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Sarcopenic obesity in older adults: aetiology, epidemiology and treatment strategies

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Abstract

The prevalence of obesity in combination with sarcopenia (the age-related loss of muscle mass and strength or physical function) is increasing in adults aged 65 years and older. A major subset of adults over the age of 65 is now classified as having sarcopenic obesity, a high-risk geriatric syndrome predominantly observed in an ageing population that is at risk of synergistic complications from both sarcopenia and obesity. This Review discusses pathways and mechanisms leading to muscle impairment in older adults with obesity. We explore sex-specific hormonal changes, inflammatory pathways and myocellular mechanisms leading to the development of sarcopenic obesity. We discuss the evolution, controversies and challenges in defining sarcopenic obesity and present current body composition modalities used to assess this condition. Epidemiological surveys form the basis of defining its prevalence and consequences beyond comorbidity and mortality. Current treatment strategies, and the evidence supporting them, are outlined, with a focus on calorie restriction, protein supplementation and aerobic and resistance exercises. We also describe weight loss-induced complications in patients with sarcopenic obesity that are relevant to clinical management. Finally, we review novel and potential future therapies

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J.A.B. and D.T.V both researched the data for the article, provided substantial contributions to discussion of the content, wrote the article and reviewed and/or edited the manuscript before submission.

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including testosterone, selective androgen receptor modulators, myostatin inhibitors, ghrelin analogues, vitamin K and mesenchymal stem cell therapy.

Adults over the age of 65 constitute 13% of the global population and are the fastest growing demographic subgroup; this group is expected to reach 2.1 billion people in 2050 (REF[1]). Within this population, obesity has steadily increased[2,3], and in the United States, 38.5% of men and 43.1% of women are currently classified as having obesity[4]. Worldwide, these rising rates presumably offset gains in life expectancy[5], with age-adjusted life expectancy dropping by roughly 0.17 years from 2014 to 2015 (REFS[6–10]).

Sarcopenia, which is the loss of muscle mass and strength or physical function, naturally occurs in ageing. Sarcopenia synergistically worsens the adverse effects of obesity in older adults, resulting in sarcopenic obesity. Sarcopenic obesity is appropriately characterized as a confluence of two epidemics — an ageing population and rising obesity rates[11]. As elevated BMI, functional impairment, increased mortality and reduction in quality of life[10] are observationally associated, addressing sarcopenic obesity is important for preventing longterm disability in the older adults at high risk[12]. In this Review, we describe the aetiology and pathogenesis of sarcopenic obesity, as well as the associated adverse outcomes for aged individuals beyond reduced function and mortality, and highlight evidence-based and novel therapies targeting this high-risk population.

Biological pathways to sarcopenic obesity

Age-related changes in body composition.

Multiple factors are responsible for changes to body composition with ageing. Body fat increases until the seventh decade of life and thereafter decreases[13,14]. Vertebral compression results in a reduction in height[15], which affects anthropometric measures such as BMI. Muscle mass declines after peaking in the fourth decade[16], such that weight is mostly gained as fat rather than lean mass. This age-related reduction in lean mass[17,18] accounts, in part, for reduced resting metabolic rates[19]. Other aetiological factors that cause a decline in resting metabolic rates include reduced physical activity[20], reduced mitochondrial volume and reduced oxidative capacity[21,22]. Age-related decreases in the components of total energy expenditure (such as, resting metabolic rates, thermic effect of food and physical activity) contribute largely to the gradual increase in body fat.

The age-related decline in resting metabolic rates can also result from factors independent of changes to body composition, such as adaptive thermogenesis[23,24], which is considered a defence mechanism against weight loss[25]. The reduction in energy expenditure as we age is not proportionally associated with a reduced drive to eat, which furthers fat build-up and leads to small yearly positive changes in energy balance that might lead to weight gain[25–27]. Considerable inter-individual variability to weight loss suggests that adaptive thermogenesis plays a part in energy balance[28] in sarcopenic obesity. Muscle mass loss with ageing[29] correlates with decreased resting metabolic rates and metabolic adaptation, which perpetuates the development of obesity[30–32]. As most individuals with sarcopenic obesity are sedentary, small changes in their muscle mass can markedly alter daily energy

expenditure, which in turn affects adaptive thermogenesis and exacerbates a vicious cycle in their metabolic development[33–36].

Sex-specific hormonal changes: oestrogen and testosterone.

Sex-specific changes in muscle and fat composition are partly due to age-related changes in oestrogen and testosterone. In women, menopause increases body weight and fat mass, specifically in visceral areas[37], but decreases fat-free mass[38]. This shift in fat deposition to the centre of the body (which accounts for 15–20% of total fat stores) expands waist circumference and reduces muscle mass[38–40]. Oestrogen can attenuate these changes[41] by modulating inflammation in skeletal muscle through satellite cell activation[42,43].

