arensberg MB, Guenter P, Sulo S, et al. Prevalence and economic burden of malnutrition diagnosis among patients presenting to United States emergency departments. Acad Emerg Med 2021;28(3):325–35.
[11] McLaughlin J, Chowdhury N, Djurkovic S, Shahab O, Sayiner M, Fang Y, et al. Clinical outcomes and financial impacts of malnutrition in sepsis. Nutr Health 2020;26(3):175–8.
[12] Yu W, Yu W, Liu X, Wan T, Chen C, Xiong L, et al. Associations between malnutrition and cognitive impairment in an elderly Chinese population: an analysis based on a 7-year database. Psychogeriatrics 2021;21(1):80–8.
[13] Salinas-Rodríguez A, Palazuelos-González R, Rivera-Almaraz A, Manrique-Espinoza B. Longitudinal association of sarcopenia and mild cognitive impairment among older Mexican adults. J Cachexia Sarcopenia Muscle 2021;12(6):1848–59.
[14] Weerink LBM, Hoorn A, Leeuwen BL, Bock GH. Low skeletal muscle mass and postoperative morbidity in surgical oncology: a systematic review and meta-analysis. J Cachexia Sarcopenia Muscle 2020;11:636–49.
[15] Chew STH, Kayambu G, Lew CCH, Ng TP, Ong F, Tan J, et al. Singapore multidisciplinary consensus recommendations on muscle health in older adults: assessment and multimodal targeted intervention across the continuum of care. BMC Geriatr 2021;21(1):314.
[16] Izquierdo M, Merchant RA, Morley JE, Anker SD, Aprahamian I, Arai H, et al. International exercise recommendations in older adults (ICFSR): expert consensus guidelines. J Nutr Health Aging 2021;25(7):824–53.
[17] Bijlsma AY, Meskers CGM, Westendorp RGJ, Maier AB. Chronology of age-related disease definitions: osteoporosis and sarcopenia. Ageing Res Rev 2012;11:320–4.
[18] Grimshaw JM, Eccles MP, Lavis JN, Hill SJ, Squires JE. Knowledge translation of research findings. Implement Sci 2012;7:50.
[19] Prado CMM, Heymsfield SB. Lean tissue imaging: a new era for nutritional assessment and intervention. J Parenter Enter Nutr 2014;38:940–53.
[20] Bauer J, Morley JE, Schols AMWJ, Ferrucci L, Cruz-Jentoft AJ, Dent E, et al. Sarcopenia: a time for action. An SCWD position paper. J Cachexia Sarcopenia Muscle 2019;10:956–61.
[21] Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Writing group for the European working group on sarcopenia in older people 2 (EWGSOP2), and the extended group for EWGSOP2. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 2019;48:16–31.
[22] 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. J Am Med Dir Assoc 2020;21:300–7. e2.
[23] Cederholm T, Jensen GL, Correia MITD, Gonzalez MC, Fukushima R, Higashiguchi T, et al., GLIM Core Leadership Committee, GLIM Working Group. GLIM criteria for the diagnosis of malnutrition - a consensus report from the global clinical nutrition community. Clin Nutr 2019;38(1):1–9.
[24] Jensen GL, Cederholm T, Correia MITD, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition: a consensus report from the global clinical nutrition community. J Parenter Enter Nutr 2019;43:32–40.
[25] Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 2011;12(5):489–95.
[26] Lengelé L, Bruyère O, Beaudart C, Reginster JY, Locquet M. Malnutrition, assessed by the Global Leadership Initiative on Malnutrition (GLIM) criteria but not by the mini nutritional assessment (MNA), predicts the incidence of sarcopenia over a 5-year in the SarcoPhAge cohort. Aging Clin Exp Res 2021;33(6):1507–17.
[27] Landi F, Cherubini A, Cesari M, Calvani R, Tosato M, Sisto A, et al. Sarcopenia and frailty: from theoretical approach into clinical practice. Eur Geriatr Med 2016;7:197–200.
[28] Faxén-Irving G, Luiking Y, Grönstedt H, Franzén E, Seiger Å, Vikström S, et al. Do malnutrition, sarcopenia and frailty overlap in nursing-home residents? J Frailty Aging 2021;10(1):17–21.
[29] Ligthart-Melis GC, Luiking YC, Kakourou A, Cederholm T, Maier AB, de van der Schueren MAE. Frailty, sarcopenia, and malnutrition frequently (co-) occur in hospitalized older adults: a systematic review and meta-analysis. J Am Med Dir Assoc 2020;21:1216–28.
[30] Findlay M, White K, Brown C, Bauer JD. Nutritional status and skeletal muscle status in patients with head and neck cancer: impact on outcomes. J Cachexia Sarcopenia Muscle 2021;12(6):2187–98.
[31] Gingrich A, Volkert D, Kiesswetter E, Thomanek M, Bach S, Sieber CC, et al. Prevalence and overlap of sarcopenia, frailty, cachexia and malnutrition in older medical inpatients. BMC Geriatr 2019;19(1):120.
[32] Petermann-Rocha F, Pell JP, Celis-Morales C, Ho FK. Frailty, sarcopenia, cachexia and malnutrition as comorbid conditions and their associations with mortality: a prospective study from UK Biobank. J Public Health 2021:fdaa226.
[33] Hu X, Zhang L, Wang H, Hao Q, Dong B, Yang M. Malnutrition-sarcopenia syndrome predicts mortality in hospitalized older patients. Sci Rep 2017;7:3171.
[34] Duan K, Gao X, Zhu D. The clinical relevance and mechanism of skeletal muscle wasting. Clin Nutr 2021;40:27–37.
[35] Scicchitano BM, Dobrowolny G, Sica G, Musarò A. Molecular insights into muscle homeostasis, atrophy and wasting. Curr Genom 2018;19:356–69.
[36] Morton RW, Traylor DA, Weijs PJM, Phillips SM. Defining anabolic resistance: implications for delivery of clinical care nutrition. Curr Opin Crit Care 2018;24:124–30.
[37] Atherton PJ, Greenhaff PL, Phillips SM, Bodine SC, Adams CM, Lang CH. Control of skeletal muscle atrophy in response to disuse: clinical/preclinical contentions and fallacies of evidence. Am J Physiol Endocrinol Metab 2016;311(3):E594–604.
[38] Argilés JM, Campos N, Lopez-Pedrosa JM, Rueda R, Rodriguez-Mañas L. Skeletal muscle regulates metabolism via interorgan crosstalk: roles in health and disease. J Am Med Dir Assoc 2016;17:789–96.
[39] Lee JH, Jun HS. Role of myokines in regulating skeletal muscle mass and function. Front Physiol 2019;10:42.
[40] Piasecki M, Ireland A, Stashuk D, Hamilton-Wright A, Jones DA, McPhee JS. Age-related neuromuscular changes affecting human vastus lateralis. J Physiol 2016;594(16):4525–36.
