Clinical Nutrition 61 (2026) 106652

Contents lists available at ScienceDirect

Clinical Nutrition

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

Narrative Review

Shaping the future of muscle health: A clinical nutrition perspective and research agenda

Arthur R.H. van Zanten [a,b,*], Nicolaas E. Deutz [c], Ana-Marija Liberati Prso [d,e], Carla M. Prado [f], Marieke G. Schooneman [g], Maarten R. Soeters [h], Marian A.E. de van der Schueren [i,j], Peter J.M. Weijs [k,l], Harriët Jager-Wittenaar [m,n,o]

[a] Gelderse Vallei Hospital, Department of Intensive Care, Willy Brandtlaan 10, 6716 RP Ede, the Netherlands
[b] Division of Human Nutrition and Health, Wageningen University & Research, Helix (Building 124), Stippenweg 4, 6708 WE Wageningen, the Netherlands
[c] Center for Translational Research in Aging & Longevity (CTRAL), Department of Kinesiology and Sport Management, College of Education and Human Development, Texas A&M University, College Station, TX, USA
[d] Clinical Hospital Sveti Duh, Centre for Obesity, Metabolic Syndrome and Clinical Nutrition, Sveti Duh 64, 10000 Zagreb, Croatia
[e] Faculty of Medicine University of Rijeka, Croatian Society for Supplements in Medicine, Croatia
[f] Department of Agricultural, Food and Nutritional Science, University of Alberta, Canada
[g] Department of Internal Medicine and Oncology, Dijklander Hospital, Hoorn/Purmerend, the Netherlands
[h] Department of Endocrinology and Metabolism, AmsterdamUMC, Location AMC, Amsterdam, the Netherlands
[i] Department of Nutrition, Dietetics, and Lifestyle, HAN University of Applied Sciences, Nijmegen, the Netherlands
[j] Division of Human Nutrition and Health, Wageningen University and Research Wageningen, the Netherlands
[k] Department of Nutrition and Dietetics, Faculty of Health, Sport and Physical Activity, Amsterdam University of Applied Sciences, the Netherlands
[l] Department of Nutrition and Dietetics, Amsterdam University Medical Center, Amsterdam, the Netherlands
[m] Hanze University of Applied Sciences Groningen, Research Group Healthy Ageing, Allied Health Care and Nursing, Groningen, the Netherlands
[n] Radboud University Medical Center, Department of Gastroenterology and Hepatology, Dietetics, Nijmegen, the Netherlands
[o] Vrije Universiteit Brussel, Faculty of Physical Education and Physiotherapy, Department of Physiotherapy, Human Physiology and Anatomy, Research Unit Experimental Anatomy, Brussels, Belgium

ARTICLE INFO

Article history:
Received 25 January 2026
Accepted 26 March 2026

Keywords:
Skeletal muscle
Sarcopenia
Malnutrition
Catabolism

SUMMARY

Muscle health, encompassing muscle mass, composition, strength, physical performance and patient-reported outcomes, is a key determinant of clinical outcomes across the life course and a wide range of disease states. Despite growing recognition of its importance, muscle health remains insufficiently integrated into routine clinical nutrition practice, and nutritional recommendations often rely on population averages rather than individual muscle status, disease phase or metabolic context.

This narrative review, developed by an international multidisciplinary expert group, synthesises current evidence on muscle health and clinical nutrition across major clinical domains, including ageing, cancer, metabolic disease, obesity, weight loss interventions and acute illness. We critically appraise methods for assessing muscle mass, function, and patient-reported outcomes, highlighting their

Abbreviations: 6MWT, Six-Minute Walk Test; AA, Amino Acids; ADL, Activities of Daily Living; ALST, Appendicular Lean Soft Tissue; BIA, Bioelectrical Impedance Analysis; CAT, Computerised Adaptive Test; CCU, Critical Care Unit (if used-otherwise delete); CHF, Chronic Heart Failure; CKD, Chronic Kidney Disease; CONCISE, Core Outcome Measures for Clinical Effectiveness Trials of Nutritional and Metabolic Interventions in Critical Illness; COPD, Chronic Obstructive Pulmonary Disease; CSA, Cross-Sectional Area; CT, Computed Tomography; DHA, Docosahexaenoic Acid; DXA, Dual-energy X-ray Absorptiometry; EAT-10, Eating Assessment Tool-10; EN, Enteral Nutrition; EPA, Eicosapentaenoic Acid; ESPEN, European Society for Clinical Nutrition and Metabolism; EWGSOP, European Working Group on Sarcopenia in Older People; FFM, Fat-Free Mass; FFMI, Fat-Free Mass Index; GLIM, Global Leadership Initiative on Malnutrition; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; GLP-1RA/GIP, Glucagon-Like Peptide-1/Glucose-Dependent Insulinotropic Polypeptide Receptor Agonist; HADS, Hospital Anxiety and Depression Scale; HCP, Healthcare Professional; HGS, Handgrip Strength; HMB, β-Hydroxy-β-Methyl-Butyrate; HRQoL, Health-Related Quality of Life; IAA, Indicator Amino Acid; ICU, Intensive Care Unit; ICU-AW, Intensive Care Unit–Acquired Weakness; IES-R, Impact of Event Scale–Revised; LOS, Length of Stay; MRC, Medical Research Council; MRI, Magnetic Resonance Imaging; ONS, Oral Nutritional Supplements; PG-SGA, Patient-Generated Subjective Global Assessment; PN, Parenteral Nutrition; PROM, Patient-Reported Outcome Measure; PROMIS, Patient-Reported Outcomes Measurement Information System; QoL, Quality of Life; REE, Resting Energy Expenditure; SCWD, Society on Cachexia Sarcopenia and Wasting Disorders; SF-12, 12-Item Short Form Health Survey; SF-36, 36-Item Short Form Health Survey; SGLT2i, Sodium-Glucose Cotransporter 2 Inhibitors; SO, Sarcopenic Obesity; SOGLI, Sarcopenic Obesity Global Leadership Initiative; SOPi, Sarcopenic Obesity Phenotype Index; SPPB, Short Physical Performance Battery; TUG, Timed Up-and-Go; UCR, Urea-to-Creatinine Ratio.

* Corresponding author. Gelderse Vallei Hospital, Department of Intensive Care, Willy Brandtlaan 10, 6716 RP Ede, the Netherlands.
E-mail addresses: zantena@zgv.nl, arthur.vanzanten@wur.nl (A.R.H. van Zanten), nep.deutz@ctral.org (N.E. Deutz), anamarijaliberati@gmail.com (A.-M. Liberati Prso), carla.prado@ualberta.ca (C.M. Prado), m.g.schooneman@dijklander.nl (M.G. Schooneman), m.r.soeters@amsterdamumc.nl (M.R. Soeters), Marian.devanderSchueren@han.nl (M.A.E. de van der Schueren), p.j.m.weijs@hva.nl (P.J.M. Weijs), ha.jager@pl.hanze.nl (H. Jager-Wittenaar).

https://doi.org/10.1016/j.clnu.2026.106652

Body composition
Patient-reported outcomes

strengths, limitations, and feasibility for clinical practice and research. In doing so, we highlight marked heterogeneity in metabolic and functional responses to nutrition and exercise interventions, underscoring the need for phenotyping, endotyping and precision nutrition to individualise protein and energy requirements.

Beyond biological mechanisms, we address key implementation challenges limiting translation into practice, including inequities in access to dietetic and other rehabilitation services, variability in health system organisation and underuse of functional and patient-centred outcomes in trials and routine care. Finally, we propose a translational research agenda to harmonise outcome measures, improve trial design and support integration of muscle health assessment and personalised nutritional strategies into clinical care pathways.

By positioning muscle health as a central and actionable outcome of clinical nutrition, this review supports a shift from uniform recommendations towards more personalised and effective nutrition care.

1. Introduction

Skeletal muscle health is increasingly recognised as a cornerstone of human health, critical not only for mobility and independence but also for metabolic regulation, immune function, and overall vitality and functioning across the life course [1,2]. Muscle dysfunction, manifesting as loss of muscle mass, strength, or altered composition, is associated with poor clinical outcomes, including increased morbidity, prolonged hospital stays, delayed recovery, impaired functioning, impaired quality of life (QoL), and higher mortality in a wide range of conditions from critical illness to cancer and natural ageing-related sarcopenia [1-8] (see Fig. 1).

The causes of muscle loss are multifactorial and vary by context, including systemic inflammation, physical inactivity, endocrine disturbances, and inadequate nutritional, in particular protein intake [9,10], but also a long-term use of some drugs like corticosteroids, incretin mimetics (e.g., Glucagon-like peptide-1 Receptor Agonists (GLP1RAs) and Glucagon-Like-Peptide-1/Glucose-Dependent-Insulinotropic-Polypeptide-Receptor-Agonist (GLP1RA/GIP) and statins [11]. Although nutritional therapy is a cornerstone of management, current strategies often fail to prevent or reverse muscle loss, in part due to limited individualisation and insufficient integration of functional outcomes into clinical decision-making [12,13]. Furthermore, existing clinical trials often rely on surrogate endpoints such as body mass index (BMI) or weight change, with limited data on muscle mass, composition, functional outcomes and patient-reported outcome measures (PROMs) [3,14,15].

Recent advances call for a paradigm shift towards more personalised, disease- and disease-phase–oriented nutritional interventions to support muscle health [16–18]. The Global Leadership Initiative on Malnutrition (GLIM)-guidelines emphasise the importance of combining phenotypic and aetiologic criteria to guide nutritional assessment and care [19]. Although functional domains are not directly captured within GLIM, their clinical relevance is acknowledged, with muscle strength proposed as an important complementary element in nutritional assessment [20]. Functional status is therefore an important stand-alone measurement but also essential to complement the diagnosis of sarcopenia and sarcopenic obesity (SO) [21,22]. Both muscle mass and function are closely related and represent different roles of skeletal muscle in human physiology [23,24]. Similarly, the concept of muscle as a vital metabolic organ has been proposed to anchor muscle health as a measurable and actionable clinical target [25].

In this expert opinion review, we aim to define a vision and research agenda for muscle health through a clinical nutrition lens. The objectives were to conceptualize the importance of muscle health incorporating both biological and functional dimensions, explore disease-specific contexts including critical illness, oncology, geriatrics, diabetes, and obesity and to highlight cross-cutting themes such as diagnostics, interventions, methodological challenges, and implementation science, and to conceptualize future research needs and discuss regulatory, policy and reimbursement challenges. By articulating these elements, we aim to elevate muscle health as a central outcome of clinical nutrition and to stimulate research, collaboration, and policy alignment that will shape future care delivery.

2. Conceptual aspects of muscle health

As noted above, muscle health encompasses more than the preservation of muscle mass alone. It reflects the integrated capacity of skeletal muscle to support mobility, metabolism, immune competence and overall vitality. It is shaped by multiple interrelated domains, such as morphological (muscle mass, and composition) and functional aspects (strength, power, muscle-specific strength, and physical performance), each providing complementary information and responding differently to disease, ageing, nutritional interventions and inactivity [22] (Figure 1). Key definitions and distinctions are summarised in Table 1.

Because these biological measures often correlate imperfectly with lived experiences, fatigue scales, activities of daily living, and quality of life instruments are essential to capture meaningful function and participation. Framing muscle as a clinical vital organ encourages routine assessment, longitudinal monitoring and early intervention across healthcare settings. Within this framework, muscle health becomes both a diagnostic construct and a therapeutic target, linking prevention, treatment and recovery across the life course.

To complement these biological and performance-based domains, PROMs provide essential insight into lived function, symptom burden and participation. Relevant PROMs for muscle health and nutrition research are summarised in Table 2.

3. Disease-specific domains and muscle health

Poor muscle health is a prevalent condition observed across the continuum of care. In this section, we will broadly discuss the available knowledge within selected clinical and non-clinical contexts.

3.1. Muscle health in geriatrics

The concept of muscle health has been extensively explored within geriatrics, where the term *sarcopenia* was first introduced. Sarcopenia affects approximately 10–16% of older adults worldwide and is increasingly recognised as a multidimensional

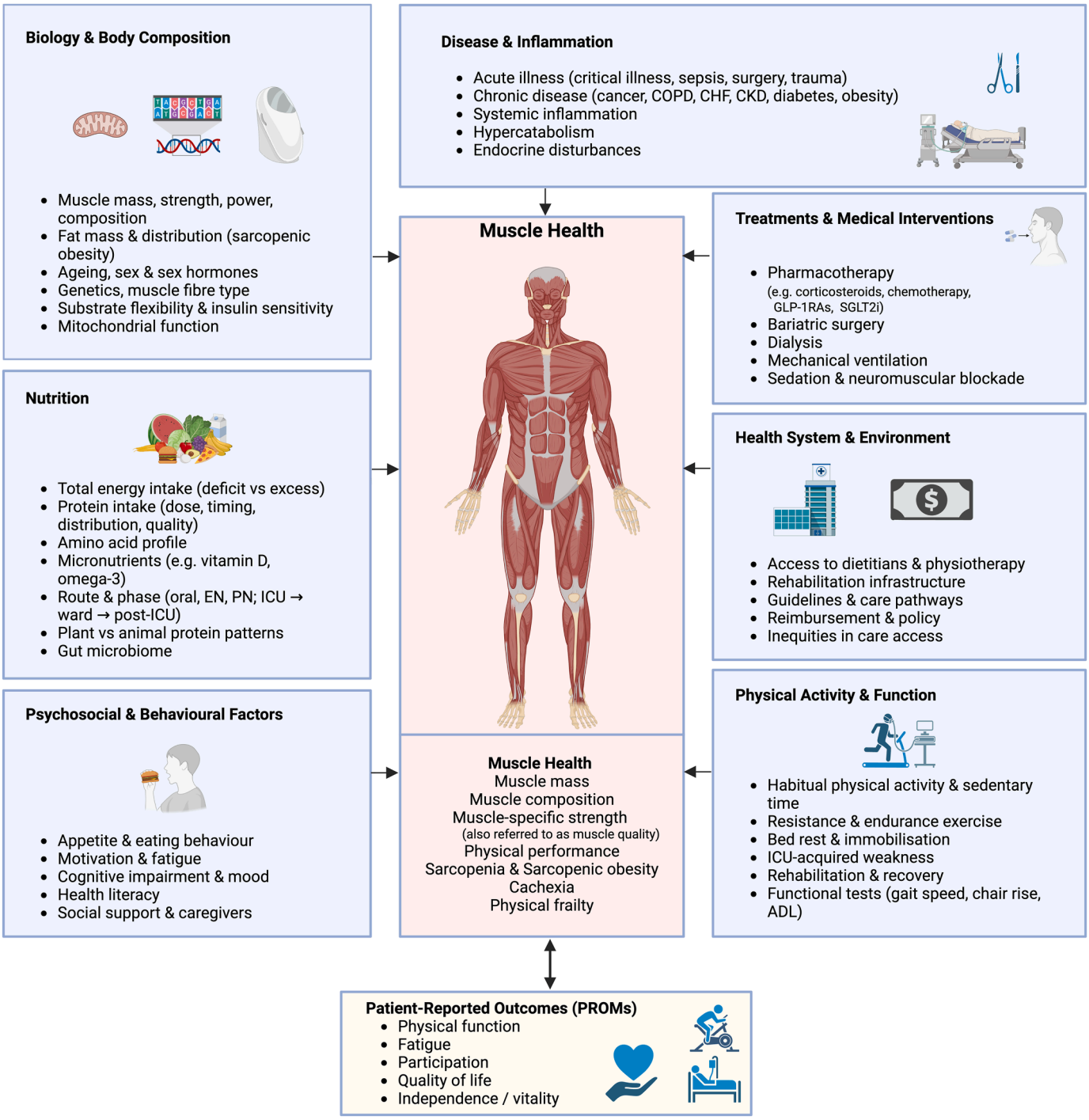

Fig. 1. Conceptual framework of multidimensional determinants of muscle health and related functional outcomes.
Created in BioRender. Van zanten, A. (2026) https://BioRender.com/5ult9t0 license number: JD299SK8IB. Muscle health is conceptualised as an integrative clinical construct encompassing muscle mass, strength, power, physical performance and patient-reported outcome measures (PROMs), and is positioned at the centre of the framework. Surrounding domains represent interacting determinants that shape muscle health across the continuum of care. These include biological and body-composition–related factors (e.g. ageing, sex hormones, genetics, muscle fibre type and metabolic flexibility); nutritional factors (energy and protein intake, timing, quality, micronutrients, route and phase of nutrition, and dietary patterns); physical activity and functional status (habitual activity, resistance and endurance exercise, immobilisation and rehabilitation); disease and inflammation (acute critical illness, chronic disease and systemic catabolism); treatment-related exposures (pharmacotherapy, surgery and organ support); psychosocial and behavioural factors (motivation, fatigue, cognition, appetite and social support); and environmental and health-system contexts (access to care, guidelines, reimbursement and the food environment). Together, the framework illustrates the rationale for phenotype- and endotype-driven, personalised nutrition and multimodal interventions to preserve or restore muscle health across diverse patient populations.
Abbreviations: ADL = Activities of Daily Living; CHF = Congestive Heart Failure; CKD = Chronic Kidney Disease; COPD = Chronic Obstructive Pulmonary Disease; EN = Enteral Nutrition; GLP-1RA = Glucagon-Like Peptide-1 Receptor Agonist; ICU = Intensive Care Unit; PN = Parenteral Nutrition; PROMs = Patient-Reported Outcome Measures; SGLT2i = Sodium–Glucose Cotransporter-2 Inhibitor.