In males, testosterone promotes muscle regeneration through satellite cell activation[44,45]. Testosterone levels decline by approximately 1% per year, which can negatively affect muscle mass and fat distribution in ageing[46]. Testosterone levels in the highest quartile (496–1,340 nmol/l) are associated with reduced lean muscle loss[47] and reduced visceral fat redistribution[48] in older men aged ≥65 years and in individuals with obesity[49]. Testosterone increases muscle protein synthesis by increasing amino acids utilization in skeletal muscle and increases androgen receptor expression[44,45,50]. Current data on supplementation for muscle strengthening are conflicting[51,52]. A 2016 study reported that treatment with testosterone for 1 year did not improve physical function in men >65 years of age with age-reduced levels of testosterone (serum testosterone concentration <275 ng/dl)[53]. Levels of dehydroepiandrosterone sulfate, the biological precursor of testosterone, also decrease with age in both men and women[54,55] (for a comprehensive review on the effects of testosterone on body composition see REF[56]).

Inflammatory pathways.

A number of inflammatory pathways are common to muscle and visceral fat. Obesity activates macrophages, mast cells and T lymphocytes, promoting a low-level inflammation that results in the secretion of tumour necrosis factor (TNF), leptin and growth hormone (GH)[57–59]. All such secretory changes lead to insulin resistance, which is increased by muscle catabolism[60], promoting gain in fat mass and a loss of muscle mass[57]. Leptin upregulates the pro-inflammatory cytokines IL-6 and TNF, which results in a reduction in the anabolic actions of insulinlike growth factor 1 (IGF1)[61]. This reduction in IGF1, along with the age-related reductions in testosterone, increases the likelihood of incident frailty[62]. Elevated cytokine levels observed in hypogonadal states are associated with truncal obesity, which exacerbates the development of sarcopenia[44,45]. Adiponectin is negatively correlated with age and obesity and counters the effects of leptin. Elevated TNF directly inhibits adiponectin[63], arresting muscle protein synthesis and mitochondrial processes[64]. Obesity also induces leptin resistance, promoting reduced muscle fatty oxidation and ectopic fat deposition[65,66].

Myocellular mechanisms.

A number of mechanisms might explain the reduction of muscle mass and strength in sarcopenic obesity, including type II muscle fibre atrophy, reduction in motor neurons, collagen deposition and fibre necrosis[67–70]. Older adults (those ≥65 years) are at risk of

developing anabolic resistance owing to reduced post-prandial amino acid availability, reduced muscle perfusion and a reduced digestive capacity resulting from splanchnic sequestration of amino acids[71].

Ageing stimulates the infiltration of fat into muscle[72,73], which might negatively affect sarcopenia[74], as described below, and obesity promotes the deposition of fat in the liver, heart, pancreas and skeletal muscle (FIG. 1). The deposition of intramyocellular lipids promotes lipotoxicity and inflammation and induces dedifferentiation of mesenchymal adipocyte-like progenitor cells that express fatty tissue genes[75]. The regeneration potential of muscle is impaired, which might promote fibrosis, thereby promoting insulin resistance[76–79], partially owing to impaired mitochondrial fatty acid oxidation and increased lipolysis[76,80]. A reduction in the number of mitochondria and elevated production of reactive oxygen species occur in muscle following the deposition of intramyocellular lipids. This process can impair muscle function and might reduce the oxidative capacity of muscle[81]. Potential mechanisms explaining these changes include age-related reductions in protea some activity, deficiencies in ubiquitylation and autophagy and impairments in removing degraded proteins and end products[82–84].

Pro-inflammatory lipids also secrete paracrine hormones and cytokines that promote a feedforward cycle by producing intramyocellular lipids. This lipotoxicity impairs muscle fibre contractility and interferes with muscle protein synthesis, exacerbating sarcopenia[82–84]. Lipid deposition can also occur in spaces previously occupied by muscle, impairing new muscle tissue growth. One study reported an increase in intramyo cellular lipid deposition after young, healthy men and women aged 19–28 years were exposed to 30 days of leg disuse, which resulted in lower extremity muscle mass loss[85]. This finding could be due to skeletal muscle preferentially depositing fat for a source of energy as opposed to glucose[86,87]. While muscle cells can regenerate through satellite mesenchymal progenitor cells, their numbers decline with age, which contributes to reduced muscle function[88,89]. Myostatin can be upregulated in skeletal muscle, inhibiting muscle genesis[90]. In sum, individuals with obesity are at risk of inflammation, which can lead to the preferential mobilization of muscle instead of fat[91].

The role of exercise.

Exercise can affect hormonal balance, reduce oxidative stress, induce mitochondrial synthesis, alter immunological and motor function and improve muscle oxidative capacity[92–95]. Increased muscle protein synthesis with exercise sensitizes muscle insulin action and promotes anabolism[96–100]. Sarcopenia is associated with reduced muscle protein synthesis, partly owing to decreased anabolic stimulation (which can result from a lack of regular exercise). Aerobic exercise[101], resistance training[102–104] and their combination[105] increase muscle protein synthesis in older adults despite age-related decreases in anabolic signalling[106–109]. Muscle satellite cells located between myofibres and their surrounding basal lamina are recruited into existing muscle fibres by physical activity[110,111]. Muscle injury activates satellite cells to regenerate muscle by releasing IGF1, fibroblast growth factor and mechano growth factor, all of which stimulate the differentiation and proliferation of muscle satellite cells[112,113]. Circulating inflammatory biomarkers, including IL-6, C-

reactive protein and TNF, are downregulated by aerobic exercise and strength training, although the relationship is less clear with combined aerobic and resistance activities[114–118]. Elevated levels of IL-6 and TNF and low levels of IGF1 are associated with reduced muscle mass, reduced muscle strength, reduced muscle mobility and reduced muscle function, suggesting a marked role of exercise in attenuating these muscular changes with ageing[117,119,120].