[41] Phillips BE, Atherton PJ, Varadhan K, Limb MC, Wilkinson DJ, Sjøberg KA, et al. The effects of resistance exercise training on macro- and micro-circulatory responses to feeding and skeletal muscle protein anabolism in older men. J Physiol 2015;593(12):2721–34.

[42] Zempo H, Isobe M, Naito H. Link between blood flow and muscle protein metabolism in elderly adults. JPFSM 2017;6(1):25–31.
[43] Wilkinson DJ, Piasecki M, Atherton PJ. The age-related loss of skeletal muscle mass and function: measurement and physiology of muscle fibre atrophy and muscle fibre loss in humans. Ageing Res Rev 2018;47:123–32.
[44] Rudrappa SS, Wilkinson DJ, Greenhaff PL, Smith K, Idris I, Atherton PJ. Human skeletal muscle disuse atrophy: effects on muscle protein synthesis, breakdown, and insulin resistance—a qualitative review. Front Physiol 2016;7:361.
[45] Ferri E, Marzetti E, Calvani R, Picca A, Cesari M, Arosio B. Role of age-related mitochondrial dysfunction in sarcopenia. IJMS 2020;21(15):5236.
[46] Molinger J, Pastva AM, Whittle J, Wischmeyer PE. Novel approaches to metabolic assessment and structured exercise to promote recovery in ICU survivors. Curr Opin Crit Care 2020;26(4):369–78.
[47] Gouspillou G, Bourdel-Marchasson I, Rouland R, Calmettes G, Biran M, Deschodt-Arsac V, et al. Mitochondrial energetics is impaired in vivo in aged skeletal muscle. Aging Cell 2014 Feb;13(1):39–48.
[48] Marzetti E, Wohlgemuth SE, Lees HA, Chung HY, Giovannini S, Leeuwenburgh C. Age-related activation of mitochondrial caspase-independent apoptotic signaling in rat gastrocnemius muscle. Mech Ageing Dev 2008;129(9):542–9.
[49] Bellanti F, Lo Buglio A, Vendemiale G. Mitochondrial impairment in sarcopenia. Biology 2021;10(1):31.
[50] Romanello V, Sandri M. The connection between the dynamic remodeling of the mitochondrial network and the regulation of muscle mass. Cell Mol Life Sci 2021;78(4):1305–28.
[51] Romanello V. The interplay between mitochondrial morphology and myomitokines in aging sarcopenia. Int J Mol Sci 2020;22(1):E91.
[52] Migliavacca E, Tay SKH, Patel HP, Sonntag T, Civiletto G, McFarlane C, et al. Mitochondrial oxidative capacity and NAD+ biosynthesis are reduced in human sarcopenia across ethnicities. Nat Commun 2019;10(1):5808.
[53] Kim KW, Baek MO, Yoon MS, Son KH. Deterioration of mitochondrial function in the human intercostal muscles differs among individuals with sarcopenia, obesity, and sarcopenic obesity. Clin Nutr 2021;40(5):2697–706.
[54] Hyatt HW, Powers SK. Mitochondrial dysfunction is a common denominator linking skeletal muscle wasting due to disease, aging, and prolonged inactivity. Antioxidants 2021;10(4):588.
[55] 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. Front Physiol 2020;11:963.
[56] Afzali AM, Müntefering T, Wiendl H, Meuth SG, Ruck T. Skeletal muscle cells actively shape (auto)immune responses. Autoimmun Rev 2018;17(5):518–29.
[57] Nelke C, Dziewas R, Minnerup J, Meuth SG, Ruck T. Skeletal muscle as potential central link between sarcopenia and immune senescence. EBioMedicine 2019;49:381–8.
[58] Pietrobon AJ, Teixeira FME, Sato MN. Immunosenescence and inflammaging: risk factors of severe COVID-19 in older people. Front Immunol 2020;11:579220.
[59] Kamper RS, Alcazar J, Andersen LL, Haddock B, Jørgensen NR, Hovind P, et al. Associations between inflammatory markers, body composition, and physical function: the Copenhagen Sarcopenia Study. J Cachexia Sarcopenia Muscle 2021;12(6):1641–52.
[60] Alemán H, Esparza J, Ramirez FA, Astiazaran H, Payette H. Longitudinal evidence on the association between interleukin-6 and C-reactive protein with the loss of total appendicular skeletal muscle in free-living older men and women. Age Ageing 2011;40(4):469–75.
[61] Granic A, Martin-Ruiz C, Dodds RM, Robinson L, Spyridopoulos I, Kirkwood TB, et al. Immunosenescence profiles are not associated with muscle strength, physical performance and sarcopenia risk in very old adults: the Newcastle 85+ Study. Mech Ageing Dev 2020;190:111321.
[62] Heymsfield SB, Fearnbach N. Can increasing physical activity prevent aging-related loss of skeletal muscle? Am J Clin Nutr 2021;114(5):1579–80.
[63] Aagaard P, Suetta C, Caserotti P, Magnusson SP, Kjaer M. Role of the nervous system in sarcopenia and muscle atrophy with aging: strength training as a countermeasure. Scand J Med Sci Sports 2010;20(1):49–64.
[64] He Q, Heo M, Heshka S, Wang J, Pierson Jr RN, Albu J, et al. Total body potassium differs by sex and race across the adult age span. Am J Clin Nutr 2003;78(1):72–7.
[65] Melton LJ, Khosla S, Riggs BL. Epidemiology of sarcopenia. Mayo Clin Proc 2000;75(Suppl):S10–2. discussion S12-13.
[66] Silva AM, Shen W, Heo M, Gallagher D, Wang Z, Sardinha LB, et al. Ethnicity-related skeletal muscle differences across the lifespan. Am J Hum Biol 2010;22(1):76–82.
[67] Miljkovic I, Kuipers AL, Cvejkus R, Bunker CH, Patrick AL, Gordon CL, et al. Myosteatosis increases with aging and is associated with incident diabetes in African ancestry men. Obesity 2016;24(2):476–82.
[68] Landi F, Calvani R, Tosato M, Martone AM, Ortolani E, Savera G, et al. Anorexia of aging: risk factors, consequences, and potential treatments. Nutrients 2016;8(2):69.
[69] Kortebein P, Ferrando A, Lombeida J, Wolfe R, Evans WJ. Effect of 10 days of bed rest on skeletal muscle in healthy older adults. JAMA 2007;297(16):1772–4.
[70] Deutz NEP, Pereira SL, Hays NP, Oliver JS, Edens NK, Evans CM, et al. Effect of β-hydroxy-β-methylbutyrate (HMB) on lean body mass during 10 days of bed rest in older adults. Clin Nutr 2013;32(5):704–12.
[71] Paddon-Jones D, Sheffield-Moore M, Urban RJ, Sanford AP, Aarsland A, Wolfe RR, et al. Essential amino acid and carbohydrate supplementation ameliorates muscle protein loss in humans during 28 days bedrest. J Clin Endocrinol Metab 2004;89(9):4351–8.