Table 1
Key definitions and distinctions in muscle health.

Term	Definition	Typical measurements	Key References
Malnutrition (synonym: Undernutrition)	A state resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat-free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease.	GLIM-criteria	[19,20,78,82]
Muscle mass	The quantity of skeletal muscle tissue in the body, reflecting structural reserve but not necessarily functional capacity. Muscle mass alone incompletely captures muscle health and clinical risk.	CT or MRI (gold standards); Ultrasound; or estimations by DXA, BIA, Anthropometry (e.g. calf circumference).	[110,120,135]
Muscle strength	The maximal force that a muscle or muscle group can generate; a robust predictor of disability, complications, and mortality, often outperforming muscle mass alone.	Handgrip strength; Knee-extension dynamometry; Chair-stand test.	[20]
Muscle composition	The qualitative characteristics of muscle tissue, including fat infiltration (myosteatosis), fibrosis, fibre type distribution, and mitochondrial integrity, influencing contractile efficiency and metabolic function.	CT muscle radiodensity; MRI (spectroscopy); Ultrasound echogenicity.	[3]
Muscle-specific strength (previously also referred to as muscle quality)	Strength relative to muscle size or mass, reflecting neuromuscular efficiency and tissue quality; integrates structural and functional muscle properties.	Strength ÷ muscle mass (DXA/BIA); torque ÷ cross-sectional area (CT/MRI); torque ÷ muscle thickness (ultrasound).	[26,121,136]
Physical performance	The ability to perform tasks relevant to mobility and daily functioning, representing integrated musculoskeletal, cardiopulmonary, and neurological capacity.	Gait speed; SPPB; TUG; 6MWT.	[20,122,123,136]
Sarcopenia	A condition characterised by low muscle strength as the primary criterion, with confirmatory low muscle mass and/or impaired physical performance, occurring across ageing and disease contexts.	Handgrip strength or chair-stand test; DXA/CT/BIA for muscle mass; Gait speed or SPPB for performance.	[1,19,26,27,137,138]
Sarcopenic obesity	The coexistence of excess adiposity with low muscle strength and/or low muscle mass or impaired physical performance, conferring higher metabolic and functional risk than either condition alone.	DXA/CT for fat and muscle mass; handgrip strength; chair-stand test; Gait speed/SPPB; SO phenotyping indices.	[21]
Cachexia	A complex metabolic syndrome associated with underlying illness and characterized by loss of muscle mass with or without loss of fat mass.	Weight loss criteria; muscle mass measures; inflammatory biomarkers; Dietary intake assessment.	[3,83]
Physical frailty	A clinical state of reduced physiological reserve and increased vulnerability to stressors, frequently involving but not limited to muscle impairment.	Fried frailty phenotype; CFS; gait speed; Grip strength.	[124,139]

Abbreviations: BIA = Bioelectrical Impedance Analysis; CFS = Clinical Frailty Scale; CT = Computed Tomography; DXA = Dual-Energy X-ray Absorptiometry; MRI = Magnetic Resonance Imaging; SO = Sarcopenic Obesity; SPPB = Short Physical Performance Battery; TUG = Timed Up-and-Go; 6MWT = Six-Minute Walk Test.

condition and a muscle disease involving the progressive loss of both muscle mass and muscle strength [26]. A comprehensive epidemiological review highlighted that physical inactivity, malnutrition, smoking, extreme sleep duration, diabetes, and a range of comorbidities, including cancer, cardiovascular and respiratory disease, osteoporosis, depression, and Parkinson's disease, were consistently associated with a higher risk of sarcopenia [27]. Notably, the authors also observed that obesity appeared to confer a protective effect when assessed using body mass index (BMI) alone; however, this association reversed when body composition was properly assessed, emphasising again the known limitations of BMI as a proxy for muscle health. They further reported that several biological markers, such as inflammatory cytokines, vitamin D, adiponectin, and measures of arterial stiffness, were significantly correlated with sarcopenia, although current evidence does not establish causality [27]. Together, these findings point out that sarcopenia reflects the interplay between lifestyle factors, comorbidity burden, body composition, and systemic biological processes.

While multiple definitions have been proposed over the years, the most widely adopted framework remains that of the European Working Group on Sarcopenia in Older People 2 (EWGSOP2) [20]. More recently, the Global Leadership Initiative in Sarcopenia (GLIS) was established to develop the first globally harmonised conceptual definition of sarcopenia and to create an operational definition suitable for both clinical practice and research settings. In their first representation, sarcopenia was presented as a condition defined by three interconnected components: reduced muscle mass, reduced muscle strength, and reduced muscle-specific strength [27]. It was noted that sarcopenia is a disease of skeletal muscle that becomes more common with age, is potentially reversible, and is defined consistently across clinical and research settings, regardless of age or clinical condition. Therefore, the concept of sarcopenia is expanded beyond geriatrics, now even to the field of paediatrics [28]. Ongoing Delphi consensus are underway and will be used to develop an operational definition of sarcopenia.

The consequences of sarcopenia include impaired physical performance, mobility limitations, increased risk of falls and fractures, greater likelihood of hospitalization or admission to nursing homes, difficulty performing daily activities, reduced quality of life, and higher mortality. With the aging of the population, the prevalence of sarcopenia is on the rise. Supporting this, the GLIS working group recently synthesized the health outcomes of sarcopenia. They reviewed evidence from systematic reviews, meta-analyses, and cohort studies and reported strong evidence that sarcopenia is associated with reduced quality of life, increased risks of falls and fractures, and higher mortality. Moderate

Table 2
Relevant PROMs for muscle health and nutrition research.

Domain	PROMs/instruments
Generic health status/ HRQoL	• SF-36/SF-12 (including physical function and role physical domains) • EQ-5D (including mobility dimension) • PROMIS global health
Physical function and mobility	• PROMIS physical function • PROMIS mobility • PROMIS fatigue • Late-life function & disability instrument (LLFDI) • Activities of daily living (ADL) scales/ Instrumental ADL (IADL) scales
Muscle-related symptoms and functional burden	• PROMIS physical function (CAT) • Sarcopenia quality of life questionnaire (SarQoL) • SARC-F (strength, Assistance with walking, rise from chair, Climb stairs, falls history)
Nutrition-related functioning	• Patient-Generated subjective global assessment (PG-SGA): Activity/function items and nutrition-focused physical exam • Eating assessment tool (EAT-10) when swallowing impairment is relevant
Post-ICU–Specific PROMs (CONCISE core outcome set)	• EQ-5D-5L (HRQoL) • PROMIS physical function • Hospital Anxiety and depression scale (HADS) • Impact of event scale–Revised (IES-R) for PTSD symptoms • Return-to-work/participation measures

Practical note: For trials, selecting one generic HRQoL measure + one physical-function PROM (e.g., PROMIS Physical Function + EQ-5D-5L) often provides the best balance of feasibility, comparability and patient relevance, and aligns with CONCISE recommendations for post-ICU studies.
Abbreviations: ADL = Activities of Daily Living; BIA = Bioelectrical Impedance Analysis; CAT = Computer Adaptive Testing; CFS = Clinical Frailty Scale; CONCISE = Core Outcome Set for ICU Survivors; CT = Computed Tomography; DXA = Dual-Energy X-ray Absorptiometry; EAT-10 = Eating Assessment Tool–10; EQ-5D = EuroQol 5-Dimension questionnaire; EQ-5D-5L = EuroQol 5-Dimension, 5-Level questionnaire; HADS = Hospital Anxiety and Depression Scale; HRQoL = Health-Related Quality of Life; IADL = Instrumental Activities of Daily Living; IES-R = Impact of Event Scale–Revised; LLFDI = Late-Life Function and Disability Instrument; MRI = Magnetic Resonance Imaging; PG-SGA = Patient-Generated Subjective Global Assessment; PROMs = Patient-Reported Outcome Measures; PROMIS = Patient-Reported Outcomes Measurement Information System; PTSD = Post-Traumatic Stress Disorder; SarQoL = Sarcopenia Quality of Life questionnaire; SARC-F = Strength, Assistance with walking, Rise from chair, Climb stairs, Falls; SF-12 = Short Form Health Survey, 12 items; SF-36 = Short Form Health Survey, 36 items; SO = Sarcopenic Obesity; SPPB = Short Physical Performance Battery; TUG = Timed Up-and-Go; 6MWT = Six-Minute Walk Test.

evidence supported an association with reduced instrumental activities of daily living, but more research is needed to support the association with other outcome measures. The group noted that some of the inconclusive evidence is largely related to the lack of longitudinal data [29].

Sarcopenia can occur concurrently to obesity, a condition referred to as sarcopenic obesity (SO). The definition, epidemiology, mechanisms, and clinical consequences of SO have recently described in detail [30]. The combination of excess adiposity and relatively low muscle mass and/or function appears to synergistically worsen metabolic and functional health beyond either condition alone. The SO definition was addressed by the Sarcopenic Obesity Global Leadership Initiative (SOGLI), a joint ESPEN-EASO (European Association for the Study of Obesity) consensus. SOGLI, which recently established unified definitions and cut-offs [21].

The global prevalence of SO is increasing, driven by population aging, rising obesity rates, and the metabolic and functional deterioration associated with chronic disease. Epidemiological data demonstrate wide variability in prevalence estimates due to heterogeneous definitions and measurement approaches across studies, which complicates comparisons across populations and underscores the need for consistent diagnostic approaches [28,31,32]. SO is associated with multiple adverse outcomes in diverse clinical settings with worse odds/hazard ratios than sarcopenia or obesity alone [28]. These outcomes include impaired physical function, disability, depression, poor quality of life, increased hospitalization, and higher mortality, with evidence drawn from large cohort studies and meta-analyses (for example, SO predicting depression, pulmonary impairment, frailty, post-operative complications, and cancer-specific mortality). In community-dwelling older adults, SO is associated with disability progression, hospitalization, and death, particularly in dynapenic abdominal obesity, characterised by the co-occurrence of low muscle strength (dynapenia) and excess abdominal fat (central/ visceral obesity) phenotypes [28].

Interventions for sarcopenia and SO largely overlap, yet both fields face similar evidence gaps. For sarcopenia, the strongest data support resistance exercise, adequate protein intake, and multimodal approaches, although the quality of evidence varies and few trials directly link these interventions to long-term clinical outcomes. A network meta-analysis evaluated interventions for treating sarcopenia in middle-aged and older adults, including different forms of exercise, nutrition alone, and exercise–nutrition combinations [33]. Across 30 randomized controlled trials involving 2485 participants, all interventions produced some improvements in muscle strength, muscle mass, and physical function. Resistance training showed the greatest overall benefits resulting in the largest improvements in grip strength, Appendicular Lean Soft Tissue (ALST) mass, and walking speed. When combined with nutrition, resistance training produced the best performance in chair stand and timed up-and-go tests and led to the largest increases in fat-free mass (FFM) [31].

For SO, the evidence base is even more limited. A landmark randomized controlled trial by Villareal and colleagues examined whether weight loss, exercise, or their combination best improved function in adults with obesity aged 65 years and older [34]. In 107 participants followed for one year, the combination of diet-induced weight loss plus exercise produced the greatest gains in physical performance, aerobic capacity, functional status, strength, balance, and gait. Although both diet alone and diet-exercise achieved similar weight loss (*i.e.*, about 10%), the diet-exercise group preserved more lean mass and hip bone density than diet alone. Exercise alone improved function but did not reduce weight. Overall, they concluded that combining weight loss with exercise provided the most robust and safest improvements in physical function and frailty-related outcomes in older adults with obesity.

In the context of sarcopenic obesity, lifestyle strategies such as resistance exercise combined with nutritional optimisation are commonly recommended; however, interventions specifically targeting this combined phenotype remain scarce, with most studies focusing on obesity or sarcopenia in isolation. Pharmacological weight loss therapies, including GLP-1 receptor agonists, generally induce weight loss without adequately preserving muscle mass. Importantly, greater weight loss during GLP-1 receptor agonist therapy has been associated with proportionally greater losses of lean body mass, used as a proxy for muscle mass, particularly in the absence of structured exercise. Trials incorporating robust assessments of muscle mass and function during incretin-based therapy are currently underway. Other weight loss strategies, including bariatric procedures, risk further exacerbating muscle loss without careful supervision. Finally, high-quality longitudinal and interventional studies are urgently

needed to clarify which therapies meaningfully improve clinically relevant outcomes [28].

3.2. Muscle health in oncology

Low muscle mass is one of the most relevant defining features of poor nutritional status in patients with cancer. Poor nutritional status may manifest as malnutrition, here used synonymously with undernutrition, but also as sarcopenia [24]. Notably, the terms low muscle mass and sarcopenia are often used interchangeably in the cancer literature, despite referring to distinct concepts [25[25]]. Sarcopenia encompasses both low muscle mass and reduced muscle strength, whereas low muscle mass refers solely to a reduction in muscle quantity. Given these distinctions, the use of precise and non-interchangeable terminology is warranted [25].

A large meta-analysis of 280 studies reported an overall prevalence of low muscle mass of approximately 35%, with higher prevalences observed in specific subgroups, including patients in curative (~40%) and palliative care settings (~49%), reflecting substantial heterogeneity across populations and definitions [35]. A key clinical challenge in cancer-related muscle loss is that patients with normal or high body weight may have severe muscle depletion, which routine weight checks fail to detect.

Low muscle mass in cancer is strongly linked to increased chemotherapy toxicity, a relationship first identified through advanced body composition methods and confirmed across many studies [36]. Patients with low muscle mass often experience symptoms resembling chemotherapy overdose, leading to dose reductions or treatment discontinuation and ultimately diminishing treatment effectiveness. Because muscle mass is a central component of lean mass, which is essential for drug distribution, metabolism, and clearance, its reduction alters key physiological processes such as hepatic metabolism, renal blood flow, and glomerular filtration rate [37]. A pivotal multicentre randomized trial demonstrated that adjusting oxaliplatin dosing based on lean mass, rather than body surface area, significantly reduced neurotoxicity, delayed its onset, lowered dose reductions, and improved quality of life without affecting survival [38]. These findings highlight the importance of body composition in personalizing chemotherapy dosing and reinforce the need for strategies to maintain or restore muscle mass.