Aerobic activity can improve the oxidative capacity of muscle by counteracting the negative effect of intra- myocellular lipids and accelerating lipolysis, which results in an increase in capillary density[121]. The synthesis of mitochondria in myocytes is upregulated to meet the demands associated with an increase in capillary density, which in turn leads to increased oxygen extraction and metabolism[122] through the induction of calcium and metabolic signalling pathways such as those involving 5'-AMP-activated serine/threonine-protein kinase (AMPK) and sirtuins[123]. These mediators stimulate mitochondrial production, which promotes improved fatty acid metabolism[124].

Myocyte apoptosis can be abrogated by physical activity[125,126], while mechanisms of cellular quality control, including autophagy, mitophagy and mitochondriogenesis[127], contribute to the development of sarcopenic obesity and could be potential targets for therapy. Reduced cytokine production can lead to improved glucose metabolism, insulin sensitivity and muscle protein synthesis, which might dampen the progression of sarcopenic obesity.

Ageing leads to reduced cardiopulmonary status owing to inefficient oxygen extraction and a concomitant reduction in metabolically active muscle mass[128]. Peak oxygen consumption is potentially inversely related to frailty[129,130], suggesting that improvements in VO2 max following aerobic training counteract frailty[131,132]. Following a 12-week diet–exercise intervention in male and female frail adults with obesity aged 69 ± 1 years, investigators reported reduced skeletal muscle levels of mRNA for *TLR4, IL6* and *TNF*, increased mechano growth factor mRNA and increased fat-free mass in the exercise group, and these results were independent of weight loss[133]. Separately, resistance exercises resulted in increased *TNF* mRNA and protein from skeletal muscle biopsy samples in frail adults[134]. Expression of skeletal muscle TNF, IL-1β and nitric oxide synthase, inducible in patients with heart failure was reduced following aerobic training, suggesting that aerobic exercise has anti-inflammatory effects[135]. Furthermore, a 12-week aerobic and resistance programme increased serum levels of ghrelin and adiponectin by 47% and 55%, respectively, and reduced circulating levels of $CD14^+$ and $CD16^+$ inflammatory monocytes, adding additional evidence to the anti-inflammatory effects of exercise[136].

Resistance exercise increases the number and size of fast twitching muscle fibres (IIA and IIX), which improve glucose metabolism in muscle and muscle protein synthesis[102,103,137–139]. Muscle protein synthesis is also improved by nutrient-stimulated vasodilation and nutrient transport to local muscle myofibrils[112,124]. Muscle fascicle length and muscle tendon stiffness reportedly increased after strength training (leg press and extension) over 14 weeks in a cohort of men and women aged over 65 years[140]. In a study of eight young adults (aged 18–29 years) and seven older adults (aged 67–81 years), isometric

knee extension at varying degrees of maximal voluntary contraction followed by a 6-week resistance programme demonstrated early increases of isometric knee extensor maximal force (which is a marker of voluntary muscle contraction) and increases in motor unit discharge rates (which is a magnitude ofthe speed of neural activation)[141]. Resistance training has also been shown to reduce levels of cytokines, such as resistin, leptin and IL-6 (REF[142]).

Leptin and adiponectin stimulate and inhibit, respectively, the deposition of intramuscular lipids (Fig. 1); however, defining their precise roles in physical activity continues to be challenging. For instance, the concentration of leptin in the systemic circulation is suppressed following resistance exercise[143] but also in individuals with overweight or obesity following a physical training intervention[143–145]. Resistance training seems to be more efficient in reducing leptin levels than aerobic training alone[146], though conflicting evidence exists[147]. A study into the effects of aerobic activity in patients who had recovered from breast cancer reported that individuals who were randomized to the aerobic exercise group demonstrated reductions in insulin and leptin and increases in the adiponectin:leptin ratio but no significant changes in adiponectin compared with participants in the usual activity group[148]. These results parallel those from studies in inactive men aged 65–82 years who were overweight. Investigators assigned participants to partake in varying intensities of resistance exercises. The investigators reported no alterations in concentrations of leptin, but participants had intensity-dependent changes in adiponectin[139,145] — high-intensity resistance training led to an increase in the concentrations of adiponectin for 24 hours after exercise in inactive adults who were overweight[139].

Summary of mechanisms.