[72] Chatzipetrou V, Bégin MJ, Hars M, Trombetti A. Sarcopenia in chronic kidney disease: a scoping review of prevalence, risk factors, association with outcomes, and treatment. Calcif Tissue Int 2022;110(1):1–31.
[73] de Melo Silva FR, de Oliveira MGOA, Souza ASR, Figueroa JN, Santos CS. Factors associated with malnutrition in hospitalized cancer patients: a cross-sectional study. Nutr J 2015;14:123.
[74] Martin L, Gioulbasanis I, Senesse P, Baracos VE. Cancer-associated malnutrition and CT-defined sarcopenia and myosteatosis are endemic in overweight and obese patients. J Parenter Enter Nutr 2020;44:227–38.
[75] Wall BT, Dirks ML, van Loon LJC. Skeletal muscle atrophy during short-term disuse: implications for age-related sarcopenia. Ageing Res Rev 2013;12(4):898–906.
[76] Covinsky KE, Palmer RM, Fortinsky RH, Counsell SR, Stewart AL, Kresevic D, et al. Loss of independence in activities of daily living in older adults hospitalized with medical illnesses: increased vulnerability with age. J Am Geriatr Soc 2003;51(4):451–8.
[77] Wandrag L, Brett SJ, Frost GS, Bountziouka V, Hickson M. Exploration of muscle loss and metabolic state during prolonged critical illness: implications for intervention? Lopez-Delgado JC. PLoS One 2019;14(11):e0224565.
[78] Schefold JC, Wollersheim T, Grunow JJ, Luedi MM, Z'Graggen WJ, Weber-Carstens S. Muscular weakness and muscle wasting in the critically ill. J Cachexia Sarcopenia Muscle 2020;11:1399–412.
[79] Puthucheary ZA, Rawal J, McPhail M, Connolly B, Ratnayake G, Chan P, et al. Acute skeletal muscle wasting in critical illness. JAMA 2013;310(15):1591–600.
[80] Looijaard WG, Dekker IM, Stapel SN, Girbes AR, Twisk JW, Oudemans-van Straaten HM, et al. Skeletal muscle quality as assessed by CT-derived skeletal muscle density is associated with 6-month mortality in mechanically ventilated critically ill patients. Crit Care 2016;20(1):386.
[81] Lew CCH, Yandell R, Fraser RJL, Chua AP, Chong MFF, Miller M. Association between malnutrition and clinical outcomes in the intensive care unit: a systematic review. J Parenter Enter Nutr 2017;41(5):744–58.
[82] Montes-Ibarra M, Oliveira CLP, Orsso CE, Landi F, Marzetti E, Prado CM. The Impact of long COVID-19 on muscle health. Clin Geriatr Med 2022;38(3):545–57. https://doi.org/10.1016/j.cger.2022.03.004.
[83] Martone AM, Tosato M, Ciciarello F, Galluzzo V, Zazzara MB, Pais C, et al., Gemelli Against COVID-19 Post-Acute Care Team. Sarcopenia as potential biological substrate of long COVID-19 syndrome: prevalence, clinical features, and risk factors. J Cachexia Sarcopenia Muscle 2022. https://doi.org/10.1002/jcsm.12931. In press.
[84] Meyer H, Wienke A, Surov A. Computed tomography-defined body composition as prognostic markers for unfavourable outcomes and in-hospital mortality in coronavirus disease 2019. J Cachexia Sarcopenia Muscle 2022;13(1):159–68.
[85] Montes-Ibarra M, Orsso CE, Limon-Miro AT, Gonzalez MC, Marzetti E, Landi F, et al. Prevalence and clinical implications of abnormal body composition phenotypes in patients with COVID-19: a systematic review. 2022 [Under review].
[86] Bedock D, Bel Lassen P, Mathian A, Moreau P, Couffignal J, Ciangura C, et al. Prevalence and severity of malnutrition in hospitalized COVID-19 patients. Clin Nutr ESPEN 2020;40:214–9.
[87] Li T, Zhang Y, Gong C, Wang J, Liu B, Shi L, et al. Prevalence of malnutrition and analysis of related factors in elderly patients with COVID-19 in Wuhan, China. Eur J Clin Nutr 2020;74(6):871–5.
[88] Niederer LE, Miller H, Haines KL, Molinger J, Whittle J, MacLeod DB, et al. Prolonged progressive hypermetabolism during COVID-19 hospitalization undetected by common predictive energy equations. Clin Nutr ESPEN 2021;45:341–50.
[89] Whittle J, Molinger J, MacLeod D, Haines K, Wischmeyer PE, LEEP-COVID Study Group. Persistent hypermetabolism and longitudinal energy expenditure in critically ill patients with COVID-19. Crit Care 2020;24(1):581.
[90] Carfì A, Bernabei R, Landi F. For the gemelli against COVID-19 post-acute care study group. Persistent symptoms in patients after acute COVID-19. JAMA 2020;324(6):603.
[91] Paneroni M, Simonelli C, Saleri M, Bertacchini L, Venturelli M, Troosters T, et al. Muscle strength and physical performance in patients without previous disabilities recovering from COVID-19 pneumonia. Am J Phys Med Rehabil 2021;100(2):105–9.
[92] Barazzoni R, Jensen GL, Correia MITD, Gonzalez MC, Higashiguchi T, Shi HP, et al. Guidance for assessment of the muscle mass phenotypic criterion for the Global Leadership Initiative on Malnutrition (GLIM) diagnosis of malnutrition. Clin Nutr 2022;41(6):1425–33.
[93] Compher C, Cederholm T, Correia MITD, Gonzalez MC, Higashiguch T, Shi HP, et al. Guidance for assessment of the muscle mass phenotypic criterion for the Global Leadership Initiative on Malnutrition diagnosis of malnutrition. J Parenter Enteral Nutr 2022;46(6):1232–42.

[94] Gonzalez MC, Correia MITD, Heymsfield SB. A requiem for BMI in the clinical setting. Curr Opin Clin Nutr Metab Care 2017;20(5):314–21.
[95] Earthman CP. Body composition tools for assessment of adult malnutrition at the bedside: a tutorial on research considerations and clinical applications. J Parenter Enter Nutr 2015;39(7):787–822.
[96] Prado CM, Ford KL, Gonzalez MC, Murnane LC, Gillis C, Wischmeyer PE, et al. Nascent to novel methods to evaluate malnutrition and frailty in the surgical patient. J Parenter Enter Nutr 2022:1–15 [Ahead of print].
[97] Goodpaster BH, Stenger VA, Boada F, McKolanis T, Davis D, Ross R, et al. Skeletal muscle lipid concentration quantified by magnetic resonance imaging. Am J Clin Nutr 2004;79(5):748–54.