In addition to muscle mass, fat infiltration within muscle, known as myosteatosis, has emerged as a powerful predictor of poor outcomes, often as detrimental as low muscle mass and in some cases even more so. Myosteatosis is linked to higher rates of postoperative complications, prolonged hospitalizations, reduced tolerance to cancer treatments, and shorter survival. These findings highlight that muscle composition, not only muscle quantity, is a key determinant of prognosis and should be incorporated into routine clinical evaluation [3,39,40].

Low muscle strength is also common in patients with cancer. After a cancer diagnosis, many patients experience a drop in physical function, a change linked to higher early mortality. Because of the known effects of low muscle mass, it is not surprising that combining measures of muscle mass and muscle strength provides a more powerful prediction of overall survival than using either one alone [41,42].

3.3. Muscle health in diabetes mellitus

Diabetes, especially when mistreated or/and not well controlled, continuously disrupts skeletal muscle metabolism, leading to muscle loss, sarcopenia and aggravating insulin resistance. Both with the glucovariability, glucotoxicity, hyperglycaemia-induced oxidative stress and advanced glycation, diabetes-related sarcopenia should be one of the targets among strategies for muscle health and functional independence preservation.

There are several mechanisms involved in the so-called “diabetic myopathy”, a chronic complication of diabetes [43–46]: protein synthesis suppression by insulin resistance, increased proteolysis via autophagy-lysosome and ubiquitin-proteasome activation, impaired mitochondrial function and catabolic signalling reinforced by oxidative stress, myocyte damage in low-grade inflammation, persistent hyperglycaemia with advanced glycation leading to reduced muscle mass and increased inter- and intramuscular fat infiltration, resulting in impaired contractility and lower metabolic substrate flexibility [47,48].

Early identification of sarcopenia in diabetic patients should be performed frequently and repeatedly, assessing muscle mass, strength and performance, combined with circulating biomarkers such as creatinine–cystatin C–based indices as surrogates of muscle mass, inflammatory markers (CRP, IL-6, TNF-α), and hormones (insulin, IGF-1, thyroid hormones) [49,50].

Preventing and slowing the progression of sarcopenia in diabetes should combine clinical nutrition, structured resistance training and individualised pharmacotherapy. For most older adults with type 2 diabetes and preserved renal function, protein intakes around 1.0–1.2 g/kg/day (up to 1.2–1.5 g/kg in high-risk individuals) divided into 25–30 g per meal, with an emphasis on leucine, arginine and glutamine-rich, high-quality proteins help overcome anabolic resistance and support muscle protein synthesis. Dietary patterns such as Mediterranean-style diets rich in fruits, vegetables, whole grains and unsaturated fats add antioxidants and minerals that support insulin sensitivity and may indirectly protect muscle by neutralizing inflammation and oxidative stress. Targeted micronutrients further refine this strategy. Vitamin D deficiency is common in both type 2 diabetes and sarcopenia. Supplementation, particularly when combined with whey protein and leucine, can improve muscle mass and function. Adequate levels of calcium, magnesium and B vitamins (especially B12 in metformin-treated patients and B9) support neuromuscular function and anabolic responses. Omega-3 fatty acids (EPA/DHA) may enhance muscle protein synthesis and reduce inflammation, with multi-nutrient formulations (protein–leucine–vitamin D–omega-3) showing additive benefits.

Adequate glycaemic control is a cornerstone of diabetes care. Poor control is consistently associated with lower muscle quality, reduced mass, slower gait speed and increased sarcopenia risk, largely via advanced glycation, microvascular damage, neuropathy and intramuscular fat accumulation. Conversely, improving glycaemic control combined with resistance training and muscle-targeted nutrition enhances both muscle outcomes and glucose homeostasis, highlighting a bidirectional relationship that should be a focus of future clinical nutrition research agendas in diabetes-related muscle health. Importantly, diabetes-related sarcopenia often coexists with obesity, producing a sarcopenic obesity phenotype that carries particularly high risks of disability, falls and mortality [51–53].

3.4. Muscle health in obesity

Obesity is associated with changes in muscle size and volume, likely a result of the mechanical demands of having to carry more body weight, as well as changes in muscle microcirculation, glucose metabolism, lipid oxidation and mitochondrial activity. This, in turn, may lead to insulin resistance and metabolic dysfunction [54].

For a long time, bariatric surgery has long been a treatment option for individuals with severe obesity. Approximately one in four patients undergoing bariatric surgery is thought to have sarcopenic obesity or develop sarcopenia [55]. Recent meta-analyses assessed the magnitude of postbariatric muscle loss and strength. Around 20% of total body weight loss was found to be loss of FFM, occurring mostly in the first three months following surgery [56]. The higher the body weight loss, the higher the loss in strength [57]. Studies on muscle composition after bariatric surgery are scarce and meta-analyses have not been performed due to heterogeneity of assessment methods. However, the authors noted that individual studies suggest an increased fat content of muscle after bariatric surgery (possibly explained by a more rapid loss of muscle mass than lipids stored in muscle) [55].

Over the last years, GLP1RAs and GLP1RA/GIPs have emerged as highly effective pharmacological tools for weight loss, in addition to bariatric surgery. A recent review has extensively summarized the pathophysiological changes in muscle volume and function in obesity and the presumed positive and negative effects of rapid weight loss induced by GLP1RAs and GLP1RA/GIPs [58]. While GLP1RAs and GLP1RA/GIP have shown rapid and extensive weight loss, concerns have been raised about their impact on muscle mass and function, which may account for up to 50% of the total weight loss [56,59–61]. A commonly cited physiological assumption is that approximately 25% of total weight loss reflects loss of FFM [56]. However, disproportionate losses of FFM, sometimes accounting for up to 50% of total weight loss, are of particular concern in individuals already at risk of sarcopenia, including older adults, those with a sedentary lifestyle or features of frailty, and patients with underlying sarcopenic obesity, such as individuals with type 2 diabetes.

On the one hand, treatment with GLP1RAs and GLP1RA/GIP has been shown to improve insulin sensitivity and improve muscle composition (reduced muscle fat content), which may also lead to improved muscle function. On the other hand, the absolute muscle loss has been associated with a disproportional loss of muscle volume, aggravating sarcopenia in those (already) at risk [52,56].

A further concern is the weight regain that occurs after discontinuation of GLP-1 RAs, which consists mainly of fat rather than muscle and thereby contributes to increased physical frailty [62,63]. One reason may be that energy expenditure related to 1 kg of FFM is about three times that of fat mass [64]. Thus, a decline in muscle mass leads to a more drastic decrease in energy expenditure than the same decline in fat mass.

To minimize the potential negative effects of weight loss from either bariatric surgery or GLP-1 RAs on muscle mass, it is recommended to combine the treatment with resistance training and adequate protein intake, especially in the older or more frail population [65]. New pharmacological approaches, such as bimagrumab, are under study and have been shown to attenuate muscle mass during weight loss trials [66]. Treatment protocols should include sarcopenia screening and treatment for those at risk. In addition, longitudinal studies using standardized assessments of muscle mass (FFM, lean soft tissue and skeletal muscle mass were used interchangeably in previous studies), strength, and physical performance are needed to clarify the long-term impact of GLP-1RAs and GLP-1RA/GIP on muscle volume and function.

3.5. Muscle health in critical illness

ICU-acquired weakness (ICU-AW) is one of the most frequent and debilitating complications of critical illness. Up to 40–70% of ICU patients develop clinically significant muscle weakness by the time of ICU-discharge, and approximately 40% continue to experience persistent deficits 6 months to 10 years after their critical illness. Muscle mass may decline by more than 15% within the first week, contributing to impaired mobility, reduced independence in activities of daily living, delayed return to work, and diminished long-term quality of life. Severe ICU-AW (MRC sum <36) has also been associated with higher mortality up to one year following ICU admission [67]. Because of this rapid and substantial loss of muscle mass and function, protein is often viewed as a potential nutritional therapeutic strategy to stimulate anabolism, support muscle recovery, and mitigate long-term functional impairment, although robust evidence remained limited until recently.

A recent systematic review and meta-analysis reported that higher protein delivery in ICU patients resulted in a modest but statistically significant short-term preservation of FFM (mean difference ≈0.7 kg, 95% CI ~0.5–0.9 kg), with most studies achieving target intake by day 4 and evaluating outcomes around day 10 [68,69]. In a mechanistic study, changes in FFM index strongly correlated with increases in normalised slow-twitch muscle fibre force, suggesting that guideline-level protein intakes may support early contractile function in selected patients [70]. Collectively, these findings indicate that moderate protein targets during the acute phase may attenuate, but are unlikely to prevent, early muscle loss.

At the same time, observational studies and recent large RCTs have challenged the long-standing belief that “more protein is better” during early critical illness. In a large international cohort using time-varying exposure models, late acute-phase protein intakes around 0.8–1.2 g/kg/day were associated with lower in-hospital mortality, while higher doses offered no additional benefit, and possible harm at higher intakes was not consistently observed across sensitivity analyses [13]. In another observational study, protein intake demonstrated a time-dependent association with outcomes: higher early intake (>0.8 g/kg/day during the first 3 ICU days) was linked to increased mortality risk, whereas higher intake later in the ICU course was not [71].

Three recent multicentre RCTs (≈5600 patients) evaluating early higher protein delivery (≈1.5–2.2 g/kg/day) versus standard dosing (≈1.0–1.3 g/kg/day) showed no improvement in clinical outcomes and signalled possible harm in select subgroups, such as those with greater illness severity or reduced renal reserve, with the PRotEin provision in Critical IllneSs (PRECISe) trial additionally reporting significantly lower quality of life in the high-protein group [72–74].

Experimental and translational studies suggest that very high amino-acid delivery early in the catabolic, highly inflamed phase may suppress protective autophagy and impair cellular housekeeping in peripheral, respiratory and cardiac muscle, despite failing to prevent macroscopic atrophy [75]. Furthermore, inflammation-induced mitochondrial dysfunction may trigger an intracellular energy deficit, activating a maladaptive proteostatic response [76]. In ICU patients, protein digestion and absorption on day 4 is similar to healthy controls, however the incorporation into skeletal muscle proteins is blunted reflecting severe anabolic resistance [77]. Together, these findings support a phase-specific approach in which aggressive protein loading in the first days of critical illness is avoided, while moderate, guideline-level dosing is provided and escalated later when catabolism and inflammation have subsided.

Against this background, individualising protein prescriptions based on FFM rather than total body weight is an important next step. Two patients with identical body weight, a “muscular phenotype” and a “sarcopenic obese phenotype”, receive identical g/kg prescriptions if actual body weight is used, yet the first will be underdosed and the second overdosed with respect to

metabolically active lean tissue. Such phenotype-based dosing is physiologically appealing, though high-quality evidence demonstrating improved clinical outcomes is still lacking. Using metabolic response biomarkers or endotyping to titrate protein dosing represents an important next step. One candidate marker for such titration is the urea-to-creatinine ratio (UCR), which reflects the balance between whole-body protein catabolism (urea production) and muscle mass (creatinine generation). Elevated and rising UCR values during ICU stay have been associated with greater muscle wasting, weakness and mortality, and may identify patients in whom high protein doses primarily fuel urea production rather than net anabolism. Integrating FFM-based dosing with dynamic biomarkers such as UCR and simple functional measures (e.g., handgrip strength) may enable future phenotype- and endotype-driven protein strategies across the ICU and post-ICU continuum [78].

The PROSPECT-I cohort highlights the vulnerability of nutrition delivery once enteral feeding stops. Following tube removal after ICU discharge, patients experienced an abrupt decline, typically exceeding 50% of target protein delivery, as intake shifted to predominantly oral nutrition, leaving most unable to meet recommended requirements [79]. These data highlight a "second window of opportunity" for muscle-directed nutrition after the acute ICU phase, precisely when patients become more anabolic but actual intake is lowest. In the PROSPECT-II study a tube feeding tapering protocol was shown to prevent the drop in protein intake and realised and intake of 97% of target [80].

Although the optimal protein dose across illness phases remains uncertain, a pragmatic strategy is to gradually advance intake over the first 4–5 ICU days toward 1.0–1.3 g/kg/day, or ≈1.8 g/kg/day when prescribed per FFM. Once stabilised (>5 days), this target should be achieved consistently, with protein needs increasing by roughly 25% after ICU discharge and a further 25% during ward-based recovery and post-hospital convalescence to support rehabilitation and regain of muscle mass [17].

4. Cross-cutting themes

4.1. Screening for and assessment of (risk of) malnutrition, sarcopenia and sarcopenic obesity

Low muscle mass is a key characteristic of malnutrition. However, in daily practice, nutritional screening often identifies patients only once overt malnutrition has already developed. Given the increasing pressure on healthcare systems, there is a need to shift from recognising and treating established malnutrition towards earlier identification and management of *risk of malnutrition*, before irreversible damage occurs. For many years, this concept lacked a clear definition [81], but the GLIM Working Group has now provided an international conceptual framework. Within this framework, the presence of malnutrition risk factors, with or without weight loss, is considered central, enabling earlier detection and preventive interventions [78].

As such, risk of malnutrition and malnutrition represent distinct stages in the nutritional care pathway, with risk of malnutrition representing the stage prior to overt malnutrition. In contrast, malnutrition is a condition that requires confirmation through diagnostic criteria. The GLIM has provided a consensus framework that combines phenotypic criteria (weight loss, low BMI, reduced muscle mass) with etiologic criteria (reduced food intake or assimilation, disease burden or inflammation) [19,82]. This dual approach ensures that malnutrition is defined not only by observable changes in body composition but also by the underlying mechanisms driving those changes. Importantly, as previously discussed, GLIM recognises muscle mass as a core phenotypic marker, underscoring the centrality of muscle health in nutritional diagnosis. However, functional measures such as muscle strength or performance are not yet fully integrated, leaving a gap between structural assessment and lived patient experience.

The aim of nutritional screening is to identify individuals requiring comprehensive nutritional assessment and nutritional interventions [83]. While future nutritional screening is expected to shift towards identifying risk factors for malnutrition, most screening tools often include criteria that reflect signs of already present malnutrition. As such, they rely on surrogate markers such as involuntary weight loss or BMI. These measures, while pragmatic, may fail to capture muscle-specific deficits that are more directly linked to clinical outcomes. As a result, patients with preserved weight but significant impaired muscle status may be overlooked. Integrating muscle-focused assessments into routine screening can bridge this gap and align nutritional care with functional recovery.

The algorithms that focus on sarcopenia and sarcopenic obesity, as outlined by the European Working Group on Sarcopenia [22] and ESPEN/EASO [21] respectively, were developed to specifically identify those individuals with impaired muscle function and/or muscle mass, with or without involuntary weight loss or low BMI. Screening consists of 'muscle specific screening', for example with the SARC-F [84,85] or clinical suspicion, followed by assessment of muscle function and muscle mass. Many patients who are malnourished are also sarcopenic or the other way around, implying that healthcare professionals should always consider both conditions and act accordingly [86,87].