The core biological factors that underlie sarcopenic obesity are age-related changes in metabolism and body composition and the presence of concurrent environmental obesogenic factors and physical illnesses that develop with the ageing process. Incremental metabolic changes over time promote fat deposition with a pro-inflammatory cascade of events. In tandem, crosstalk with biologically active muscle tissue leads to a negative feedback cycle that promotes progressive gain in fat mass and loss of lean mass and muscle strength. In a pre-frail and frail population, a strategy combining physical training and nutritional intervention was more likely to result in stable or reduced IL-6 levels in individuals who demonstrated improved physical performance than in those with lower physical performance[149]. Calorie restriction and physical activity might impede and halt these processes. While we have a better understanding of the role of physical activity in reversing sarcopenic obesity, the effect of a lifetime of inactivity on the development of sarcopenic obesity is still unclear.

Assessing body composition

Gold standard methods to assess body composition, including CT and MRI, allow clinicians to accurately analyse adipose tissue and muscle mass[150] (FIG. 2). Steven Heymsfield and colleagues have argued the importance of using measures beyond muscle mass when diagnosing sarcopenic obesity[151]. The strengths and limitations of each method to assess

body composition to diagnose sarcopenia and sarcopenic obesity have been reviewed elsewhere[152–155].

Dual-energy X-ray absorptiometry (DXA) is recommended for the assessment of appendicular lean mass in the diagnosis of sarcopenia[156] owing to its affordability, availability and diagnostic accuracy[157]. DXA correlates well with gold standard measures of body composition, such as MRI, and with bioelectrical impedance, which can also measure fat and segmental muscle mass[158–160]. Assessments of lean mass are highly reproducible and can be used for clinical monitoring, while a detailed assessment of visceral fat is not as accurate[150,161–163]. In a 2013 report by the International Society for Clinical Densitometry, the recommendation to perform DXA for assessing total body composition and for a regional analysis of fat and muscle in patients with muscle weakness or poor physical function was categorized as fair[157].

Bioelectrical impedance is a simple, non-invasive, inexpensive, rapid and portable diagnostic tool. Reductions in muscle mass result in an increase in connective tissue[164–166] that can interfere with the assessment of muscle mass. Variable hydration status also impacts its accuracy[167]. To use bioelectrical impedance, tissue hydration must be constant and the body must be cylindrical[168,169]; both assumptions are challenged in sarcopenia and obesity. Thus, an overestimation of the total volume of water and extracellular fluid in the body leads to aberrant values. Further, whether the bioelectrical impedance prediction equations are valid when applied to different ethnic groups is unclear[170], despite specific adaptations and adjustments[171–173]. Biological differences between different ethnic populations might influence the relationship between skeletal mass and resistance[174]. Other notable limitations include large standard errors and population specificity[175]. Cut-off points might not capture such determinants, particularly when levels of fat mass are high, which questions the utility of bioelectrical impedance for the assessment of body composition by professional societies[169] who recommend adjustment to population-specific, age-appropriate equations[169,176]. Further validation of bioelectrical impedance results is needed in individuals aged ≥80 years, as they are at increased risk of sarcopenic obesity[177,178]. Of note, current bioelectrical impedance systems permit an improved protocol that involves segmental analyses in clinical settings, as reviewed elsewhere[179].

An evolving definition

The current definitions of sarcopenic obesity are based on the individual definitions of sarcopenia and obesity (TABLE 1), but presently there is no consensus that defines the cut-off points for either of these diseases, which makes arriving at an accurate diagnosis of sarcopenic obesity challenging. The term sarcopenia is defined differently throughout the literature (TABLE 1), leading to confusion in the medical community and preventing any inter-study comparisons. Without a consistent definition of sarcopenia, investigators are limited in their ability to identify participants for interventional research.

Current definitions of sarcopenia incorporate variations of muscle mass, strength and anthropometric measures including mid-arm and calf circumference. The International Working Group for the Study of Sarcopenia (IWGS) provided a consensus definition for

sarcopenia[180] as the combination of low whole-body or appendicular lean mass and poor physical functioning (gait speed ≤1 m/s). The European Working Group for the Study of Sarcopenia (EWGSOP)[156] identified sarcopenia cut-off points and tools for its measurement. They recognized the lack of diagnostic criteria for sarcopenia but integrated low muscle mass and function (strength or performance) in their terminology, believing that the relationship between these two measures is not linear nor bidirectional[73,156,181]. This algorithm was meant for clinical application using gait speed (<0.8 m/s) before muscle mass or strength measurement. EWGSOP recommended that muscle mass is assessed by DXA or bioelectrical impedance, using mathematical thresholds and formulas presented in their consensus document. Hand grip strength cut-off points are dependent on an individual's BMI.

The Foundation for the National Institutes of Health (FNIH) Sarcopenia Project[182] suggested a causal, indirect relationship between muscle mass and function in their definition of sarcopenia. The FNIH suggested testing for low lean mass using DXA (defined using appendicular lean mass) and reduced muscle function using handgrip strength. FNIH stated that sex-specific cut-off points could be adjusted for BMI. The separate criteria for muscle mass and strength implied the need to target interventions for individuals with low mass or low strength. FNIH deliberately avoided the term sarcopenia to differentiate between qualitative (strength) and quantitative (mass) components.