[98] van Zijl PCM, Brindle K, Lu H, Barker PB, Edden R, Yadav N, et al. Hyperpolarized MRI, functional MRI, MR spectroscopy and CEST to provide metabolic information in vivo. Curr Opin Chem Biol 2021;63:209–18.
[99] Looijaard WGPM, Stapel SN, Dekker IM, Rusticus H, Remmelzwaal S, Girbes ARJ, et al. Identifying critically ill patients with low muscle mass: agreement between bioelectrical impedance analysis and computed tomography. Clin Nutr 2020;39:1809–17.
[100] Gonzalez MC, Barbosa-Silva TG, Heymsfield SB. Bioelectrical impedance analysis in the assessment of sarcopenia. Curr Opin Clin Nutr Metab Care 2018;21(5):366–74.
[101] Arab A, Karimi E, Vingrys K, Shirani F. Is phase angle a valuable prognostic tool in cancer patients' survival? A systematic review and meta-analysis of available literature. Clin Nutr 2021;40:3182–90.
[102] da Silva BR, Gonzalez MC, Cereda E, Prado CM. Exploring the potential role of phase angle as a marker of oxidative stress: a narrative review. Nutrition 2021;93:111493.
[103] Osuna-Padilla IA, Rodríguez-Moguel NC, Rodríguez-Llamazares S, Aguilar-Vargas A, Casas-Aparicio GA, Ríos-Ayala MA, et al. Low phase angle is associated with 60-day mortality in critically ill patients with COVID-19. J Parenter Enter Nutr 2021;46(4):828–35.
[104] Chernyak BV, Popova EN, Prikhodko AS, Grebenchikov OA, Zinovkina LA, Zinovkin RA. COVID-19 and oxidative stress. Biochemistry (Mosc) 2020;85(12):1543–53.
[105] Jung YW, Hong N, Kim CO, Youm Y, Choi JY, Rhee Y. The diagnostic value of phase angle, an integrative bioelectrical marker, for identifying individuals with dysmobility syndrome: the Korean Urban-Rural Elderly Study. Osteoporos Int 2021;32(5):939–49.
[106] Di Vincenzo O, Marra M, Di Gregorio A, Pasanisi F, Scalfi L. Bioelectrical impedance analysis (BIA)-derived phase angle in sarcopenia: a systematic review. Clin Nutr 2021;40:3052–61.
[107] Norman K, Stobäus N, Pirlich M, Bosy-Westphal A. Bioelectrical phase angle and impedance vector analysis–clinical relevance and applicability of impedance parameters. Clin Nutr 2012;31(6):854–61.
[108] Dittmar M. Reliability and variability of bioimpedance measures in normal adults: effects of age, gender, and body mass. Am J Phys Anthropol 2003;122(4):361–70.
[109] Bosy-Westphal A, Danielzik S, Dörhöfer RP, Later W, Wiese S, Müller MJ. Phase angle from bioelectrical impedance analysis: population reference values by age, sex, and body mass index. J Parenter Enter Nutr 2006;30(4):309–16.
[110] Aleixo GFP, Shachar SS, Nyrop KA, Muss HB, Malpica L, Williams GR. Myosteatosis and prognosis in cancer: systematic review and meta-analysis. Crit Rev Oncol Hematol 2020;145:102839.
[111] Lambell KJ, Tierney AC, Wang JC, Nanjayya V, Forsyth A, Goh GS, et al. Comparison of ultrasound-derived muscle thickness with computed tomography muscle cross-sectional area on admission to the intensive care unit: a pilot cross-sectional study. J Parenter Enter Nutr 2021;45:136–45.
[112] Paris MT, Letofsky N, Mourtzakis M. Site-specific skeletal muscle echo intensity and thickness differences in subcutaneous adipose tissue matched older and younger adults. Clin Physiol Funct Imag 2021;41(2):156–64.
[113] Sabatino A, Maggiore U, Regolisti G, Rossi GM, Di Mario F, Gentile M, et al. Ultrasound for non-invasive assessment and monitoring of quadriceps muscle thickness in critically ill patients with acute kidney injury. Front Nutr 2021;8:622823.
[114] Stock MS, Thompson BJ. Echo intensity as an indicator of skeletal muscle quality: applications, methodology, and future directions. Eur J Appl Physiol 2021;121(2):369–80.
[115] Barbosa-Silva TG, Gonzalez MC, Bielemann RM, Santos LP, Costa CDS, Menezes AMB, COCONUT Study Group. Brazil. 2 + 2 (+ 2) = 4: a new approach for appendicular muscle mass assessment by ultrasound. Nutrition 2021;83:111056.
[116] Turton P, Hay R, Welters I. Assessment of peripheral muscle thickness and architecture in healthy volunteers using hand-held ultrasound devices; a comparison study with standard ultrasound. BMC Med Imag 2019;19(1):69.
[117] Young HJ, Jenkins NT, Zhao Q, Mccully KK. Measurement of intramuscular fat by muscle echo intensity. Muscle Nerve 2015;52(6). 963-671.
[118] Popuri K, Cobzas D, Esfandiari N, Baracos V, Jägersand M. Body composition assessment in axial CT images using FEM-based automatic segmentation of skeletal muscle. IEEE Trans Med Imag 2016;35(2):512–20.
[119] Cespedes Feliciano EM, Popuri K, Cobzas D, Baracos VE, Beg MF, Khan AD, et al. Evaluation of automated computed tomography segmentation to assess body composition and mortality associations in cancer patients. J Cachexia Sarcopenia Muscle 2020;11:1258–69.
[120] Lee YS, Hong N, Witanto JN, Choi YR, Park J, Decazes P, et al. Deep neural network for automatic volumetric segmentation of whole-body CT images for body composition assessment. Clin Nutr 2021;40(8):5038–46.
[121] Rozynek M, Kucybała I, Urbanik A, Wojciechowski W. Use of artificial intelligence in the imaging of sarcopenia: a narrative review of current status and perspectives. Nutrition 2021;89:111227.
[122] Shen W, Punyanitya M, Wang Z, Gallagher D, St-Onge MP, Albu J, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. J Appl Physiol 2004;97:2333–8.
[123] Tolonen A, Pakarinen T, Sassi A, Kyttä J, Cancino W, Rinta-Kiikka I, et al. Methodology, clinical applications, and future directions of body composition analysis using computed tomography (CT) images: a review. Eur J Radiol 2021;145:109943.
[124] Derstine BA, Holcombe SA, Ross BE, Wang NC, Su GL, Wang SC. Skeletal muscle cutoff values for sarcopenia diagnosis using T10 to L5 measurements in a healthy US population. Sci Rep 2018;8(1):11369.
[125] van der Werf A, Langius JAE, de van der Schueren MAE, Nurmohamed SA, van der Pant KAMI, Blauwhoff-Buskermolen S, et al. Percentiles for skeletal muscle index, area and radiation attenuation based on computed tomography imaging in a healthy Caucasian population. Eur J Clin Nutr 2018;72(2):288–96.