Weight loss during illness and its treatment may be accompanied by a disproportionate loss of muscle mass or FFM, in some cases accounting for up to half of the total weight loss. However, most commonly used nutritional screening tools do not explicitly assess low or declining muscle mass. As a result, clinically relevant muscle loss may remain undetected. This limitation is particularly relevant in chronically ill populations, where muscle loss often develops gradually and may not exceed the predefined thresholds within the time frame evaluated by screening tools. Moreover, in individuals with concurrent malnutrition and obesity, fixed cut-off values perform poorly, further reducing the sensitivity for detecting critically low muscle mass [88]. Ongoing efforts are therefore focused on integrating direct or proxy measures of muscle mass and function into nutritional screening and assessment pathways, with the aim of improving early detection of clinically relevant muscle loss.

4.2. Therapeutic approaches to support muscle health across clinical settings

Approaches to support muscle health are applicable in both public health and clinical care. A healthy lifestyle includes adherence to general recommendations for daily physical activity, encompassing both endurance activities (e.g., step-based movement) and muscle-strengthening exercises. While these recommendations apply to the general population, adherence is particularly important in older adults. In clinical practice, lifestyle-based approaches are not consistently implemented. However, with appropriate adaptations, they can be applied across a wide range of patient groups.

The same principles apply to adequate dietary protein intake, preferably achieved through regular protein-rich foods. When necessary, protein-enriched products and supplements can provide additional support. In clinical settings, nutritional strategies range from optimized institutional catering and oral nutritional supplements to enteral and parenteral nutrition. Although both

nutrition and physical activity have received increasing attention, their combined implementation within an interdisciplinary framework involving dietitians, physiotherapists, and other healthcare professionals has still not reached its full potential.

A review of ongoing clinical trials investigating nutrition-based strategies for low muscle mass, sarcopenia, and cachexia shows substantial interest in specific nutrients and ingredients [89]. Across 113 planned or ongoing randomized trials, most studies focus on adults with clinical conditions, particularly cancer, metabolic disease, and musculoskeletal disorders, while one-third address age-related muscle loss. Nearly half of the interventions involve food supplements, most commonly protein, amino acids, and beta-hydroxy-β-methylbutyrate (HMB), a leucine-derived metabolite. Trials predominantly assess changes in muscle mass, strength, and physical performance, though only a small number evaluate muscle protein synthesis. Overall, the growing body of work highlights key nutrients of interest but also reveals significant methodological heterogeneity, underscoring the need for standardized guidelines to support future evidence-based recommendations [87].

In the Netherlands, the Vitamin study demonstrated improved muscle health through a home-based functional exercise programme using meaningful, participant-centred activities [90]. Physical activity frequency successfully increased to three sessions per week. The programme was personalised with support from an exercise coach and a digital tablet. In addition to a control and exercise-only group, an exercise plus protein group received guidance on protein-rich supermarket foods. This combined approach was most effective in improving protein intake and maintaining muscle mass, strength and physical performance. Importantly, dietary advice emphasised increasing protein intake without increasing total energy intake [91].

In patients with cancer, early and ongoing nutrition intervention is essential to prevent and reverse muscle loss [5,92]. Starting support at the beginning of treatment, paired with secured follow-up, helps maintain weight, improve protein and calorie intakes, and enhance quality of life [93,94]. Individualized nutrition care, including tailored meals, food fortification, and oral nutritional supplements (ONS), supported by dietary counselling reduces functional decline and improves clinical outcomes. A key focus is achieving adequate protein intake, as protein requirements increase during treatment. Evidence from 35 RCTs shows that high-protein supplementation improves muscle mass, strength, and physical performance in patients with cancer [95]. Findings from the PRIMe trial show that while achieving 2 g/kg/day is challenging, individualized counselling by a dietitian significantly increases intake and supports muscle preservation [96]. Specific nutrients also show to benefit muscle health.

Omega-3 fatty acids, particularly eicosapentaenoic acid (EPA), demonstrate anticatabolic effects, with some trials showing improvements in muscle health and treatment tolerance [97]. Supplementation with HMB, has strong evidence for reducing muscle breakdown and supporting muscle synthesis, with over 30 clinical studies supporting its use [98]. Finally, a multimodal approach combining nutrition, physical activity, and targeted ingredients to optimize muscle maintenance during cancer therapy should be recommended [5]. Nutrition intervention is positioned as a core component of supportive oncology care, essential for improving tolerance to treatment, reducing complications, and supporting survival.

A more specific approach can be applied to excess body weight. Many options for treatment are available, each with their challenges. But basically, the therapeutics of adequate physical activity including strength training as well as adequate protein intake is or should be part of any approach. In the case of overweight and obesity usually the best option is to include caloric restriction. Adherence to diet is not always easy [99] and therefore the behavioural component should be adequately addressed with appropriate behaviour change techniques [100]. While this is true for adults in general, a recent European study group has explicitly addressed systematic reviews and meta-analyses in the older adults around retirement age, which provides a window of opportunity for intervention [101–103].

In most studies proxies for muscle mass are lean mass and/or FFM and much less appendicular lean soft tissue mass. In general, risks of both sarcopenia and obesity are reasonably well understood, however the risk of sarcopenic obesity has not been addressed as well. Considering the ESPEN-EASO consensus definition of SO the risk for early mortality, based on criteria for fat mass percentage, lean mass by weight and muscle strength, could be as high as three times normal risk [104]. To improve insight into the risks of different SO phenotypes a sarcopenic obesity phenotype index (SOPi score) has been developed, to support assessment and monitoring of any patient at any stage of disease of SO [105].

Although more rigorous, comparable lifestyle and nutritional–physical interventions remain essential during incretin-based obesity treatment [106]. Lifestyle approaches that combine resistance-type exercise with protein supplementation or higher protein intake alongside caloric restriction have been shown to preserve muscle mass during weight loss and to improve muscle strength and physical performance [101,107]. In older adults with obesity, maintenance of muscle mass during weight loss required protein intakes exceeding 1.2 g/kg/day, which has been proposed as an exploratory protein requirement under these conditions [108,109].

For clinical application, these principles must be tailored to specific patient groups. Clear and consistent terminology, as defined by frameworks such as GLIM, GLIS, and SOGLI, is essential to guide assessment and intervention. In advanced disease states, including critical illness, it may not be feasible to maintain or restore muscle mass and strength over the longer term. In such contexts, therapeutic goals should shift towards attenuation of loss, preservation of function where possible, and alignment with overall prognosis and patient-centred outcomes.

4.3. Methodological challenges in muscle health

While muscle mass is of substantial interest, it remains challenging to assess in practice. This depends on the accuracy of the methodology, feasibility or availability of the measurement, time, costs, and expertise. The availability and precision of available body composition techniques used to assess muscle mass vary widely [24]. In addition, confusion and inconsistency in terminology remain a major barrier to accurate reporting and interpretation of the literature. To address this, an international expert working group has recently proposed methodological standards and standardized terminology based on body-composition levels and models as the first of a planned series of consensus publications [110].

Accurate assessment of muscle mass can be achieved by Magnetic Resonance Imaging (MRI) as it precisely assesses muscle volume and consequently mass, as well as myosteatosis. Although MRI is not so accessible and highly reserved for diagnostic purposes, it has been extensively used to assess upper leg muscle mass in research settings, which represents a very large part of skeletal muscle mass. Computer Tomography (CT), however provides an accurate assessment of muscle cross-sectional area, although its use is limited mainly due to radiation and the opportunistic availability of images in medical records. However, as for MRI, also availability, cost, and expertise need to be

considered. Moreover, the availability of specific anatomical imaging sites is limited, with the 3rd lumbar spine level as most prominent in the literature, due to its correlation with whole-body volumes [111].

Another option in clinical practice is the use of ultrasound [112]. Several variables can be assessed, but most used is the muscle layer thickness. While availability is high and costs are relatively low, accurate assessment requires a moderate level of operator expertise. One advantage is that specific muscles can be targeted, however, validated prediction equations are needed to estimate whole body muscle mass. This may also be a limitation, as different muscles can respond differently to disease and treatment. Importantly, although promising, ultrasound-based assessment of muscle mass is not yet sufficiently standardised for routine clinical implementation [113].

In (clinical) practice and many guidelines, the assessment of muscle mass is based on dual-energy X-ray absorptiometry (DXA) and/or bioelectrical impedance analysis (BIA) estimates. While DXA is based on radiation as CT is, exposure is minimal and its availability is substantially higher than CT. Although DXA provides only provides a 2-D representation of the body, it enables assessment of specific regions of interest. Imaging of the arms and legs provides an accurate estimate of ALST [110]. Although correlated with clinical outcomes, ALST is a close proxy assessment of muscle mass (in the absence of MRI and CT) but includes connective tissue, water, and skin. DXA is sufficiently accurate enough to assess responses to nutrition and exercise interventions [114]. Notably, country-specific radiation regulations may apply and may limit the availability of DXA assessments.

Body composition assessment is often performed or required in health care settings that may only have a weighing scale but could easily be upgraded with BIA. In most cases, single-frequency, devices (typically 50 kHz) are used, although multi-frequency and bioimpedance spectroscopy devices are also available. Overall, BIA is relatively accessible, low-cost, and feasible to implement, and is included in clinical guidelines [28,30,33]. The main drawback of BIA is that it estimates body composition based on predictive equations and as such, skeletal muscle mass, as with other compartments, is not directly measured, and estimates are population- and device-specific. Therefore, BIA provides an indirect assessment of muscle mass but may still be useful as a pragmatic proxy for identifying low muscle mass. When used for monitoring, BIA should be performed using standardized protocols.

Another major limitation in assessing low muscle mass is the lack of standardised cut-off points [115,116]. Studies use different approaches, including percentile or standard deviation-based or thresholds, receiver operating characteristic-derived values, and mortality-associated cut-points, which leads to inconsistent classifications and prevalence estimates. Because each method depends on the reference population, outcome chosen, and measurement technique, results may not be directly comparable across studies. This heterogeneity limits evidence synthesizes and weakens the interpretability and clinical applicability of findings related to low muscle mass. Available cut-off points can therefore be highly context-specific and may not be generalize across disease settings age groups, or body sizes, further complicating risk stratification and clinical decision-making. This underscores the need for harmonized, outcome-validated, and population-appropriate standards for defining low muscle mass. Ongoing work from the GLIM muscle-assessment subgroup aims to address this challenge by developing harmonized cut-points derived from a large meta-analysis of healthy young reference populations.

Another important limitation is the lack of consensus on how to standardize body composition measures, particularly whether lean soft tissue should be indexed to height^2 or weight [30]. Indexing by height^2 (as in ALST/height^2) adjusts for body size but tends to classify individuals with higher body weight, including those with overweight or obesity, as having “normal” muscle, potentially masking clinically relevant muscle depletion. Conversely, indexing by weight (*e.g.*, ALST/weight) can overestimate the prevalence of low muscle mass among individuals with higher adiposity, because excess fat artificially lowers the ratio even when absolute muscle mass is adequate. These approaches can lead to different prevalence estimates and consequently inconsistent identification of low muscle mass across populations. This lack of harmonization limits comparability across studies and complicates risk stratification in both research and clinical practice.

5. Precision nutrition and diversity

One of the key questions in clinical nutrition is to what extent precision nutrition can be applied to optimise muscle health, given marked heterogeneity in muscle phenotype and metabolic response across patients. Before this bridge is crossed, however, it is essential to recognise the fundamental distinction between nutritional recommendations for healthy individuals and those for specific patient populations. Historically, protein requirements were established in younger, healthy adults and subsequently extrapolated to older adults [117]. A similar translational approach has been applied to other nutrient recommendations, yet these have rarely been validated in specific diseases or targeted clinical populations. In this context, we focus on protein intake recommendations in relation to muscle health.

Protein requirements were originally estimated in healthy individuals using nitrogen balance studies, in which protein intake over several days was related to nitrogen excretion during the same period. This approach requires accurate quantification of dietary nitrogen intake and measurement of nitrogen losses, primarily via urinary excretion (as urea and/or ammonia), with correction for additional losses such as faecal excretion [118]. Across a large and heterogeneous body of studies encompassing a wide range of nitrogen intakes, a relationship was established between intake and nitrogen balance. The intake level at which nitrogen balance was neutral was interpreted as meeting nitrogen requirements and subsequently translated into protein requirements.

This methodology illustrates that current protein requirement estimates are population-based, indirect, and inherently imprecise, limiting their applicability to individual patients. Consequently, there is a clear need for alternative approaches to more accurately estimate individual protein requirements. Notably, robust studies assessing protein requirements in clinical populations are lacking, as are studies stratified by biological sex, age, or combinations of these characteristics.

5.1. Individualisation based on biological sex, age, disease

It is beyond doubt that certain conditions, as discussed earlier in this paper, require specific attention to achieve optimal protein intake. Nevertheless, many nutritional guidelines for clinical populations have been developed based on assumed disease characteristics and anticipated requirements, rather than on direct empirical evidence. With respect to protein requirements, general recommendations have historically been derived from healthy populations and subsequently adapted by expert opinion, for example by suggesting that requirements should be “20% higher to be on the safe side”. However, such adaptations were rarely supported by studies conducted in specific clinical populations.

The need for individualisation beyond disease-level recommendations, at the level of the individual patient, can be illustrated by several examples. First, biological sex substantially influences muscle mass. On average, women are shorter than men, resulting in lower absolute muscle mass. Moreover, women and men with the same BMI differ in body composition, with women generally having lower muscle mass and a higher proportion of biologically relevant adipose tissue. With advancing age and menopause, women experience accelerated muscle loss, although older men also lose muscle and gain fat. In addition, both acute and chronic diseases induce varying degrees of insulin resistance and anabolic resistance, thereby affecting protein synthesis.

While these considerations remain relatively general, insights from glucose metabolism offer a useful parallel. A landmark study published in 2015 demonstrated marked interindividual variability in the metabolic response to glucose ingestion, which could be explained by a range of contributing factors [119]. It is reasonable to assume that similar variability exists for protein metabolism. Genetic background and epigenetic modifications are likely to influence muscle maintenance and accretion, as exemplified by differences in muscle fibre type and ethnicity. Pharmacotherapy may further modulate protein metabolism, while physical activity levels, exercise responsiveness, and trainability also play important roles. Nutritional habits and their effects on the gut microbiome are increasingly recognised as relevant, particularly in the context of a shift towards more plant-derived diets. We recently showed that hospitalised patients who predominantly consume plant-derived nutrition often fail to meet protein and energy requirements, underscoring the need to incorporate this factor into dietary recommendations.

Although many of these determinants may be less relevant in the steady state or when assessing nitrogen balance in healthy individuals, they become critically important when protein requirements change in response to the metabolic demands of acute or chronic illness. Attempts have been made to determine protein requirements at the individual level, but these approaches have proven cumbersome. Traditional nitrogen balance methods and stable isotope-based techniques such as the Indicator amino acid oxidation (IAA) method [120] require subjects to be studied across multiple protein intake levels, rendering them impractical for individualised assessment. Furthermore, methodological limitations include insufficient adaptation periods to altered protein intakes (which may require 10–14 days), inadequate phenylalanine intake at higher amino acid levels, and ambiguity regarding what is measured, protein requirements versus maximal protein anabolism [121,122].

Recently, a novel method was proposed to estimate protein requirements on an individual basis [123]. This approach is based on the concept that the human body experiences a constant net loss of protein due to the obligatory loss of indispensable amino acids. Measuring this loss in the morning after an overnight fast allows estimation of 24-h protein loss and, consequently, protein requirements to maintain balance. To quantify this morning loss, a pulse tracer method was employed, providing insight into intracellular amino acid losses, in contrast to previous approaches that only measured amino acids appearing in plasma and therefore underestimated true protein loss [122].

Support for this approach comes from a recent study examining the effects of seven days of complete starvation, in which an 8% loss of lean mass was observed [124]. This closely aligns with our previously calculated lean mass loss of approximately 1.2% per day (8.4% over seven days), suggesting that the pulse tracer–based method can indeed estimate protein requirements with reasonable accuracy.