These definitions provide excellent negative percent agreements on the absence of sarcopenia; however, there is poor overlap in identifying individuals with sarcopenia[183]. Ethnic-specific differences result in inaccurate prevalence estimates[184]. The Asian Working Group for Sarcopenia[185] provided guidance for individuals of Asian descent. They suggested using handgrip strength and gait speed for initial testing and/or screening followed by the EWGSOP approach for muscle mass measurement, strength and physical performance, with different, lower, cut-off points (TABLE 1).

Obesity is defined as an unhealthy excess body fat that increases the risk of medical illness and mortality[186]. As with sarcopenia, no consensus defines obesity cutoff points. Instead, cutoff points are premised on sex-specific, whole-body DXA. The American Association of Clinical Endocrinology[187] recommends the use of the WHO body fat thresholds for the diagnosis of obesity — (men >25% body fat and women >35% body fat). The WHO thresholds also used BMI for obesity (≥30 kg/m^2) or waist circumference (men ≥102 cm and women ≥88 cm) as a visceral fat surrogate. The International Society of Clinical Densitometry, the American Heart Association and The Obesity Society all recognize the lack of specific thresholds, while the American College of Sports Medicine suggests cut-off points of 28% and 35% for men and women, respectively[188,189]. Others applied mathematical body fat thresholds of reference populations to provide sufficient power that might not be based on distal outcomes[190,191]. Body fat has better predictive validity on the development of the metabolic syndrome[192] and cardiovascular disease risk[193] than BMI.

Body composition modalities have advantages and disadvantages in assessing changes in fat or muscle distribution. We suggest DXA for research purposes, as it is more readily available to provide the necessary information. If DXA is unavailable, a stand-alone or

portable bioelectrical impedance system can be used. We advocate caution when using bioelectrical impedance equations; they must account for age, sex, levels of physical activity, body fat and ethnicity. Feasible anthropometric indices as surrogates for adiposity, including BMI and waist circumference, have poor sensitivity. In one study, BMI correctly classified 41.0% of men and 45.1% of women as being obese and waist circumference correctly classified 64.2% of men and 81.0% ofwomen as being obese[194]. We believe that anthropometric measures should be used with great caution when assessing body composition and only if other imaging is unavailable.

With ageing, fat preferentially accumulates both viscerally and ectopically rather than as abdominal subcutaneous fat. Rapid accumulation of intra-abdominal fat is exacerbated by physical inactivity, hormonal changes, reduced responsiveness to thyroid hormone and leptin resistance[186]. As central fat accumulation predominates, and loss of muscle occurs peripherally, the prototype of sarcopenic obesity is easily recognized (‘fat frail’). This prototype is not inconsistent with intramuscular fat accumulation, which contributes to inflammation, mitochondrial dysfunction and insulin resistance within muscle and reduces muscle protein synthesis[74,195].

Prevalence of sarcopenic obesity

A shortcoming in ascertaining accurate prevalence rates for sarcopenic obesity is the lack of a consistent definition for either sarcopenia or obesity. A review of eight definitions for sarcopenic obesity noted a 19-fold to 26-fold variation in sex-specific rates[178]. The analysis showed that definitions for sarcopenia were highly dependent on mathematical thresholds, reference populations and muscle mass definitions. A comparison of the rates of sarcopenic obesity using bioelectrical impedance to define sarcopenia and percentage of body fat to define obesity showed increasing rates with age[196]. In another study, the authors identified individuals with a BMI ≥35 kg/m^2 and evaluated the prevalence of sarcopenic obesity using DXA-defined body fat in 120 predominantly female adults (46.9 ± 11.0 years). The investigators reported rates that ranged from 0–84.5% in women to 0–100% in males depending upon the definition applied[197]. In a population-based cohort using National Health and Nutrition Examination Survey (NHANES) data that applied the aforementioned FNIH criteria for appendicular lean mass, rates of sarcopenic obesity were 12.6% in men and 33.5% in women. The rates of sarcopenic obesity increased with age, reaching 48.0% and 27.5% in females and males, respectively, in those aged over 80 years[198]. In a cohort of individuals from South Korea’s Korean Sarcopenic Obesity Study, an ongoing epidemiological, prospective cohort of healthy volunteers aged 20–80 years, prevalence of sarcopenic obesity ranged from 1.3–15.4% in men to 0.8–22.3% in women[199].

The prevalence of low muscle strength with obesity is less clear. Data from the InCHIANTI study noted rates of 3.2–8.7% using the low knee extensor strength with either high BMI or waist circumferrence[200]. Investigators from the Cardiovascular Health Study used low grip strength and high waist circumference to define low muscle strength and obesity. Rates approached 11.1%[201], while data from FNIH classified 4.1% of men and 14.0% of women as having sarcopenic obesity using high BMI and low grip strength as measures of obesity and low muscle strength, respectively[202]. Overlap using different diagnostic criteria of

sarcopenic obesity is limited[183] but ranges from 2.1% to 4.1%. These findings are also observed when evaluating the overlap of sarcopenia-only definitions, which is less than 50%[183].