[126] Bahat G, Turkmen BO, Aliyev S, Catikkas NM, Bakir B, Karan MA. Cut-off values of skeletal muscle index and psoas muscle index at L3 vertebra level by computerized tomography to assess low muscle mass. Clin Nutr 2021;40(6):4360–5.
[127] Navin PJ, Moynagh MR, Atkinson EJ, Tirumanisetty P, LeBrasseur NK, Kumar A, et al. Establishment of normative biometric data for body composition based on computed tomography in a North American cohort. Clin Nutr 2021;40(4):2435–42.
[128] Magudia K, Bridge CP, Bay CP, Babic A, Fintelmann FJ, Troschel FM, et al. Population-scale CT-based body composition analysis of a large outpatient population using deep learning to derive age-, sex-, and race-specific reference curves. Radiology 2021;298(2):319–29.
[129] Ahn H, Kim DW, Ko Y, Ha J, Shin YB, Lee J, et al. Updated systematic review and meta-analysis on diagnostic issues and the prognostic impact of myosteatosis: a new paradigm beyond sarcopenia. Ageing Res Rev 2021;70:101398.
[130] Xiao J, Caan BJ, Cespedes Feliciano EM, Meyerhardt JA, Peng PD, Baracos VE, et al. Association of low muscle mass and low muscle radiodensity with morbidity and mortality for colon cancer surgery. JAMA Surg 2020;155(10).942-249.
[131] Lee CM, Kang J. Prognostic impact of myosteatosis in patients with colorectal cancer: a systematic review and meta-analysis. J Cachexia Sarcopenia Muscle 2020;11:1270–82.
[132] West MA, van Dijk Dpj, Gleadowe F, Reeves T, Primrose JN, Abu Hilal M, et al. Myosteatosis is associated with poor physical fitness in patients undergoing hepatopancreatobiliary surgery. J Cachexia Sarcopenia Muscle 2019;10(4):860–71.
[133] Akazawa N, Harada K, Okawa N, Tamura K, Moriyama H. Muscle mass and intramuscular fat of the quadriceps are related to muscle strength in non-ambulatory chronic stroke survivors: a cross-sectional studyMogi M, editor. PLoS One 2018;13(8):e0201789.
[134] Miljkovic I, Vella CA, Allison M. Computed tomography-derived myosteatosis and metabolic disorders. Diabetes Metab J 2021;45(4):482–91.
[135] Martin L, Hopkins J, Malietzis G, Jenkins JT, Sawyer MB, Brisebois R, et al. Assessment of computed tomography (CT)-defined muscle and adipose tissue features in relation to short-term outcomes after elective surgery for colorectal cancer: a multicenter approach. Ann Surg Oncol 2018;25(9):2669–80.
[136] Buckinx F, Landi F, Cesari M, Fielding RA, Visser M, Engelke K, et al. Pitfalls in the measurement of muscle mass: a need for a reference standard. J Cachexia Sarcopenia Muscle 2018;9:269–78.
[137] Cawthon PM, Manini T, Patel SM, Newman A, Travison T, Kiel DP, et al. Putative cut-points in sarcopenia components and incident adverse health outcomes: an SDOC analysis. J Am Geriatr Soc 2020;68(7):1429–37.
[138] Bhasin S, Travison TG, Manini TM, Patel S, Pencina KM, Fielding RA, et al. Sarcopenia definition: the position statements of the sarcopenia definition and outcomes Consortium. J Am Geriatr Soc 2020;68(7):1410–8.
[139] Sutter T, Duboeuf F, Chapurlat R, Cortet B, Lespessailles E, Roux JP. DXA body composition corrective factors between Hologic Discovery models to conduct multicenter studies. Bone 2021;142:115683.
[140] Van Loan MD, Keim NL, Berg K, Mayclin PL. Evaluation of body composition by dual energy x-ray absorptiometry and two different software packages. Med Sci Sports Exerc 1995;27(4):587–91.
[141] Sheean P, Gonzalez MC, Prado CM, McKeever L, Hall AM, Braunschweig CA. American Society for Parenteral and Enteral Nutrition Clinical Guidelines: the validity of body composition assessment in clinical populations. J Parenter Enter Nutr 2020;44(1):12–43.
[142] Evans WJ, Hellerstein M, Orwoll E, Cummings S, Cawthon PM. D3-Creatine dilution and the importance of accuracy in the assessment of skeletal muscle mass. J Cachexia Sarcopenia Muscle 2019;10(1):14–21.
[143] Clark RV, Walker AC, Miller RR, O'Connor-Semmes RL, Ravussin E, Cefalu WT. Creatine (methyl-d3) dilution in urine for estimation of total body skeletal muscle mass: accuracy and variability vs. MRI and DXA. J Appl Physiol 2018;124:1–9.

[144] Zhu K, Wactawski-Wende J, Ochs-Balcom HM, LaMonte MJ, Hovey KM, Evans W, et al. The association of muscle mass measured by D3-creatine dilution method with dual energy X-ray absorptiometry and physical function in postmenopausal women. J Gerontol A Biol Sci Med Sci 2021;76(9):1591–9.
[145] Cawthon PM, Orwoll ES, Peters KE, Ensrud KE, Cauley JA, Kado DM, et al. Osteoporotic Fractures in Men (MrOS) Study Research Group. Strong relation between muscle mass determined by D3-creatine dilution, physical performance, and incidence of falls and mobility limitations in a prospective cohort of older men. J Gerontol A Biol Sci Med Sci 2019;74(6):844–52.
[146] 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. J Gerontol A Biol Sci Med Sci 2021;76:123–30.
[147] Heymsfield SB, Prado CM, Gonzalez MC, Cederholm T, Jensen GL, Barazzoni R, et al. Response to "Lean body mass should not be used as a surrogate measurement of muscle mass in malnourished men and women: comment on Compher et al.". J Parenter Enter Nutr 2022:10.1002/jpen.2414. In press.
[148] Bruyère O, Beaudart C, Reginster J-Y, Buckinx F, Schoene D, Hirani V, et al. Assessment of muscle mass, muscle strength and physical performance in clinical practice: an international survey. Eur Geriatric Med 2016;7:243–6.
[149] Santos LP, Gonzalez MC, Orlandi SP, Bielemann RM, Barbosa-Silva TG, Heymsfield SB, COCONUT Study Group. New prediction equations to estimate appendicular skeletal muscle mass using calf circumference: results from NHANES 1999–2006. J Parenter Enter Nutr 2019;43:998–1007.
[150] Tresignie J, Scafoglieri A, Pieter Clarys J, Cattrysse E. Reliability of standard circumferences in domain-related constitutional applications. Am J Hum Biol 2013;25(5):637–42.
[151] Gonzalez MC, Mehrnezhad A, Razaviarab N, Barbosa-Silva TG, Heymsfield SB. Calf circumference: cutoff values from the NHANES 1999-2006. Am J Clin Nutr 2021;113(6):1679–87.