Using this approach, expected differences in estimated protein requirements between males and females and across different disease conditions were demonstrated (see Table 3) [123]. Importantly, this method enables assessment of protein requirements at the individual level, requiring only a pulse administration of phenylalanine and tyrosine tracers, followed by approximately 2 h of plasma sampling and subsequent mass spectrometric analysis.

5.2. Trial population diversity

Nutrition research is complex due to multifactorial aetiologies, heterogeneous study designs, and substantial interindividual variability in response to nutritional interventions. Emerging frameworks increasingly emphasise personalised and interdisciplinary approaches, as single-component or standardised interventions often fail to account for differences in metabolism, body composition, and functional reserve. Evidence indicates that tailored nutritional support delivered by multidisciplinary teams improves outcomes. Nevertheless, variability in protein requirements remains a major challenge.

Trial population diversity may represent a particular obstacle. In studies investigating protein requirements, diversity exists at several levels. First, there is interindividual diversity within trials. Although trial outcomes are typically reported as averages, these averages represent composites of heterogeneous patient populations, even when strict inclusion and exclusion criteria are applied. As a result, estimates such as mean protein requirements reflect a mixture of patients who respond well and those who do not, leading to loss of clinically relevant information at the individual level.

Second, there is intraindividual diversity. Protein requirements may vary from day to day, depending on dynamic biological and pathophysiological factors that influence anabolic resistance and metabolic demand, as discussed earlier in this section. Third, there is diversity between trials. Patients with chronic conditions such as chronic obstructive pulmonary disease or type 2 diabetes mellitus, both associated with sarcopenia, differ fundamentally from patients with acute conditions, such as those in intensive care or recovering from major surgery, who experience rapid and profound muscle loss. Although extrapolation across these populations may be tempting, it is unlikely to yield valid conclusions.

5.3. Integration with omics and phenotype-driven nutrition

Returning to the central question of this section, it is evident that protein requirements and muscle mass are influenced by numerous interacting factors. Some determinants, such as sex, age, and disease, are readily observable, whereas many others remain hidden. Despite recent methodological advances, accurately quantifying individual protein requirements remains complex. To address this challenge, both known and unknown determinants should be identified, integrated, and modelled using computational approaches.

Although earlier studies attempted to individualise nutritional interventions, integration with physiological and omics data has remained limited. Collecting such multidimensional data may enable the development of predictive models that more accurately estimate individual protein requirements. The concept of endotyping, classifying patients according to underlying biological or metabolic characteristics, is increasingly recognised as a promising strategy. In critical illness, it has recently been highlighted that combining phenotyping (*e.g.*, body composition, age, treatment phase) with endotyping (metabolic biomarkers and

Table 3
Sex-specific estimated protein requirements for various populations.

Population	N =	Sex	Age (y)	Body weight (kg)	Requirements (gram protein/d)	Requirements (gram protein/kg BW/d)
Healthy young adults	85	Male	22.2	79.1	131.4	1.66
		Female	23.5	66.2	91.0	1.37
Older adults (50–70y)	101	Male	62.9	81.1	75.6	0.93
		Female	61.8	67.4	60.2	0.89
Older adults (70–95y)	94	Male	77.1	79.9	47.9	0.60
		Female	74.3	67.4	60.7	0.75
Obese adults	77	Male	51.1	104.3	102.2	1.10
		Female	53.4	91.2	65.3	0.92
COPD	304	Male	69.2	88.9	55.1	0.62
		Female	68.4	71.4	43.7	0.61
Critically ill patients	51	Male	61.4	85.6	63.8	0.75
		Female	67.4	83.3	59.5	0.71

Mean net postabsorptive protein breakdown was estimated as the rate of conversion of phenylalanine to tyrosine as measured by compartmental analysis, using the intracellular production of tyrosine, converted to gram protein/day by using 1 mmol net protein breakdown (phenylalanine) represents about 4.13 g of protein. Data are from the MEDIT database.
Abbreviations: BW = body weight; COPD = chronic obstructive pulmonary disease; d = day; kg = kilogram; MEDIT = Metabolic Dietary Intake and Turnover database; N = number of participants; y = years.

tolerance) may replace the current one-size-fits-all paradigm and support personalised energy and protein strategies [75].

6. Implementation challenges

Despite increasing recognition of muscle health as a critical determinant of clinical and functional outcomes, translation of evidence into routine practice remains limited. Muscle health continues to be underprioritised relative to traditional nutritional endpoints such as body weight or BMI, and many healthcare professionals receive limited training in muscle-focused assessment and intervention, resulting in insufficient awareness of its prognostic relevance [125].

Although pragmatic assessment tools such as handgrip strength and bioelectrical impedance analysis (BIA) are available, their integration into routine clinical care remains limited [126]. Similarly, functional measures and patient-reported outcome measures (PROMs) are still insufficiently used in everyday practice [125,127], despite their increasing recognition as essential for capturing patient-centred outcomes and lived experience [127,128]. At the system level, current reimbursement structures and clinical guidelines provide little incentive for routine muscle health assessment or for delivering multimodal interventions that combine nutrition and exercise. Fragmented care pathways and siloed professional responsibilities, for example between dietitians, physiotherapists and physicians, further impede effective interprofessional collaboration [129]. In addition, unequal access to dietetic and rehabilitation services, particularly in resource-constrained settings, exacerbates disparities in muscle-related outcomes [130,131].

Finally, the evidence base required to support policy change remains underdeveloped. Implementation science in muscle health is still emerging, with relatively few studies evaluating real-world strategies for integrating muscle-focused care into existing pathways or assessing their impact on independence, quality of life and healthcare utilisation [132,133]. Robust data on cost-effectiveness and scalability are therefore urgently needed to inform guideline development, reimbursement frameworks and health policy decisions.

Collectively, these barriers highlight the need for a coordinated, multifaceted approach that includes strengthening professional education, standardising pragmatic assessment tools and core outcome sets, aligning reimbursement with muscle-focused care, and expanding implementation research to identify effective, equitable and scalable strategies. Addressing these challenges is essential for muscle health to move from a neglected concept to a routine, measurable and actionable target across healthcare systems.

7. Muscle health and nutrition research agenda

A persistent barrier in low muscle-mass research is the chronic underfunding and underdevelopment of rigorous RCTs. Most studies remain small, heterogeneous, and insufficiently powered to detect clinically meaningful changes in muscle mass, composition, strength, or function [92]. This underpowered evidence base limits our ability to establish effective nutrient recommendations, evaluate synergistic interventions, or translate promising findings into practice. Without adequately funded, well-designed trials, including longer-duration interventions and standardized outcomes, the field continues to rely heavily on expert opinion rather than high-quality data. Strengthening trial design and sample size is therefore essential to advance evidence-based strategies for preventing and treating low muscle mass, and its related conditions such as sarcopenia, and cachexia. Only very recently, a framework was proposed to enhance the design, comparability, and translational impact of future research in clinical nutrition in specifically older and other clinically vulnerable populations [134]. These efforts must be co-designed with patients and caregivers and intentionally integrated across transitions of care, ensuring that hospitalized patients receive continuous, coordinated support for nutrition and muscle health from admission through discharge and into the community.

Beyond limitations in trial funding and design, major gaps remain in how muscle-related endpoints are defined, measured, and translated into effective nutritional interventions across care settings. Current evidence is fragmented across populations, disease states, and methodologies, limiting comparability between studies and hampering implementation into routine clinical practice. Moreover, most nutritional trials continue to rely on population-based recommendations, with limited consideration of individual phenotypes, disease phase, or patient-centred outcomes.

To address these challenges, a coordinated and translational research agenda that spans mechanistic, clinical, methodological, and implementation perspectives is needed. Such an agenda

Table 4
Tentative research agenda – Muscle health in clinical nutrition.

Research theme	Key questions/Focus areas
1. Core outcome set for muscle health	• Harmonise measures of muscle mass, strength, function and PROMs across trials and care settings.
2. Phenotyping in routine care	• Implement tools such as BIA, ultrasound, CT, DXA, handgrip strength, gait speed, walking distance, and chair-stand tests. • Develop simple, setting-specific algorithms for ICU, ward, outpatient and primary care.
3. Critical illness & ICU nutrition	• Determine optimal phase-specific protein and energy requirements (ICU, post-ICU, ward) using functional and patient-centred outcomes. • Test phenotype- and endotype-driven nutritional strategies (e.g., highly catabolic vs less catabolic patients; high vs low inflammation, biomarker-guided (UCR)).
4. Oncology & cachexia	• Evaluate combined nutrition–exercise–pharmacological interventions for cancer-related muscle loss. • Focus on tolerance, timing around treatment cycles, and long-term effects on function and quality of life.
5. Geriatrics & healthy ageing	• Test scalable interventions (e.g., diet + resistance exercise + behaviour change) to prevent or reverse sarcopenia in community-dwelling older adults and long-term care residents.
6. Diabetes, obesity, bariatric surgery & GLP-1 therapy	• Quantify long-term effects of rapid weight loss (surgery or GLP-1 receptor agonists) on muscle mass, strength and function. • Identify optimal protein intake and resistance-training strategies to preserve muscle during weight loss. • Validate definitions and risk-stratification tools for sarcopenic obesity.
7. Precision nutrition & individual protein requirements	• Develop and validate methods to estimate individual protein requirements (e.g., tracer-based approaches, modelling). • Link phenotypes (body composition, activity) and endotypes (metabolic biomarkers, inflammation) to differential responses to nutrition and exercise.
8. Trial design & methodology	• Design adequately powered multicentre trials using standardised muscle-related endpoints and long-term follow-up. • Explore adaptive and platform trial designs for nutritional interventions.
9. Implementation & health systems research	• Identify barriers and facilitators to integrating muscle health assessment and interventions into routine care pathways (ICU, oncology, geriatrics, diabetes clinics). • Develop in co-creation with patients and professionals and test implementation strategies (digital tools, decision support, care bundles, reimbursement models) and evaluate effects on practice and outcomes.
10. Equity, diversity & global perspectives	• Ensure inclusion of under-represented groups (sex, age, ethnicity, socioeconomic status, geography). • Adapt and evaluate muscle health interventions in low- and middle-income settings.

Abbreviations: BIA = Bioelectrical Impedance Analysis; CT = Computed Tomography; DXA = Dual-Energy X-ray Absorptiometry; GLP-1 = Glucagon-Like Peptide-1; ICU = Intensive Care Unit; PROMs = Patient-Reported Outcome Measures; UCR = Urea-to-Creatinine Ratio.

should prioritise harmonisation of outcome measures, integration of feasible muscle assessment tools into routine care, and development of personalised nutrition and exercise strategies informed by biological and clinical heterogeneity. Equally important is the evaluation of scalable, real-world interventions and health-system approaches that ensure equitable access to muscle-focused care across diverse populations and resource settings.

8. Call to action

Advancing muscle health requires coordinated action across research, clinical practice, policy and education. While the preceding sections have addressed methodological, nutritional and implementation aspects in detail, Table 4 synthesises these insights into a coherent research and action agenda. This framework highlights key priorities across mechanistic, clinical, methodological and implementation domains, and provides a structured roadmap for future muscle health and clinical nutrition research.

Central to this agenda is the distinction between phenotypes and endotypes. Phenotypes describe clinically observable manifestations, such as low muscle mass, reduced strength and impaired physical performance, whereas endotypes capture the underlying biological mechanisms driving these impairments. Aligning nutritional and exercise interventions with both phenotype and endotype is essential to move beyond one-size-fits-all recommendations towards truly personalised strategies (Figure 1).

We therefore call on the clinical nutrition and muscle health communities to prioritise standardised, muscle-related outcomes in future trials; to adopt phenotype- and endotype-driven intervention strategies; and to ensure equitable inclusion across populations and care settings, as outlined in Table 3. Funding bodies and policymakers should support interdisciplinary, implementation-focused research that bridges evidence to practice, while healthcare systems must embed routine muscle health assessment and intervention into care pathways spanning intensive care, hospital wards and community settings.

Through coordinated, interprofessional collaboration across disciplines, sectors and regions, muscle health can be repositioned from a neglected consequence of disease to a core determinant of recovery, resilience and healthy ageing.

9. Conclusions

Muscle health should be regarded as a central and measurable target of clinical nutrition, rather than a secondary or downstream outcome. Across a wide range of conditions, including critical illness, cancer, ageing, diabetes, and obesity, loss of muscle mass, strength, and physical function consistently predicts poorer survival, delayed recovery, and reduced quality of life. In this review, we propose a conceptual framework that integrates biological, functional, and patient-reported outcomes, summarise disease-specific evidence and remaining knowledge gaps, and identify cross-cutting challenges in diagnostics, therapeutics, and methodology.

Future nutrition research and clinical practice must move beyond one-size-fits-all prescriptions towards phase-specific, phenotype- and endotype-driven strategies. Within such approaches, protein and energy targets, exercise modalities, and adjunctive therapies should be tailored to individual needs, disease trajectories, and care settings. Successful implementation will require improved standardisation of muscle-related endpoints, broader incorporation of patient-reported outcome measures, and closer alignment between clinical guidelines, reimbursement structures, and healthy-ageing policies.

Finally, a coordinated research agenda is needed to generate actionable evidence across key domains, including individualised protein dosing, muscle loss associated with GLP-1 and GLP-1RA/GIP therapies and bariatric surgery, sarcopenic obesity, and real-world implementation strategies. By embracing personalised, interdisciplinary, and sustainable approaches, the clinical

nutrition community can help ensure that preserving and restoring muscle health becomes a routine, equitable, and impactful component of patient care.

Author contributions

Conceptualisation: All authors.
Framework Development, Drafting, Reviewing: All authors.
Final Approval: All authors.

Funding statement

No author received any financial support from public, commercial, or not-for-profit funding agencies for the preparation of this narrative review.

Conflict of interest

Arthur R.H. van Zanten reported receiving honoraria for advisory board participation, lectures, research activities, and travel expenses from AOP Pharma, Abbott Nutrition, Baxter, Cardinal Health, Danone-Nutricia, Dutch Medical Food, Fresenius Kabi, GE Healthcare, GSK, InBody, Nestle Health Science, PAION, and Rousselot.

Nicolaas E. Deutz reported receiving honoraria for advisory board participation, lectures, research activities, and travel expenses from Abbott Nutrition.

Ana-Marija Liberati Prso reported no conflicts of interest.

Carla M. Prado reports speaking engagements or consultancy for Abbott Nutrition, Nutricia, Nestle Health Science, and Novo Nordisk.

Marieke G. Schooneman reported no conflicts of interest.

Maarten R. Soeters reported no conflicts of interest.

Marian A.E. de van der Schueren reported no conflicts of interest.

Peter J.M. Weijs reported receiving honoraria for advisory board participation, lectures, research activities, and travel expenses from Baxter, Danone-Nutricia, Fresenius Kabi, and Nestlé.

Harriët Jager-Wittenaar reported being a co-developer of the PG-SGA–based Pt-Global web tool.

Acknowledgements

The authors thank Abbott Nutrition for facilitating the initiation meeting of the author group held in May 2025 in Leersum, the Netherlands. The authors received no honoraria for the preparation of this manuscript. Abbott Nutrition had no role in the conceptualisation of the manuscript, the development of the framework or research agenda, nor in the writing, editing, or approval of the final manuscript.

References

[1] Cruz-Jentoft AJ, Sayer AA. Sarcopenia. Lancet 2019 Jun 29;393(10191):2636–46. https://doi.org/10.1016/S0140-6736(19)31138-9. Epub 2019 Jun 3. Erratum in: Lancet. 2019 Jun 29;393(10191):2590. doi: 10.1016/S0140-6736(19)31465-5. PMID: 31171417.