Consequences of sarcopenic obesity

Cross-sectional and longitudinal studies are subject to the same definitional challenges as prevalence studies. Despite the crucial need for a consensus definition, here we describe the clinical importance of sarcopenic obesity.

Disability or impairments.

Richard Baumgartner and colleagues were the first to characterize the association between sarcopenia (as defined by appendicular lean mass) and percent body fat on incident disability[191]. In their analysis, when compared with a healthy body composition, sarcopenic obesity was associated with a relative risk of incident disability over 8 years that was 2.63 (95% CI 1.19–5.85). In addition, when compared with a healthy body composition, a combination of obesity, as defined by percentage of body fat, with low muscle mass represented odds ratios of difficulty ascending and descending stairs that were 2.60 and 2.35 higher, respectively[203]. The Concord Health and Aging project[204] used the FNIH criteria for sarcopenia with elevated body fat to evaluate frailty and reported that sarcopenic obesity resulted in an increased risk of frailty (OR 2.00, 95% CI 1.42–2.82), activity of daily living disability (OR 1.58, 95% CI 1.12–2.24) and instrumental activity of daily living disability (OR 1.36, 95% CI 1.05–1.76). The above results contrast with an earlier cross-sectional study that defined sarcopenic obesity by low muscle mass and elevated body fat and did not demonstrate differences in disability compared with controls[205]. Another group used DXA to assess body mass and its relationship with physical capacity and found mixed results[188]. Data from the Quebec Longitudinal Study applied definitions of sarcopenic obesity comprising Baumgarter's definitions of sarcopenia and obesity as defined by body fat[191] and found global physical capacity scores were no different between obese groups (sarcopenia versus non-sarcopenia ($P = 0.14$ in men and $P = 0.19$ in women)), but lower scores were observed than with the non-sarcopenic non-obese group ($P < 0.05$)[188]. Women with sarcopenia alone had higher scores than people with obesity without sarcopenia and than individuals with obesity and sarcopenia ($P < 0.01$).

Muscle strength is a stronger predictor of long-term functional decline than muscle mass[206]. Data from the Osteoarthritis Initiative showed that a combination of low knee extensor strength with high BMI was associated with reduced gait speed and reduced Late-Life Function and Disability Index and Short Form-12 scores[207], which indicate a lower degree of physical function[208] and decreased self-reported health status[209].

Low handgrip strength and elevated BMI were strongly associated with an increased risk of functional decline[210]. In addition, data from the UK Biobank study found an association between high BMI, low grip strength and reduced long-term physical activity[211]. Data from the InCHIANTI study showed that mobility disability trajectories and gait speed over 6 years were steepest in individuals with obesity as defined by BMI and low muscle strength[200]. An increase in mobility disability and risk of hospitalization (OR 2.10, 95% CI

1.14–3.88) was associated with low muscle strength and abdominal obesity in an 11-year follow-up study (OR 1.36, 95% CI 1.04–1.78). High BMI and low muscle strength were related to limitation in mobility at 2-year follow-up (OR 3.88, 95% CI 1.08–13.91)[212]. In another study, abdominal visceral fat and quadriceps muscle area served as markers for central obesity and sarcopenia, respectively, and were associated with postural instability[213].

Metabolic impairments.

A study from the South Korean NHANES conducted an evaluation of sarcopenia (as defined by muscle mass) with obesity (as defined by a BMI ≥25 kg/m^2). The authors reported that individuals with sarcopenic obesity were at an increased risk of dyslipidaemia (OR 2.82, 95% CI 1.76–4.51)[214] and had significant positive associations with insulin resistance as defined by HOMA scores and triglycerides[215]. In another study, low handgrip strength and high waist circumference and/or BMI were significantly associated with elevated levels of IL-6, C-reactive protein and IL-1 (REF[57]) but conflicted with results using the FNIH criteria to define low lean mass[216]. By contrast, low muscle strength (as defined by the FNIH criteria) with an elevated BMI was not associated with differences in metabolic components among groups of postmenopausal women aged 55–75 years[217].

Comorbidities.

Individuals with sarcopenic obesity have a higher risk (OR 3.51, 95% CI 2.15–5.75) of radiographic knee osteoarthritis[218] than individuals in the non-sarcopenic obesity group. One study reported that risk of falling was highest in individuals with low muscle mass and/or strength with obesity as defined by percentage of body fat[219], but spine and total BMD were lower in individuals who were sarcopenic obese and dynapenic obese than in individuals with obesity alone[220]. A study that evaluated participants over 6 years reported that the combination of obesity as defined by BMI and low handgrip strength suggested an increased risk of type 2 diabetes mellitus (OR 3.57, 95% CI 2.04–6.24), an association that was not observed with cardiovascular disease[221]. The rate of depression has been reported as being highest in patients with sarcopenic obesity (defined as low handgrip strength and obesity defined by BMI) (OR 1.79, 95% CI 1.10–2.89) over 4 years[222] compared with non-obese individuals in the highest tertile of grip strength. These data were confirmed in another study that defined sarcopenic obesity as low muscle mass or muscle strength, with obesity defined by percentage of body fat[223]. Individuals with low muscle mass and high waist circumference had worse psychological health and higher stress than individuals with normal muscle mass and normal waist circumference. Finally, an area of interest for researchers now is the role of sarcopenic obesity in cancer[224], which further demonstrates its relationship with adverse health events.