[152] Ishida Y, Maeda K, Nonogaki T, Shimizu A, Yamanaka Y, Matsuyama R, et al. Impact of edema on length of calf circumference in older adults. Geriatr Gerontol Int 2019;19(10):993–8.
[153] Prado CM, Purcell SA, Laviano A. Nutrition interventions to treat low muscle mass in cancer. J Cachexia Sarcopenia Muscle 2020;11:366–80.
[154] Prado CM, Anker SD, Coats AJS, Laviano A, Haehling S. Nutrition in the spotlight in cachexia, sarcopenia and muscle: avoiding the wildfire. J Cachexia Sarcopenia Muscle 2021;12(1):3–8.
[155] Gielen E, Beckwée D, Delaere A, De Breucker S, Vandewoude M, Bautmans I. Sarcopenia Guidelines Development Group of the Belgian Society of Gerontology and Geriatrics (BSGG). Nutritional interventions to improve muscle mass, muscle strength, and physical performance in older people: an umbrella review of systematic reviews and meta-analyses. Nutr Rev 2021;79(2):121–47.
[156] Nunes EA, Colenso-Semple L, McKellar SR, Yau T, Ali MU, Fitzpatrick-Lewis D, et al. Systematic review and meta-analysis of protein intake to support muscle mass and function in healthy adults. J Cachexia Sarcopenia Muscle 2022;13:795–810.
[157] Mikkelsen MK, Lund CM, Vinther A, Tolver A, Johansen JS, Chen I, et al. Effects of a 12-week multimodal exercise intervention among older patients with advanced cancer: results from a randomized controlled trial. Oncol 2022;27:67–78.
[158] Phillips SM, Glover EI, Rennie MJ. Alterations of protein turnover underlying disuse atrophy in human skeletal muscle. J Appl Physiol 2009;107:645–54.
[159] Paulussen KJM, McKenna CF, Beals JW, Wilund KR, Salvador AF, Burd NA. Anabolic resistance of muscle protein turnover comes in various shapes and sizes. Front Nutr 2021;8:615849.
[160] Orsso CE, Montes-Ibarra M, Findlay M, van der Meij BS, de van der Schueren MAE, Landi F, et al. Mapping ongoing nutrition intervention trials in muscle, sarcopenia, and cachexia: a scoping review of future research. J Cachexia Sarcopenia Muscle 2022;13:1442–59.
[161] Volkert D, Beck AM, Cederholm T, Cruz-Jentoft A, Goisser S, Hooper L, et al. ESPEN guideline on clinical nutrition and hydration in geriatrics. Clin Nutr 2019;38:10–47.
[162] Muscaritoli M, Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, et al. ESPEN practical guideline: clinical nutrition in cancer. Clin Nutr 2021;40(5):2898–913.
[163] Domingues-Faria C, Vasson MP, Goncalves-Mendes N, Boirie Y, Walrand S. Skeletal muscle regeneration and impact of aging and nutrition. Ageing Res Rev 2016;26:22–36.
[164] Atherton PJ, Etheridge T, Watt PW, Wilkinson D, Selby A, Rankin D, et al. Muscle full effect after oral protein: time-dependent concordance and discordance between human muscle protein synthesis and mTORC1 signaling. Am J Clin Nutr 2010;92:1080–8.
[165] Deane C, Bass J, Crossland H, Phillips B, Atherton P. Animal, plant, collagen and blended dietary proteins: effects on musculoskeletal outcomes. Nutrients 2020;12(9):2670.
[166] Bohé J, Low JFA, Wolfe RR, Rennie MJ. Rapid report: latency and duration of stimulation of human muscle protein synthesis during continuous infusion of amino acids. J Physiol 2001;532:575–9.
[167] Gorissen SHM, Witard OC. Characterising the muscle anabolic potential of dairy, meat and plant-based protein sources in older adults. Proc Nutr Soc 2018;77(1):20–31.
[168] Tang JE, Moore DR, Kujbida GW, Tarnopolsky MA, Phillips SM. Ingestion of whey hydrolysate, casein, or soy protein isolate: effects on mixed muscle protein synthesis at rest and following resistance exercise in young men. J Appl Physiol 2009;107:987–92.
[169] Park S, Church DD, Schutzler SE, Azhar G, Kim IY, Ferrando AA, et al. Metabolic evaluation of the dietary guidelines' ounce equivalents of protein food sources in young adults: a randomized controlled trial. J Nutr 2021;151(5):1190–6.
[170] Yang Y, Churchward-Venne TA, Burd NA, Breen L, Tarnopolsky MA, Phillips SM. Myofibrillar protein synthesis following ingestion of soy protein isolate at rest and after resistance exercise in elderly men. Nutr Metab 2012;9(1):57.
[171] Impey SG, Hammond KM, Naughton R, Langan-Evans C, Shepherd SO, Sharples AP, et al. Whey protein augments leucinemia and postexercise p70s6k1 activity compared with a hydrolyzed collagen blend when in recovery from training with low carbohydrate availability. Int J Sport Nutr Exerc Metabol 2018;28:651–9.
[172] Oikawa SY, Macinnis MJ, Tripp TR, Mcglory C, Baker SK, Phillips SM. Lactalbumin, not collagen, augments muscle protein synthesis with aerobic exercise. Med Sci Sports Exerc 2020;52:1394–403.
[173] Wu G. Dietary protein intake and human health. Food Funct 2016;7(3):1251–65.
[174] Hays NP, Kim H, Wells AM, Kajkenova O, Evans WJ. Effects of whey and fortified collagen hydrolysate protein supplements on nitrogen balance and body composition in older women. J Am Diet Assoc 2009;109(6):1082–7.
[175] Brook MS, Scaife P, Bass JJ, Cegielski J, Watanabe S, Wilkinson DJ, et al. A collagen hydrolysate/milk protein-blend stimulates muscle anabolism equivalently to an isoenergetic milk protein-blend containing a greater quantity of essential amino acids in older men. Clin Nutr 2021;40(6):4456–64.
[176] Ford KL, Arends J, Atherton PJ, Engelen MPKJ, Gonçalves TJM, Laviano A, et al. The importance of protein sources to support muscle anabolism in cancer: an expert group opinion. Clin Nutr 2022;41:192–201.
[177] Atherton PJ, Smith K, Etheridge T, Rankin D, Rennie MJ. Distinct anabolic signalling responses to amino acids in C2C12 skeletal muscle cells. Amino Acids 2010;38(5):1533–9.
[178] Wilkinson DJ, Hossain T, Hill DS, Phillips BE, Crossland H, Williams J, et al. Effects of leucine and its metabolite β-hydroxy-β-methylbutyrate on human skeletal muscle protein metabolism. J Physiol 2013;591:2911–23.