[2] Wolfe RR. The underappreciated role of muscle in health and disease. Am J Clin Nutr 2006 Sep;84(3):475–82. https://doi.org/10.1093/ajcn/84.3.475. PMID: 16960159.

[3] Costa-Pereira JP, Cristina Gonzalez M, Cruz-Jentoft AJ, Goodpaster BH, Daly RM, Fayh APT, et al. "Muscle quality": rethinking an imprecise term. Eur Geriatr Med 2025 Dec;6. https://doi.org/10.1007/s41999-025-01373-y. Epub ahead of print. PMID: 41351652.

[4] Puthucheary ZA, Rawal J, McPhail M, Connolly B, Ratnayake G, Chan P, et al. Acute skeletal muscle wasting in critical illness. JAMA 2013 Oct 16;310(15):1591–600. https://doi.org/10.1001/jama.2013.278481. Erratum in: JAMA. 2014 Feb 12;311(6):625. Padhke, Rahul [corrected to Phadke, Rahul]. PMID: 24108501.

[5] Prado CM, Purcell SA, Laviano A. Nutrition interventions to treat low muscle mass in cancer. J Cachexia Sarcopenia Muscle 2020 Apr;11(2):366–80. https://doi.org/10.1002/jcsm.12525. Epub 2020 Jan 8. PMID: 31916411; PMCID: PMC7113510.

[6] 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 Oct;10(5):956–61. https://doi.org/10.1002/jcsm.12483. Epub 2019 Sep 15. PMID: 31523937; PMCID: PMC6818450.

[7] Deutz NE, Bauer JM, Barazzoni R, Biolo G, Boirie Y, Bosy-Westphal A, et al. Protein intake and exercise for optimal muscle function with aging: recommendations from the ESPEN expert group. Clin Nutr 2014 Dec;33(6):929–36. https://doi.org/10.1016/j.clnu.2014.04.007. Epub 2014 Apr 24. PMID: 24814383; PMCID: PMC4208946.

[8] Vieira FT, Cai Y, Gonzalez MC, Goodpaster BH, Prado CM, Haqq AM. Poor muscle quality: a hidden and detrimental health condition in obesity. Rev Endocr Metab Disord 2025 Oct;26(5):723–44. https://doi.org/10.1007/s11154-025-09941-0. Epub 2025 Jan 21. PMID: 39833502.

[9] Mellen RH, Girotto OS, Marques EB, Laurindo LF, Grippa PC, Mendes CG, et al. Insights into pathogenesis, nutritional and drug approach in Sarcopenia: a systematic review. Biomedicines 2023 Jan 5;11(1):136. https://doi.org/10.3390/biomedicines11010136. PMID: 36672642; PMCID: PMC9856128.

[10] Barone M, Baccaro P, Molfino A. An overview of sarcopenia: focusing on nutritional treatment approaches. Nutrients 2025 Apr 1;17(7):1237. https://doi.org/10.3390/nu17071237. PMID: 40218995; PMCID: PMC11990658.

[11] Miyoshi K, Aoyama T, Kameda S, Ishibashi N, Sakai Y, Yamanaka T, et al. Age different effects of SGLT2 inhibitors on body composition in individuals with type 2 diabetes: a retrospective cohort study. J Diabet Complicat 2025 Aug;39(8):109068. https://doi.org/10.1016/j.jdiacomp.2025.109068. Epub 2025 May 11. PMID: 40367582.

[12] Bear DE, Wandrag L, Merriweather JL, Connolly B, Hart N, Grocott MPW, Enhanced Recovery After Critical Illness Programme Group (ERACIP) investigators. The role of nutritional support in the physical and functional recovery of critically ill patients: a narrative review. Crit Care 2017 Aug 26;21(1):226. https://doi.org/10.1186/s13054-017-1810-2. PMID: 28841893; PMCID: PMC6389279.

[13] Hartl WH, Kopper P, Bender A, Scheipl F, Day AG, Elke G, et al. Protein intake and outcome of critically ill patients: analysis of a large international database using piece-wise exponential additive mixed models. Crit Care 2022 Jan 11;26(1):7. https://doi.org/10.1186/s13054-021-03870-5. PMID: 35012618; PMCID: PMC8751086.

[14] Norman K, Stobäus N, Gonzalez MC, Schulzke JD, Pirlich M. Hand grip strength: outcome predictor and marker of nutritional status. Clin Nutr 2011 Apr;30(2):135–42. https://doi.org/10.1016/j.clnu.2010.09.010. Epub 2010 Oct 30. PMID: 21035927.

[15] Davies TW, van Gassel RJJ, van de Poll M, Gunst J, Casaer MP, Christopher KB, et al. Core outcome measures for clinical effectiveness trials of nutritional and metabolic interventions in critical illness: an international modified Delphi consensus study evaluation (CONCISE). Crit Care 2022 Aug 6;26(1):240. https://doi.org/10.1186/s13054-022-04113-x. PMID: 35933433; PMCID: PMC9357332.

[16] van Zanten ARH, De Waele E, Wischmeyer PE. Nutrition therapy and critical illness: practical guidance for the ICU, post-ICU, and long-term convalescence phases. Crit Care 2019 Nov 21;23(1):368. https://doi.org/10.1186/s13054-019-2657-5. PMID: 31752979; PMCID: PMC6873712.

[17] Chapple LA, Chapman MJ, Lange K, Deane AM, Heyland DK. Nutrition support practices in critically ill head-injured patients: a global perspective. Crit Care 2016 Jan 7;20:6. https://doi.org/10.1186/s13054-015-1177-1. PMID: 26738550; PMCID: PMC4704404.

[18] Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr 2019 Feb;38(1):48–79. https://doi.org/10.1016/j.clnu.2018.08.037. Epub 2018 Sep 29. PMID: 30348463.

[19] 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 Feb;38(1):1–9. https://doi.org/10.1016/j.clnu.2018.08.002. Epub 2018 Sep 3. PMID: 30181091.

[20] Cederholm T, Jensen GL, Correia MITD, Gonzalez MC, Fukushima R, Pisprasert V, et al. The GLIM consensus approach to diagnosis of malnutrition: a 5-year update. Clin Nutr 2025 Jun;49:11–20. https://doi.org/10.1016/j.clnu.2025.03.018. Epub 2025 Apr 5. PMID: 40222089.

[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 Jan 1;48(1):16–31. https://doi.org/10.1093/ageing/afy169. Erratum in: Age Ageing. 2019 Jul 1;48(4):601. doi: 10.1093/ageing/afz046. PMID: 30312372; PMCID: PMC6322506.

[22] Donini LM, Busetto L, Bischoff SC, Cederholm T, Ballesteros-Pomar MD, Batsis JA, et al. Definition and diagnostic criteria for sarcopenic obesity: ESPEN and EASO consensus statement. Obes Facts 2022;15(3):321–35.

https://doi.org/10.1159/000521241. Epub 2022 Feb 23. PMID: 35196654; PMCID: PMC9210010.
[23] Heymsfield SB, Prado CM, Gonzalez MC. Skeletal muscle-focused guideline development: hierarchical model incorporating muscle form, function, and clinical outcomes. Appl Physiol Nutr Metabol 2023 Oct 1;48(10):751–6. https://doi.org/10.1139/apnm-2023-0176. Epub 2023 Jul 20. PMID: 37473448.
[24] Cruz-Jentoft AJ, Gonzalez MC, Prado CM. Sarcopenia ≠ low muscle mass. Eur Geriatr Med 2023 Apr;14(2):225–8. https://doi.org/10.1007/s41999-023-00760-7. PMID: 36869279.
[25] Prado CM, Landi F, Chew STH, Atherton PJ, Molinger J, Ruck T, et al. Advances in muscle health and nutrition: a toolkit for healthcare professionals. Clin Nutr 2022 Oct;41(10):2244–63. https://doi.org/10.1016/j.clnu.2022.07.041. Epub 2022 Aug 7. PMID: 36081299.
[26] Yuan S, Larsson SC. Epidemiology of sarcopenia: prevalence, risk factors, and consequences. Metabolism 2023 Jul;144:155533. https://doi.org/10.1016/j.metabol.2023.155533. Epub 2023 Mar 11. PMID: 36907247.
[27] Kirk B, Cawthon PM, Arai H, Ávila-Funes JA, Barazzoni R, Bhasin S, et al., Global Leadership Initiative in Sarcopenia (GLIS) group. The conceptual definition of Sarcopenia: Delphi consensus from the global leadership initiative in Sarcopenia (GLIS). Age Ageing 2024 Mar 1;53(3):afae052. https://doi.org/10.1093/ageing/afae052. PMID: 38520141; PMCID: PMC10960072.
[28] Flores-Opazo M, Monsalves-Álvarez M, Sepúlveda-Guzmán C, Jannas-Vela S, Fernández Valero P, Burrows R, et al. Perspective review: advancing toward the diagnosis of sarcopenia in the pediatric population. Pediatr Res 2025 Dec;26. https://doi.org/10.1038/s41390-025-04716-4. Epub ahead of print. PMID: 41454144.
[29] Beaudart C, Alcazar J, Aprahamian I, Batsis JA, Yamada Y, Prado CM, et al., Global Leadership Initiative in Sarcopenia (GLIS) group. Health outcomes of sarcopenia: a consensus report by the outcome working group of the Global Leadership Initiative in Sarcopenia (GLIS). Aging Clin Exp Res 2025 Mar 22;37(1):100. https://doi.org/10.1007/s40520-025-02995-9. PMID: 40120052; PMCID: PMC11929733.
[30] Prado CM, Batsis JA, Donini LM, Gonzalez MC, Siervo M. Sarcopenic obesity in older adults: a clinical overview. Nat Rev Endocrinol 2024 May;20(5):261–77. https://doi.org/10.1038/s41574-023-00943-z. Epub 2024 Feb 6. PMID: 38321142.
[31] Donini LM, Busetto L, Bauer JM, Bischoff S, Boirie Y, Cederholm T, et al. Critical appraisal of definitions and diagnostic criteria for sarcopenic obesity based on a systematic review. Clin Nutr 2020 Aug;39(8):2368–88. https://doi.org/10.1016/j.clnu.2019.11.024. Epub 2019 Nov 27. PMID: 31813698.
[32] Gortan Cappellari G, Guillet C, Poggiogalle E, Ballesteros Pomar MD, Batsis JA, Boirie Y, et al. SOGLI expert panel. Sarcopenic obesity research perspectives outlined by the sarcopenic obesity global leadership initiative (SOGLI) - proceedings from the SOGLI consortium meeting in rome November 2022. Clin Nutr 2023 May;42(5):687–99. https://doi.org/10.1016/j.clnu.2023.02.018. Epub 2023 Feb 24. PMID: 36947988.
[33] Geng Q, Zhai H, Wang L, Wei H, Hou S. The efficacy of different interventions in the treatment of sarcopenia in middle-aged and elderly people: a network meta-analysis. Medicine (Baltim) 2023 Jul 7;102(27):e34254. https://doi.org/10.1097/MD.0000000000034254. PMID: 37417618; PMCID: PMC10328700.
[34] Villareal DT, Chode S, Parimi N, Sinacore DR, Hilton T, Armamento-Villareal R, et al. Weight loss, exercise, or both and physical function in obese older adults. N Engl J Med 2011 Mar 31;364(13):1218–29. https://doi.org/10.1056/NEJMoa1008234. PMID: 21449785; PMCID: PMC3114602.
[35] Ryan AM, Sullivan ES. Impact of musculoskeletal degradation on cancer outcomes and strategies for management in clinical practice. Proc Nutr Soc 2021 Feb;80(1):73–91. https://doi.org/10.1017/S0029665120007855. Epub 2020 Nov 3. PMID: 32981540.
[36] Prado CM, Cushen SJ, Orsso CE, Ryan AM. Sarcopenia and cachexia in the era of obesity: clinical and nutritional impact. Proc Nutr Soc 2016 May;75(2):188–98. https://doi.org/10.1017/S0029665115004279. Epub 2016 Jan 8. PMID: 26743210.
[37] Prado CM, Maia YL, Ormsbee M, Sawyer MB, Baracos VE. Assessment of nutritional status in cancer–the relationship between body composition and pharmacokinetics. Anti Cancer Agents Med Chem 2013 Oct;13(8):1197–203. https://doi.org/10.2174/18715206113139990322. PMID: 23919745.
[38] Assenat E, Ben Abdelghani M, Gourgou S, Perrier H, Akouz FK, Desgrippes R, et al. Impact of lean body mass-based oxaliplatin dose calculation on neurotoxicity in adjuvant treatment of stage III Colon cancer: results of the phase II randomized LEANOX trial. J Clin Oncol 2025 Aug 10;43(23):2616–27. https://doi.org/10.1200/JCO-24-02754. Epub 2025 Jun 20. Erratum in: J Clin Oncol. 2025 Dec 10;43(35):3774. doi: 10.1200/JCO-25-02239. PMID: 40540704; PMCID: PMC12316125.
[39] Chang YY, Cheng B. Prognostic impact of myosteatosis in patients with colorectal cancer undergoing curative surgery: an updated systematic review and meta-analysis. Front Oncol 2024 Jun 19;14:1388001. https://doi.org/10.3389/fonc.2024.1388001. PMID: 38962266; PMCID: PMC11219791.
[40] 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 Jan;145:102839. https://doi.org/10.1016/j.critrevonc.2019.102839. Epub 2019 Dec 20. PMID: 31877534.
[41] Sehl M, Lu X, Silliman R, Ganz PA. Decline in physical functioning in first 2 years after breast cancer diagnosis predicts 10-year survival in older women. J Cancer Surviv 2013 Mar;7(1):20–31. https://doi.org/10.1007/s11764-012-0239-5. Epub 2012 Dec 12. PMID: 23232922; PMCID: PMC3568656.
[42] Calixto-Lima L, de Oliveira LC, Pimenta NG, de Albuquerque NMC, Chaves GV, Wiegert EVM. Effect of low skeletal muscle mass combined with low muscle strength to predict survival in patients with incurable cancer. Clin Nutr ESPEN 2022 Oct;51:445–51. https://doi.org/10.1016/j.clnesp.2022.07.002. Epub 2022 Jul 14. PMID: 36184241.
[43] D'Souza DM, Al-Sajee D, Hawke TJ. Diabetic myopathy: impact of diabetes mellitus on skeletal muscle progenitor cells. Front Physiol 2013 Dec 20;4:379. https://doi.org/10.3389/fphys.2013.00379.
[44] Travis C, Srivastava PS, Hawke TJ, Kalaitzoglou E. Diabetic bone disease and diabetic myopathy: manifestations of the impaired muscle-bone unit in type 1 diabetes. J Diabetes Res 2022 May 12;2022:2650342. https://doi.org/10.1155/2022/2650342.
[45] Badu-Mensah A, Valinski P, Parsaud H, Hickman JJ, Guo X. Hyperglycemia negatively affects IPSC-derived myoblast proliferation and skeletal muscle regeneration and function. Cells 2022 Nov 18;11(22):3674. https://doi.org/10.3390/cells11223674.
[46] Bassi-Dibai D, Santos-de-Araújo AD, Dibai-Filho AV, de Azevedo LFS, Goulart CDL, Luz GCP, et al. Rehabilitation of individuals with diabetes mellitus: focus on diabetic myopathy. Front Endocrinol 2022 Apr 14;13:869921. https://doi.org/10.3389/fendo.2022.869921.
[47] Li M, Chi X, Wang Y, Setrerrahmane S, Xie W, Xu H. Trends in insulin resistance: insights into mechanisms and therapeutic strategy. Signal Transduct Targeted Ther 2022;7:216. https://doi.org/10.1038/s41392-022-01073-0. PMID: 35794109; PMCID: PMC9259665.
[48] Chapela SP, Simancas-Racines D, Montalvan M, Frias-Toral E, Simancas-Racines A, Muscogiuri G, et al. Signals for muscular protein turnover and insulin resistance in critically ill patients: a narrative review. Nutrients 2023 Feb 21;15(5):1071. https://doi.org/10.3390/nu15051071.
[49] Dai H, Xu J. Creatinine-to-cystatin C ratio as a marker of sarcopenia for identifying osteoporosis in male patients with type 2 diabetes mellitus. BMC Muscoskelet Disord 2022 Jul 14;23(1):672. https://doi.org/10.1186/s12891-022-05636-8. Erratum in: BMC Musculoskelet Disord. 2022 Aug 1;23(1):737. doi: 10.1186/s12891-022-05707-w. PMID: 35836165; PMCID: PMC9281094.
[50] Jimenez-Gutierrez GE, Martínez-Gómez LE, Martínez-Armenta C, Pineda C, Martínez-Nava GA, Lopez-Reyes A. Molecular mechanisms of inflammation in Sarcopenia: diagnosis and therapeutic update. Cells 2022 Aug 1;11(15):2359. https://doi.org/10.3390/cells11152359. PMID: 35954203; PMCID: PMC9367570.
[51] Feng L, Gao Q, Hu K, Wu M, Wang Z, Chen F, et al. Prevalence and risk factors of sarcopenia in patients with diabetes: a meta-analysis. J Clin Endocrinol Metab 2022 Apr 19;107(5):1470–83. https://doi.org/10.1210/clinem/dgab884.
[52] Marcotte-Chénard A, Oliveira B, Little JP, Candow DG. Sarcopenia and type 2 diabetes: pathophysiology and potential therapeutic lifestyle interventions. Diabetes Metabol Syndr: Clin Res Rev 2023;17(9):102835.
[53] Bai H, Liu Y, Zhang L, Song L, Pan Y, Long Z, et al. Sarcopenia as a predictor of negative health outcomes in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. Diabetol Metab Syndr 2025 Nov 5;17(1):416. https://doi.org/10.1186/s13098-025-01998-w.
[54] Ceasovschih A, Asaftei A, Lupo MG, Kotlyarov S, Bartušková H, Balta A, et al. Glucagon-like peptide-1 receptor agonists and muscle mass effects. Pharmacol Res 2025 Oct;220:107927. https://doi.org/10.1016/j.phrs.2025.107927. Epub 2025 Aug 24. PMID: 40858197.
[55] Vieira FT, Prado CM, Thorlakson J, Stoklossa CJ, Jin J, Donini LM, et al. Sarcopenic obesity in Metabolic and bariatric surgery: a scoping review. Obes Rev 2025 Dec;26(12):e13973. https://doi.org/10.1111/obr.13973. Epub 2025 Jun 24. PMID: 40556340; PMCID: PMC12620107.
[56] Nuijten MAH, Eijsvogels TMH, Monpellier VM, Janssen IMC, Hazebroek EJ, Hopman MTE. The magnitude and progress of lean body mass, fat-free mass, and skeletal muscle mass loss following bariatric surgery: a systematic review and meta-analysis. Obes Rev 2022 Jan;23(1):e13370. https://doi.org/10.1111/obr.13370. Epub 2021 Oct 19. PMID: 34664391; PMCID: PMC9285034.
[57] Ibacache-Saavedra P, Martínez-Rosales E, Jerez-Mayorga D, Miranda-Fuentes C, Artero EG, Cano-Cappellacci M. Effects of bariatric surgery on muscle strength and quality: a systematic review and meta-analysis. Obes Rev 2024 Sep;25(9):e13790. https://doi.org/10.1111/obr.13790. Epub 2024 Jun 10. PMID: 38859617.
[58] Linge J, Birkenfeld AL, Neeland IJ. Muscle mass and glucagon-like Peptide-1 receptor agonists: adaptive or maladaptive response to weight loss? Circulation 2024;150(16):1288–98.
[59] Koceva A, Janež A, Jensterle M. Impact of incretin-based therapy on skeletal muscle health. Medicina (Kaunas) 2025 Sep 18;61(9):1691. https://doi.org/10.3390/medicina61091691.
[60] Neeland IJ, Linge J, Birkenfeld AL. Changes in lean body mass with glucagon-like peptide-1-based therapies and mitigation strategies. Diabetes Obes Metabol 2024 Sep;26(Suppl 4):16–27. https://doi.org/10.1111/dom.15728. Epub 2024 Jun 27.