Mortality.

Epidemiological studies investigating the relationship between sarcopenic obesity and mortality have reported conflicting results[198,204,221,225–228]. A longitudinal study from 2017 demonstrated small differences in all-cause mortality between obesity as defined by both BMI and low muscle strength and low muscle strength alone[229]. Others showed that mortality was significantly elevated in people with sarcopenic obesity, which was defined using mid-arm circumference (HR 1.46, 95% CI 1.23–1.73) and muscle strength with waist

circumference (HR 1.23, 95% CI 1.09–1.38)[230]. Sarcopenic obesity (defined by muscle mass assessed by bioelectrical impedance and percentage of body fat) was associated with an increased mortality (HR 1.29, 95% CI 1.03–1.60)[230]. Muscle strength also affects mortality independent of muscle mass. Investigators from the Health, Aging and Body Composition study reported that low quadriceps strength was associated with increased mortality[231]. Similar results were reported in another study that showed that reduced leg isometric strength and increased waist circumference were associated with increased mortality[232] (HR 2.46, 95% CI 1.34–4.52). These results were further corroborated in the MiniFinland Health Examination Study, which also showed that reduced muscle strength is associated with increased mortality (HR 1.30, 95% CI 1.09–1.54)[228]. Cutoffs specific to individuals from South Korea predicted higher mortality risk than the FNIH cut-off[233]. Finally, a recent meta-analysis found that mortality was highest in patients with sarcopenic obesity (HR 1.24, 95% CI 1.12–1.37) compared with healthy individuals, but the authors acknowledged that they had used multiple definitions of sarcopenic obesity in their study[230].

Quality of life.

Few studies have evaluated the effect of sarcopenic obesity on quality of life. Sarcopenic obesity (as defined by low appendicular lean mass normalized for height^2 and increased BMI) was associated with unfavourable scores on the Medical Outcomes Survey[234]. Another study reported no differences in Short Form-36 scores, which provide a measure of quality of life[235], between individuals with obesity and low handgrip strength and individuals with normal indices[236]. The EuroQOL score was dependent on cardiovascular fitness rather than sarcopenic obesity[237]. Future studies need to focus on health-related quality of life and patient-reported outcomes in sarcopenic obesity before we are able to draw firm conclusions.

Institutionalization and health-care utilization.

Few studies, and no known longitudinal studies, have evaluated the relationship between sarcopenic obesity and institutionalization. Peggy Cawthon and colleagues[238] reported that neither sarcopenia nor the components that define weakness increased the risk of hospitalization or short-term nursing facility stay. A population-based cohort study that defined sarcopenia using the EWGSOP criteria found an increased incidence of long-term care certification in patients with sarcopenia[239]. Low muscle mass or strength is causally associated with long-term care placement. The relationship with obesity is clearer, whereby an elevated BMI is associated with admission to a nursing home[240]. Midlife obesity also increases the risk of long-term care placement[241], an association that persists in older adults with obesity[242].

Treatments for sarcopenic obesity

Lifestyle interventions, including calorie restriction and physical activity, are hallmarks of treating sarcopenic obesity (TABLE 2). Few clinical trials specifically focus on sarcopenic obesity[243]; however, intentional weight loss in older adults improves morbidity and physical function[186]. Following a meta-analysis of randomized trials of adults with obesity aged ≥55 years, which had follow-up times of ≥4 years, investigators reported a 16% reduction in

mortality (95% CI 0.71–0.99)[243]. In the United States, while Medicare covers weight loss therapy[244], no major societies outline targeted therapies for sarcopenic obesity[187,245].

Dennis Villareal's work best corresponds to participants with sarcopenic obesity as defined by obesity with evidence of physical frailty[246,247]. In this cohort of patients, weight loss alone or exercise alone improved physical function; however, a combination of weight loss and regular exercise improved physical function and ameliorated frailty more than either intervention alone[246]. Moreover, another study reported that weight loss plus combined aerobic and resistance exercise was the most effective method for improving functional status of adults aged 65 years and older with obesity[247] (FIG. 3). Hung-Ting Chen and colleagues[248] evaluated four groups of individuals with sarcopenic obesity according to different exercise interventions (aerobic, resistance, combined aerobic and resistance), and controls who were prohibited from engaging in exercise, and demonstrated that individuals in the resistance training group had the greatest improvements in strength.

Dietary strategies: calorie restriction and protein supplementation.

Dieticians are multidisciplinary team members integral to developing lifestyle interventions whose delivery is often grounded in behavioural theories and motivational interviewing[249]. Weight loss trials tend to restrict calories by 500–1,000 kcal per day[250]. Initial weight loss goals of ~0.5 kg per week can lead to an 8–10% loss in 6 months, with most patients sustaining an 8–10 kg loss in weight during this period of time. We are unaware of specifically tested diets in sarcopenic obesity. As in other populations, diets in patients with sarcopenic obesity lead to weight loss[251], with adherence to a diet predicting weight loss success[252].