[179] Komar B, Schwingshackl L, Hoffmann G. Effects of leucine-rich protein supplements on anthropometric parameter and muscle strength in the elderly: a systematic review and meta-analysis. J Nutr Health Aging 2015;19(4):437–46.
[180] Osuka Y, Kojima N, Sasai H, Wakaba K, Miyauchi D, Tanaka K, et al. Effects of exercise and/or β-hydroxy-β-methylbutyrate supplementation on muscle mass, muscle strength, and physical performance in older women with low muscle mass: a randomized, double-blind, placebo-controlled trial. Am J Clin Nutr 2021;114(4):1371–85.
[181] Bear DE, Langan A, Dimidi E, Wandrag L, Harridge SDR, Hart N, et al. β-Hydroxy-β-methylbutyrate and its impact on skeletal muscle mass and physical function in clinical practice: a systematic review and meta-analysis. Am J Clin Nutr 2019;109:1119–32.
[182] Prado CM, Orsso CE, Pereira SL, Atherton PJ, Deutz NEP. Effects of β-hydroxy β-methylbutyrate (HMB) supplementation on muscle mass, function, and other outcomes in patients with cancer: a systematic review. J Cachexia Sarcopenia Muscle 2022;13:1623–41.
[183] Dzik KP, Kaczor JJ. Mechanisms of vitamin D on skeletal muscle function: oxidative stress, energy metabolism and anabolic state. Eur J Appl Physiol 2019;119(4):825–39.
[184] Hirani V, Cumming RG, Naganathan V, Blyth F, Le Couteur DG, Hsu B, et al. Longitudinal associations between vitamin D metabolites and sarcopenia in older Australian men: the concord health and aging in men project. J Gerontol A Biol Sci Med Sci 2018;73:131–8.
[185] Choi M, Park H, Cho S, Lee M. Vitamin D3 supplementation modulates inflammatory responses from the muscle damage induced by high-intensity exercise in SD rats. Cytokine 2013;63(1):27–35.
[186] Prietl B, Pilz S, Wolf M, Tomaschitz A, Obermayer-Pietsch B, Graninger W, et al. Vitamin D supplementation and regulatory T cells in apparently healthy subjects: vitamin D treatment for autoimmune diseases? Isr Med Assoc J 2010;12(3):136–9.
[187] Anagnostis P, Dimopoulou C, Karras S, Lambrinoudaki I, Goulis DG. Sarcopenia in post-menopausal women: is there any role for vitamin D? Maturitas 2015;82(1):56–64.
[188] Beaudart C, Dawson A, Shaw SC, Harvey NC, Kanis JA, Binkley N, et al., IOF-ESCEO Sarcopenia Working Group. Nutrition and physical activity in the prevention and treatment of sarcopenia: systematic review. Osteoporos Int 2017;28(6):1817–33.
[189] Gkekas NK, Anagnostis P, Paraschou V, Stamiris D, Dellis S, Kenanidis E, et al. The effect of vitamin D plus protein supplementation on sarcopenia: a systematic review and meta-analysis of randomized controlled trials. Maturitas 2021;145:56–63.

[190] Smith GI, Julliand S, Reeds DN, Sinacore DR, Klein S, Mittendorfer B. Fish oil-derived n-3 PUFA therapy increases muscle mass and function in healthy older adults. Am J Clin Nutr 2015;102(1):115–22.
[191] Murphy RA, Mourtzakis M, Chu QSC, Baracos VE, Reiman T, Mazurak VC. Nutritional intervention with fish oil provides a benefit over standard of care for weight and skeletal muscle mass in patients with nonsmall cell lung cancer receiving chemotherapy. Cancer 2011;117(8):1775–82.
[192] Aredes MA, da Camara AO, de Paula NS, Fraga KYD, do Carmo M das GT, Chaves GV. Efficacy of ω-3 supplementation on nutritional status, skeletal muscle, and chemoradiotherapy toxicity in cervical cancer patients: a randomized, triple-blind, clinical trial conducted in a middle-income country. Nutrition 2019;67–68:110528.
[193] Bird JK, Troesch B, Warnke I, Calder PC. The effect of long chain omega-3 polyunsaturated fatty acids on muscle mass and function in sarcopenia: a scoping systematic review and meta-analysis. Clin Nutr ESPEN 2021;46:73–86.
[194] Lam CN, Watt AE, Isenring EA, de van der Schueren MAE, van der Meij BS. The effect of oral omega-3 polyunsaturated fatty acid supplementation on muscle maintenance and quality of life in patients with cancer: a systematic review and meta-analysis. Clin Nutr 2021;40(6):3815–26.
[195] Jackman SR, Brook MS, Pulsford RM, Cockcroft EJ, Campbell MI, Rankin D, et al. Tart cherry concentrate does not enhance muscle protein synthesis response to exercise and protein in healthy older men. Exp Gerontol 2018;110:202–8.
[196] Pollack RM, Barzilai N, Anghel V, Kulkarni AS, Golden A, O'Broin P, et al. Resveratrol improves vascular function and mitochondrial number but not glucose metabolism in older adults. J Gerontol A Biol Sci Med Sci 2017;72(12):1703–9.
[197] Baldwin C, Spiro A, Ahern R, Emery PW. Oral nutritional interventions in malnourished patients with cancer: a systematic review and meta-analysis. J Natl Cancer Inst 2012;104(5):371–85.
[198] Collins J, Porter J. The effect of interventions to prevent and treat malnutrition in patients admitted for rehabilitation: a systematic review with meta-analysis. J Hum Nutr Diet 2015;28(1):1–15.
[199] Li M, Zhao S, Wu S, Yang X, Feng H. Effectiveness of oral nutritional supplements on older people with anorexia: a systematic review and meta-analysis of randomized controlled trials. Nutrients 2021;13(3):835.
[200] Xueting H, Li L, Meng Y, Yuqing C, Yutong H, Lihong Q, et al. Home enteral nutrition and oral nutritional supplements in postoperative patients with upper gastrointestinal malignancy: a systematic review and meta-analysis. Clin Nutr 2021;40:3082–93.
[201] de van der Schueren MAE, Laviano A, Blanchard H, Jourdan M, Arends J, Baracos VE. Systematic review and meta-analysis of the evidence for oral nutritional intervention on nutritional and clinical outcomes during chemo(radio)therapy: current evidence and guidance for design of future trials. Ann Oncol 2018;29(5):1141–53.
[202] Chew STH, Tan NC, Cheong M, Oliver J, Baggs G, Choe Y, et al. Impact of specialized oral nutritional supplement on clinical, nutritional, and functional outcomes: a randomized, placebo-controlled trial in community-dwelling older adults at risk of malnutrition. Clin Nutr 2021;40:1879–92.
[203] Schuetz P, Fehr R, Baechli V, Geiser M, Deiss M, Gomes F, et al. Individualised nutritional support in medical inpatients at nutritional risk: a randomised clinical trial. Lancet 2019;393(10188):2312–21.