[61] Gatto A, Liu K, Milan N, Wong S. The effects of GLP-1 agonists on musculoskeletal health and orthopedic care. Curr Rev Musculoskelet Med 2025 Oct;18(10):469–80. https://doi.org/10.1007/s12178-025-09978-3. Epub 2025 May 15.
[62] Dulloo AG. Physiology of weight regain: lessons from the classic Minnesota starvation experiment on human body composition regulation. Obes Rev 2021;22(Suppl 2):e13189.
[63] West S, Scragg J, Aveyard P, Oke JL, Willis L, Haffner SJP, et al. Weight regain after cessation of medication for weight management: systematic review and meta-analysis. BMJ 2026 Jan 7;392:e085304. https://doi.org/10.1136/bmj-2025-085304. PMID: 41500720; PMCID: PMC12776922.
[64] Christoffersen B, Sanchez-Delgado G, John LM, Ryan DH, Raun K, Ravussin E. Beyond appetite regulation: targeting energy expenditure, fat oxidation, and lean mass preservation for sustainable weight loss. Obesity 2022;30(4):841–57.
[65] Mozaffarian D, Agarwal M, Aggarwal M, Alexander L, Apovian CM, Bindlish S, et al. Nutritional priorities to support GLP-1 therapy for obesity: a joint advisory from the American college of lifestyle medicine, the American society for nutrition, the obesity medicine association, and the obesity society. Am J Clin Nutr 2025;122(1):344–67.
[66] Heymsfield SB, Coleman LA, Miller R, Rooks DS, Laurent D, Petricoul O, et al. Effect of bimagrumab vs placebo on body fat mass among adults with type 2 diabetes and obesity: a phase 2 randomized clinical trial. JAMA Netw Open 2021;4(1):e2033457.
[67] Boelens YFN, Melchers M, van Zanten ARH. Poor physical recovery after critical illness: incidence, features, risk factors, pathophysiology, and evidence-based therapies. Curr Opin Crit Care 2022 Aug 1;28(4):409–16. https://doi.org/10.1097/MCC.0000000000000955. Epub 2022 Jul 5. PMID: 35796071; PMCID: PMC9594146.
[68] van Ruijven IM, Abma J, Brunsveld-Reinders AH, Stapel SN, van Etten-Jamaludin F, Boirie Y, et al. High protein provision of more than 1.2 g/kg improves muscle mass preservation and mortality in ICU patients: a systematic review and meta-analyses. Clin Nutr 2023 Dec;42(12):2395–403. https://doi.org/10.1016/j.clnu.2023.09.026. Epub 2023 Sep 29. PMID: 37862825.
[69] van Ruijven IM, Brunsveld-Reinders AH, Stapel SN, Weijs PJM. Reply - Letter to the editor: reconsidering 1.2-1.5 g/kg as beneficially high protein provision in critically ill patients. Clin Nutr 2024 Apr;43(4):1077–8. https://doi.org/10.1016/j.clnu.2023.11.035. Epub 2023 Nov 29. PMID: 38049354.
[70] Claassen WJ, van Ruijven IM, van den Berg M, Baelde RJ, Fortes Monteiro A, Balesar RMN, et al. In vitro and in vivo muscle mass and strength during the first week of critical illness. Intensive Care Med Exp 2025 Jun 3;13(1):57. https://doi.org/10.1186/s40635-025-00755-7. PMID: 40461646; PMCID: PMC12133653.
[71] Koekkoek WACK, van Setten CHC, Olthof LE, Kars JCNH, van Zanten ARH. Timing of PROTein INtake and clinical outcomes of adult critically ill patients on prolonged mechanical VENTilation: the PROTINVENT retrospective study. Clin Nutr 2019 Apr;38(2):883–90. https://doi.org/10.1016/j.clnu.2018.02.012. Epub 2018 Feb 17. PMID: 29486907.
[72] Heyland DK, Patel J, Compher C, Rice TW, Bear DE, Lee ZY, et al. The effect of higher protein dosing in critically ill patients with high nutritional risk (EFFORT protein): an international, multicentre, pragmatic, registry-based randomised trial. Lancet 2023;401(10376):568–76.
[73] Bels JLM, Thiessen S, van Gassel RJJ, Beishuizen A, De Bie Dekker A, Fraipont V, et al. Effect of high versus standard protein provision on functional recovery in people with critical illness (PRECISe): an investigator-initiated, double-blinded, multicentre, parallel-group, randomised controlled trial in Belgium and the Netherlands. Lancet 2024;404(10453):659–69.
[74] Summers MJ, Chapple LS, Karahalios A, Bellomo R, Chapman MJ, Ferrie S, et al. Augmented enteral protein during critical illness: the TARGET protein randomized clinical trial. JAMA 2025;334(4):319–28.
[75] Vanhorebeek I, Casaer M, Gunst J. Nutrition and autophagy deficiency in critical illness. Curr Opin Crit Care 2023 Aug 1;29(4):306–14. https://doi.org/10.1097/MCC.0000000000001056. Epub 2023 Jun 8. PMID: 37306474; PMCID: PMC10328539.
[76] Andréasson C, Ott M, Büttner S. Mitochondria orchestrate proteostatic and metabolic stress responses. EMBO Rep 2019 Oct 4;20(10):e47865. https://doi.org/10.15252/embr.201947865. Epub 2019 Sep 18. PMID: 31531937; PMCID: PMC6776902.
[77] Chapple LS, Kouw IWK, Summers MJ, Weinel LM, Gluck S, Raith E, et al. Muscle protein synthesis after protein administration in critical illness. Am J Respir Crit Care Med 2022 Sep 15;206(6):740–9. https://doi.org/10.1164/rccm.202112-2780OC. PMID: 35584344.
[78] van Zanten ARH. Editorial: personalized nutrition therapy in critical illness and convalescence: moving beyond one-size-fits-all to phenotyping and endotyping. Curr Opin Crit Care 2023 Aug 1;29(4):281–5. https://doi.org/10.1097/MCC.0000000000001060. PMID: 37431268; PMCID: PMC10328525.
[79] Slingerland-Boot R, van der Heijden I, Schouten N, Driessen L, Meijer S, Mensink M, et al. Prospective observational cohort study of reached protein and energy targets in general wards during the post-intensive care period: the PROSPECT-I study. Clin Nutr 2022 Oct;41(10):2124–34. https://doi.org/10.1016/j.clnu.2022.07.031. Epub 2022 Aug 9. PMID: 36067584.
[80] Paulus MC, Kouw IWK, van Beek-Westeneng N, de Leeuw I, van Lingen EC, Holverda M, et al. The impact of an individually tailored, stepwise nutrition protocol on energy and protein adequacy in post-ICU patients: the PROSPECT-II observational cohort study. Clin Nutr 2025 Nov;54:120–31. https://doi.org/10.1016/j.clnu.2025.09.011. Epub 2025 Sep 25. PMID: 41061513.
[81] Jager-Wittenaar H, Sealy M, Naumann E, de van der Schueren M. Nutritional risk screening: a need to guide Alice in Nutritionland. Curr Opin Clin Nutr Metab Care 2024 Sep 1;27(5):381–6. https://doi.org/10.1097/MCO.0000000000001051. Epub 2024 Jun 5. PMID: 38837037.
[82] 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. JPEN - J Parenter Enter Nutr 2019;43(1):32–40.
[83] Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. Clin Nutr 2017 Feb;36(1):49–64. https://doi.org/10.1016/j.clnu.2016.09.004.
[84] Malmstrom TK, Morley JE. SARC-F: a simple questionnaire to rapidly diagnose sarcopenia. J Am Med Dir Assoc 2013 Aug;14(8):531e2. https://doi.org/10.1016/j.jamda.2013.05.018.
[85] Woo J, Leung J, Morley JE. Validating the SARC-F: a suitable community case finding tool for sarcopenia? J Am Med Dir Assoc 2014 Sep;15(9):630e4. https://doi.org/10.1016/j.jamda.2014.04.021.
[86] 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 Sep;21(9):1216–28. https://doi.org/10.1016/j.jamda.2020.03.006. Epub 2020 Apr 21. PMID: 32327302.
[87] Verlaan S, Ligthart-Melis GC, Wijers SLJ, Cederholm T, Maier AB, de van der Schueren MAE. High prevalence of physical frailty among community-dwelling malnourished older Adults-A systematic review and meta-analysis. J Am Med Dir Assoc 2017 May 1;18(5):374–82. https://doi.org/10.1016/j.jamda.2016.12.074. Epub 2017 Feb 24. PMID: 28238676.
[88] Mwala NN, In 't Hulst JJFA, van der Meij BS, Vasse E, Borkent JW, van Dronkelaar C, et al. Navigating complexity: the challenge of reaching consensus on the diagnosis of malnutrition in patients with obesity via a modified Delphi study. Clin Nutr ESPEN 2025 Aug;68:591–601. https://doi.org/10.1016/j.clnesp.2025.05.043. Epub 2025 Jun 7. Erratum in: Clin Nutr ESPEN. 2025 Oct;69:822. doi: 10.1016/j.clnesp.2025.07.001. PMID: 40490222.
[89] 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 Jun;13(3):1442–59. https://doi.org/10.1002/jcsm.12954. Epub 2022 Mar 17. PMID: 35301816; PMCID: PMC9178172.
[90] van den Helder J, Mehra S, van Dronkelaar C, Ter Riet G, Tieland M, Visser B, et al. Blended home-based exercise and dietary protein in community-dwelling older adults: a cluster randomized controlled trial. J Cachexia Sarcopenia Muscle 2020 Dec;11(6):1590–602. https://doi.org/10.1002/jcsm.12634. Epub 2020 Oct 26. PMID: 33103379; PMCID: PMC7749597.
[91] Wu Y, de Crom TOE, Chen Z, Benz E, van der Schaft N, Pinel A, et al. Dietary protein intake and body composition, sarcopenia and sarcopenic obesity: a prospective population-based study. Clin Nutr 2025 Aug 6;53:26–34. https://doi.org/10.1016/j.clnu.2025.07.033. Epub ahead of print. PMID: 40845421.
[92] Prado CM, Anker SD, Coats AJS, Laviano A, von Haehling S. Nutrition in the spotlight in cachexia, sarcopenia and muscle: avoiding the wildfire. J Cachexia Sarcopenia Muscle 2021 Feb;12(1):3–8. https://doi.org/10.1002/jcsm.12673. Epub 2020 Dec 31. PMID: 33382196; PMCID: PMC7890147.
[93] Bargetzi L, Brack C, Herrmann J, Bargetzi A, Hersberger L, Bargetzi M, et al. Nutritional support during the hospital stay reduces mortality in patients with different types of cancers: secondary analysis of a prospective randomized trial. Ann Oncol 2021 Aug;32(8):1025–33. https://doi.org/10.1016/j.annonc.2021.05.793. Epub 2021 May 19. PMID: 34022376.
[94] Cereda E, Cappello S, Colombo S, Klersy C, Imarisio I, Turri A, et al. Nutritional counseling with or without systematic use of oral nutritional supplements in head and neck cancer patients undergoing radiotherapy. Radiother Oncol 2018 Jan;126(1):81–8. https://doi.org/10.1016/j.radonc.2017.10.015. Epub 2017 Oct 27. PMID: 29111172.
[95] Orsso CE, Caretero A, Poltronieri TS, Arends J, de van der Schueren MA, Kiss N, et al. Effects of high-protein supplementation during cancer therapy: a systematic review and meta-analysis. Am J Clin Nutr 2024 Dec;120(6):1311–24. https://doi.org/10.1016/j.ajcnut.2024.08.016. PMID: 39631998; PMCID: PMC11619795.
[96] Ford KL, Sawyer MB, Ghosh S, Trottier CF, Disi IR, Easaw J, et al. Feasibility of two levels of protein intake in patients with colorectal cancer: findings from the protein Recommendation to Increase Muscle (PRIMe) randomized controlled pilot trial. ESMO Open 2024 Jul;9(7):103604. https://doi.org/10.1016/j.esmoop.2024.103604. Epub 2024 Jun 26. PMID: 38935990; PMCID: PMC11260369.
[97] Aredes MA, da Camara AO, de Paula NS, Fraga KYD, do Carmo MDGT, 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 Nov-Dec;67–68:110528. https://doi.org/10.1016/j.nut.2019.06.009. Epub 2019 Jun 14. PMID: 31445316.
[98] 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 Jun;13(3):1623–41. https://doi.org/10.1002/jcsm.12952. Epub 2022 Mar 17. PMID: 35301826; PMCID: PMC9178154.
[99] Bauer S, Reiter L, Weijs PJM, Schoufour JD, Boirie Y, Topinková E, et al., SO-NUTS consortium. Adherence to resistance training and hypocaloric diet among persons near retirement age - a secondary data analysis of three randomized controlled trials. J Nutr Health Aging 2024 Oct;28(10):100344. https://doi.org/10.1016/j.jnha.2024.100344. Epub 2024 Aug 26. PMID: 39191118.
[100] Collazo-Castiñeira P, Sánchez-Izquierdo M, Reiter LJ, Bauer S, Cruz-Jentoft AJ, Schoufour JD, et al. Analysis of behavioral change techniques used in exercise and nutritional interventions targeting adults around retirement age with sarcopenic obesity in a systematic review. Arch Gerontol Geriatr 2024 Aug;123:105437. https://doi.org/10.1016/j.archger.2024.105437. Epub 2024 Apr 16. PMID: 38653002.
[101] Eglseer D, Traxler M, Embacher S, Reiter L, Schoufour JD, Weijs PJM, et al., SO-NUTS consortium. Nutrition and exercise interventions to improve body composition for persons with overweight or obesity near retirement age: a systematic review and network meta-analysis of randomized controlled trials. Adv Nutr 2023 May;14(3):516–38. https://doi.org/10.1016/j.advnut.2023.04.001. Epub 2023 Apr 6. PMID: 37028708; PMCID: PMC10201832.
[102] Eglseer D, Traxler M, Schoufour JD, Weijs PJM, Voortman T, Boirie Y, et al., SO-NUTS Consortium. Nutritional and exercise interventions in individuals with sarcopenic obesity around retirement age: a systematic review and meta-analysis. Nutr Rev 2023 Aug 10;81(9):1077–90. https://doi.org/10.1093/nutrit/nuad007. Erratum in: Nutr Rev. 2024 May 10;82(6):848. doi: 10.1093/nutrit/nuad087. PMID: 36882046; PMCID: PMC10413430.
[103] Reiter L, Bauer S, Traxler M, Schoufour JD, Weijs PJM, Cruz-Jentoft A, et al. Effects of nutrition and exercise interventions on persons with sarcopenic obesity: an umbrella review of meta-analyses of randomised controlled trials. Curr Obes Rep 2023 Sep;12(3):250–63. https://doi.org/10.1007/s13679-023-00509-0. Epub 2023 May 30. PMID: 37249818; PMCID: PMC10482763.
[104] Benz E, Pinel A, Guillet C, Capel F, Pereira B, De Antonio M, et al. Sarcopenia and sarcopenic obesity and mortality among older people. JAMA Netw Open 2024 Mar 4;7(3):e243604. https://doi.org/10.1001/jamanetworkopen.2024.3604. PMID: 38526491; PMCID: PMC10964118.
[105] Benz E, Pinel A, Guillet C, Capel F, Pereira B, Rizopoulos D, Cruz-Jentoft AJ, Eglseer D, Topinkova E, Barazzoni R, Donini L, Rivadeneira F, Steur M, Voortman T, Weijs PJM, Schoufour JD, Boirie Y. Sarcopenic-obesity phenotype index (SOPi) and its associated factors: a population-based study. J Cachexia Sarcopenia Muscle.
[106] Minnetti M, Barazzoni R, Batsis JA, Busetto L, Yumuk V, Poggiogalle E, et al. The integration of lifestyle modification advice and diet and physical exercise interventions: cornerstones in the management of obesity with Incretin mimetics. Obes Facts 2025 Nov;18:1–16. https://doi.org/10.1159/000548370. Epub ahead of print. PMID: 41252315; PMCID: PMC12707955.
[107] Verreijen AM, Verlaan S, Engberink MF, Swinkels S, de Vogel-van den Bosch J, Weijs PJ. A high whey protein-, leucine-, and vitamin D-enriched supplement preserves muscle mass during intentional weight loss in obese older adults: a double-blind randomized controlled trial. Am J Clin Nutr 2015 Feb;101(2):279–86. https://doi.org/10.3945/ajcn.114.090290. Epub 2014 Nov 26. PMID: 25646324.
[108] Weijs PJM, Wolfe RR. Exploration of the protein requirement during weight loss in obese older adults. Clin Nutr 2016 Apr;35(2):394–8. https://doi.org/10.1016/j.clnu.2015.02.016. Epub 2015 Mar 6. PMID: 25788405.
[109] Weijs PJM. Protein requirement in obesity. Curr Opin Clin Nutr Metab Care 2025 Jan 1;28(1):27–32. https://doi.org/10.1097/MCO.0000000000001087. Epub 2024 Nov 5. PMID: 39514335.
[110] Prado CM, Gonzalez MC, Norman K, Barazzoni R, Cederholm T, Compher C, et al. Methodological standards for body composition-an expert-endorsed guide for research and clinical applications: levels, models, and terminology. Am J Clin Nutr 2025 Aug;122(2):384–91. https://doi.org/10.1016/j.ajcnut.2025.05.022. Epub 2025 Jul 17. PMID: 40754386; PMCID: PMC12405783.
[111] 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 Dec;97(6):2333–8. https://doi.org/10.1152/japplphysiol.00744.2004. Epub 2004 Aug 13. PMID: 15310748.
[112] van Ruijven IM, Stapel SN, Molinger J, Weijs PJM. Monitoring muscle mass using ultrasound: a key role in critical care. Curr Opin Crit Care 2021 Aug 1;27(4):354–60. https://doi.org/10.1097/MCC.0000000000000846. PMID: 33973896.
[113] Perkisas S, Welch C, Soulis G. The sarcopenia conundrum: why muscle ultrasound does (or does not) have a future. Eur Geriatr Med 2025 Oct 27. https://doi.org/10.1007/s41999-025-01335-4. Epub ahead of print. Erratum in: Eur Geriatr Med. 2025 Nov 24. doi: 10.1007/s41999-025-01350-5. PMID: 41144087.
[114] Memelink RG, Pasman WJ, Bongers A, Tump A, van Ginkel A, Tromp W, et al. Effect of an enriched protein drink on muscle mass and glycemic control during combined lifestyle intervention in older adults with obesity and type 2 diabetes: a double-blind RCT. Nutrients 2020 Dec 28;13(1):64. https://doi.org/10.3390/nu13010064. PMID: 33379181; PMCID: PMC7823734.
[115] 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. JPEN - J Parenter Enter Nutr 2022 Aug;46(6):1232–42. https://doi.org/10.1002/jpen.2366. Epub 2022 Apr 19. PMID: 35437785.
[116] 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 Jun;41(6):1425–33. https://doi.org/10.1016/j.clnu.2022.02.001. Epub 2022 Apr 19. PMID: 35450768.
[117] Joint WHO/FAO/UNU Expert Consultation. Protein and amino acid requirements in human nutrition. World Health Organ Tech Rep Ser 2007;935:1–265. back cover. PMID: 18330140.
[118] Rand WM, Pellett PL, Young VR. Meta-analysis of nitrogen balance studies for estimating protein requirements in healthy adults. Am J Clin Nutr 2003 Jan;77(1):109–27. https://doi.org/10.1093/ajcn/77.1.109. PMID: 12499330.
[119] Zeevi D, Korem T, Zmora N, Israeli D, Rothschild D, Weinberger A, et al. Personalized nutrition by prediction of glycemic responses. Cell 2015 Nov 19;163(5):1079–94. https://doi.org/10.1016/j.cell.2015.11.001. PMID: 26590418.
[120] Elango R, Ball RO, Pencharz PB. Indicator amino acid oxidation: concept and application. J Nutr 2008 Feb;138(2):243–6. https://doi.org/10.1093/jn/138.2.243. PMID: 18203885.
[121] Millward DJ. Post-prandial tracer studies of protein and amino acid utilisation: what can they tell us about human amino acid and protein requirements? Br J Nutr 2024 Jun 28;131(12):2005–30. https://doi.org/10.1017/S0007114524000734. Epub 2024 Apr 12. PMID: 38606599; PMCID: PMC11361918.
[122] Malowany JM, van Lieshout GAA, Verdijk LB, Moore DR, van Loon LJC, Trommelen J. The indicator amino acid oxidation (IAAO) technique: a novel approach to assess protein intakes that maximize whole-body protein anabolism. Crit Rev Food Sci Nutr 2025 Aug;1:1–10. https://doi.org/10.1080/10408398.2025.2541895. Epub ahead of print. PMID: 40748779.
[123] Deutz NEP, Knezek SB, Engelen MPKJ. A novel pulse tracer method to estimate the relationship between amino acid meal composition and its intracellular disposal. Clin Nutr 2025 Dec;55:196–207. https://doi.org/10.1016/j.clnu.2025.10.002. Epub 2025 Oct 22. PMID: 41260190.
[124] Kolnes KJ, Nilsen ETF, Brufladt S, Meadows AM, Jeppesen PB, Skattebo Ø, et al. Effects of seven days' fasting on physical performance and metabolic adaptation during exercise in humans. Nat Commun 2025 Jan 2;16(1):122. https://doi.org/10.1038/s41467-024-55418-0. PMID: 39747857; PMCID: PMC11695724.
[125] Beaudart C, Rolland Y, Cruz-Jentoft AJ, Bauer JM, Sieber C, Cooper C, et al. Assessment of muscle function and physical performance in daily clinical practice : a position paper endorsed by the European Society for clinical and economic aspects of osteoporosis, osteoarthritis and musculoskeletal diseases (ESCEO). Calcif Tissue Int 2019 Jul;105(1):1–14. https://doi.org/10.1007/s00223-019-00545-w.
[126] Swan WI, Vivanti A, Hakel-Smith NA, Hotson B, Orrevall Y, Trostler N, et al. Nutrition care process and model update: toward realizing people-centered care and outcomes management. J Acad Nutr Diet 2017 Dec;117(12):2003–14. https://doi.org/10.1016/j.jand.2017.07.015. Epub 2017 Oct 5. PMID: 28988837.
[127] Lehmann J, Dragan T, Rammant E, de Ligt KM, Lai-Kwon J, Lidington E, et al. Exploring the integration of patient-reported outcome measures in clinical practice: a cross-sectional survey of EORTC healthcare professionals. Eur J Cancer 2025 May 2;220:115333. https://doi.org/10.1016/j.ejca.2025.115333.
[128] Bonsel JM, Itiola AJ, Huberts AS, Bonsel GJ, Penton H. The use of patient-reported outcome measures to improve patient-related outcomes - a systematic review. Health Qual Life Outcome 2024 Nov 26;22(1):101. https://doi.org/10.1186/s12955-024-02312-4.
[129] Boxum SD, van Exter SH, Reinders JJ, Koenders N, Drenth H, van den Berg MGA, et al. Interprofessional management of (risk of) malnutrition and Sarcopenia: a grounded theory study from the perspective of professionals. J Multidiscip Healthc 2024;17:4677–92.
[130] Cardenas D, Ferreira IR, Correia MITD, Barbagallo MD, Lal S, Barazzoni R, et al., Working Group. Tackling disease-related malnutrition in resource-limited settings: an international position paper based on expert consensus. Clin Nutr 2025 Aug;51:381–5. https://doi.org/10.1016/j.clnu.2025.04.010.
[131] Nishioka S, Takayama M, Okamoto T, Miyai I. Implementation of nutritional screening tools, nutritional assessment tools, and diagnostic criteria for malnutrition in convalescent rehabilitation wards: a nationwide survey. Clin Nutr ESPEN 2024 Aug;62:102–7. https://doi.org/10.1016/j.clnesp.2024.04.026.
[132] van Dongen EJI, Haveman-Nies A, Doets EL, Dorhout BG, de Groot LCPGM. Effectiveness of a diet and resistance exercise intervention on muscle health in older adults: promuscle in practice. J Am Med Dir Assoc 2020 Aug;21(8):