[204] Cereda E, Pisati R, Rondanelli M, Caccialanza R. Whey protein, leucine- and vitamin-D-enriched oral nutritional supplementation for the treatment of sarcopenia. Nutrients 2022;14(7):1524.
[205] Tan S, Meng Q, Jiang Y, Zhuang Q, Xi Q, Xu J, et al. Impact of oral nutritional supplements in post-discharge patients at nutritional risk following colorectal cancer surgery: a randomised clinical trial. Clin Nutr 2021;40:47–53.
[206] Deane CS, Wilkinson DJ, Phillips BE, Smith K, Etheridge T, Atherton PJ. "Nutraceuticals" in relation to human skeletal muscle and exercise. Am J Physiol Endocrinol Metab 2017;312:E282–99.
[207] Joncquel-Chevalier Curt M, Voicu PM, Fontaine M, Dessein AF, Porchet N, Mention-Mulliez K, et al. Creatine biosynthesis and transport in health and disease. Biochimie 2015;119:146–65.
[208] Kunkel SD, Suneja M, Ebert SM, Bongers KS, Fox DK, Malmberg SE, et al. mRNA expression signatures of human skeletal muscle atrophy identify a natural compound that increases muscle mass. Cell Metabol 2011;13(6):627–38.
[209] Mobley CB, Hornberger TA, Fox CD, Healy JC, Ferguson BS, Lowery RP, et al. Effects of oral phosphatidic acid feeding with or without whey protein on muscle protein synthesis and anabolic signaling in rodent skeletal muscle. J Int Soc Sports Nutr 2015;12(1):32.
[210] Kirwan RP, Mazidi M, Rodríguez García C, Lane KE, Jafari A, Butler T, et al. Protein interventions augment the effect of resistance exercise on appendicular lean mass and handgrip strength in older adults: a systematic review and meta-analysis of randomized controlled trials. Am J Clin Nutr 2021;115(3):897–913.
[211] Yamada M, Kimura Y, Ishiyama D, Nishio N, Otobe Y, Tanaka T, et al. Synergistic effect of bodyweight resistance exercise and protein supplementation on skeletal muscle in sarcopenic or dynapenic older adults. Geriatr Gerontol Int 2019;19(5):429–37.
[212] Yang H, Chang J, Chen W, Zhao L, Qu B, Tang C, et al. Treadmill exercise promotes interleukin 15 expression in skeletal muscle and interleukin 15 receptor alpha expression in adipose tissue of high-fat diet rats. Endocrine 2013;43(3):579–85.
[213] Duggal NA, Niemiro G, Harridge SDR, Simpson RJ, Lord JM. Can physical activity ameliorate immunosenescence and thereby reduce age-related multi-morbidity? Nat Rev Immunol 2019;19(9):563–72.
[214] Harper C, Gopalan V, Goh J. Exercise rescues mitochondrial coupling in aged skeletal muscle: a comparison of different modalities in preventing sarcopenia. J Transl Med 2021;19(1):71.
[215] Hsieh TJ, Su SC, Chen CW, Kang YW, Hu MH, Hsu LL, et al. Individualized home-based exercise and nutrition interventions improve frailty in older adults: a randomized controlled trial. Int J Behav Nutr Phys Activ 2019;16(1):119.
[216] Ng TP, Feng L, Nyunt MS, Feng L, Niti M, Tan BY, et al. Nutritional, physical, cognitive, and combination interventions and frailty reversal among older adults: a randomized controlled trial. Am J Med 2015;128(11):1225–36.
[217] Akanni O, Smith M, Ory M. Cost-effectiveness of a community exercise and nutrition program for older adults: texercise Select. IJERPH 2017;14(5):545.
[218] Dorhout BG, Haveman-Nies A, van Dongen EJI, Wezenbeek NLW, Doets EL, Bulten A, et al. Cost-effectiveness of a diet and resistance exercise intervention in community-dwelling older adults: ProMuscle in Practice. J Am Med Dir Assoc 2021;22:792–802.e2.
[219] Apóstolo J, Cooke R, Bobrowicz-Campos E, Santana S, Marcucci M, Cano A, et al. Effectiveness of interventions to prevent pre-frailty and frailty progression in older adults: a systematic review. JBI Database System Rev Implement Rep 2018;16(1):140–232.
[220] Malmstrom TK, Miller DK, Simonsick EM, Ferrucci L, Morley JE. SARC-F: a symptom score to predict persons with sarcopenia at risk for poor functional outcomes. J Cachexia Sarcopenia Muscle 2016;7:28–36.
[221] Stratton RJ, Hackston A, Longmore D, Dixon R, Price S, Stroud M, et al. Malnutrition in hospital outpatients and inpatients: prevalence, concurrent validity and ease of use of the "malnutrition universal screening tool" ('MUST') for adults. Br J Nutr 2004;92(5):799–808.
[222] Ferguson M, Capra S, Bauer J, Banks M. Development of a valid and reliable malnutrition screening tool for adult acute hospital patients. Nutrition 1999;15(6):458–64.
[223] Kondrup J, Allison SP, Elia M, Vellas B, Plauth M. Educational and clinical practice committee, European society of parenteral and enteral nutrition (ESPEN). ESPEN guidelines for nutrition screening 2002. Clin Nutr 2003;22:415–21.
[224] Ž Krznarić, Bender DV, Laviano A, Cuerda C, Landi F, Monteiro R, et al. A simple remote nutritional screening tool and practical guidance for nutritional care in primary practice during the COVID-19 pandemic. Clin Nutr 2020;39(7):1983–7.
[225] Hung Y, Wijnhoven H, Visser M, Verbeke W. Appetite and protein intake strata of older adults in the European Union: socio-demographic and health characteristics, diet-related and physical activity behaviours. Nutrients 2019;11(4):777.
[226] Avgerinou C, Bhanu C, Walters K, Croker H, Liljas A, Rea J, et al. Exploring the views and dietary practices of older people at risk of malnutrition and their carers: a qualitative study. Nutrients 2019;11(6):1281.
[227] Van Ancum JM, Meskers CGM, Reijnierse EM, Yeung SSY, Jonkman NH, Trappenburg MC, et al. Lack of knowledge contrasts the willingness to counteract sarcopenia among community-dwelling adults. J Aging Health 2020;32(7–8):787–94.
[228] Meck Higgins M, Barkley MC. Barriers to nutrition education for older adults, and nutrition and aging training opportunities for educators, healthcare providers, volunteers and caregivers. J Nutr Elder 2004;23:99–121.
[229] Thomas DR. Loss of skeletal muscle mass in aging: examining the relationship of starvation, sarcopenia and cachexia. Clin Nutr 2007;26(4):389–99.
[230] Rea J, Walters K, Avgerinou C. How effective is nutrition education aiming to prevent or treat malnutrition in community-dwelling older adults? A systematic review. Eur Geriatr Med 2019;10(3):339–58.