1065–1072.e3. https://doi.org/10.1016/j.jamda.2019.11.026. Epub 2020 Jan 14. PMID: 31948853.
[133] Strijker D, Drager L, van Asseldonk M, Atsma F, van den Berg M, van Daal E, et al. Multimodal prehabilitation (Fit4Surgery) in high-impact surgery to enhance surgical outcomes: study protocol of F4S PREHAB, a single center stepped wedge trial. PLoS One 2024 Jul 5;19(7):e0303829. https://doi.org/10.1371/journal.pone.0303829. PMID: 38968183; PMCID: PMC11226070.
[134] Van Dronkelaar C, Soeters MR, Schuetz P, Prado CM, Kiss N, Tieland M, et al. A holistic perspective on malnutrition in older adults: towards an integrated clinical nutrition research guiding framework. Accepted Clin Nutr 2026 Mar;58:106583. https://doi.org/10.1016/j.clnu.2026.106583. Epub 2026 Jan 22. PMID: 41633064.
[135] Reiter R, Wernly B, Oswald J, Gomahr J, Eberhardt J, Schaffler-Schaden D, et al. How to define low muscle mass: a critical exploration of current definitions supports a reference equation-based approach. Clin Nutr 2025 Dec;55:104–12. https://doi.org/10.1016/j.clnu.2025.10.016. Epub 2025 Oct 31. PMID: 41202660.
[136] Barbat-Artigas S, Pion CH, Leduc-Gaudet JP, Rolland Y, Aubertin-Leheudre M. Exploring the role of muscle mass, obesity, and age in the relationship between muscle quality and physical function. J Am Med Dir Assoc 2014 Apr;15(4):303.e13–20. https://doi.org/10.1016/j.jamda.2013.12.008. Epub 2014 Feb 22. PMID: 24566449.
[137] Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol 1994 Mar;49(2):M85–94. https://doi.org/10.1093/geronj/49.2.m85. PMID: 8126356.
[138] Pavasini R, Guralnik J, Brown JC, di Bari M, Cesari M, Landi F, et al. Short physical performance battery and all-cause mortality: systematic review and meta-analysis. BMC Med 2016 Dec 22;14(1):215. https://doi.org/10.1186/s12916-016-0763-7. PMID: 28003033; PMCID: PMC5178082.
[139] Lekan DA, Collins SK, Hayajneh AA. Definitions of frailty in qualitative research: a qualitative systematic review. J Aging Res 2021 Jun 2;2021:6285058. https://doi.org/10.1155/2021/6285058. PMID: 34123425; PMCID: PMC8189777.