Strategies that optimize protein anabolism during weight loss, such as consumption before exercise or spreading out of protein during the day, can prevent weight loss-induced sarcopenia[247,250]. Energy deficits created by acute calorie restriction could downregulate muscle protein synthesis and increase proteolysis, which contributes to reduced muscle mass[247,253,254]; however, chronic calorie restriction does not seem to reduce muscle protein synthesis, but it might increase it[105,255]. Increased dietary protein stimulates muscle protein synthesis[71,256]. The source of protein, timing of intake[257] and specific amino acid constituents can also be factors in increasing muscle mass and strength. High protein intake (1.2 g of protein per kg per day) during weight loss might eliminate the beneficial effect of weight loss on insulin sensitivity in skeletal muscle[258]. Distributing protein intake throughout the day[259] or pulse feeding at main meals[260] could be beneficial for the stimulation of muscle protein synthesis in patients with sarcopenic obesity.

The PROT-Age group recommends 1.0–1.1 g/kg protein per day in divided doses, acknowledging that a 'one size fits all protein recommendation' fails to account for the complex physiological changes of ageing[71]. Generally, 25.0–30.0 g of protein containing 2.5–2.8 g of leucine can slow frailty[261,262]. Early pilot studies demonstrate that meals enhanced with protein and coupled with a weight loss intervention improve physical function[263]. For example, a high- protein diet in conjunction with resistance training preserved appendicular lean mass during weight loss[264]. In a pilot study, participants with sarcopenic obesity undergoing a weight loss programme augmented by a high-protein diet

showed improvements in muscle strength and Short Form-36 scores (REF[265]). We need further evidence to support the effect of supplemental protein on functional outcomes in patients with sarcopenic obesity[266–268]. High-protein diets consisting of 1.0–1.2 g per kg per day should be prescribed with caution to prevent renal dysfunction[269] as evidenced by observational data[270–272], as higher doses have recently demonstrated no changes in lean mass[273]. We recommend the importance of ensuring adequate protein intake in countering weight loss-induced sarcopenia in individuals with sarcopenic obesity participating in programmes. Careful medical monitoring and dietary planning are required when optimizing protein intake while limiting calorie restriction, and this often needs to be administered under the auspices of a registered dietician with expertise in this population. The challenges in limiting calories are recognized, and hence we believe that alternative approaches are crucially needed to augment muscle mass and strength.

Resistance training and aerobic exercise.

Several professional societies[3,187,245,274] recommend that all older adults engage in at least 150 min per week of moderate to vigorous aerobic exercise, with two sessions of resistance exercises consisting of strength training, flexibility and balance. Aerobic exercise and resistance training are safe, even in patients who are at a high risk of falling[275]. Aerobic exercise improves cardiorespiratory fitness and has beneficial effects on mortality[276–278]. Even minimal resistance exercise improves muscle strength and mass[279,280], and progressive resistance exercises counter sarcopenia by increasing strength. As with any exercise programme, clinical consultation and medical clearance is advised.

A Cochrane review reporting physical outcomes of progressive resistance exercises for older people identified 33 trials that significantly improved physical abilities (standardized mean difference 0.14, 95% CI 0.05–0.22) in 2,172 participants, with improvements in muscle strength (standardized mean difference 0.84, 95% CI 0.67–1.00) in 73 trials[281] (3,059 participants). The LIFE study[282], a structured, moderate-intensity physical activity programme, demonstrated reduced persistent mobility disability (HR 0.72, 95% CI 0.57–0.91) compared with a health education programme. Evaluation of four groups of men and women aged 60–75 years with sarcopenia demonstrated that 2 days of high-resistance concentric exercise with one bout of low-resistance exercise increased muscle expression of pro-inflammatory cytokine receptors, maximized muscle mass and total lean mass and improved knee extension[283]. A secondary subset analysis ofthe LIFE pilot study found that the short physical performance battery — an objective assessment tool for the evaluation of lower extremity function (higher score equals better function)[284] — of patients with sarcopenia improved from 7.4 to 8.7 when compared with the successful ageing group[285]. Although the LIFE study is considered a standard for physical activity in older adults[282], we acknowledge its lack of evidence in sarcopenic obesity and the lack of power in this pilot trial.

High-intensity resistance training combined with short resting intervals improves body composition, muscle and functional performance in men aged 68 ± 4.1 years[286]. High-speed resistance training over 12 weeks induced greater improvements in muscle power and functional capacity than low-speed training[287]. In this study of 60 women of Hispanic

descent aged over 60 years, high-speed training consisted of individuals performing exercises as fast as possible (1 second or less) and was compared with low-speed resistance training (3 seconds). The authors of this study also demonstrated that two versus three training sessions per week for 12 weeks of high-speed resistance training were equally effective for improving physical performance and quality of life[288]. High-velocity knee extension training at 240° of movement per second increases the expression of *MYH6* and *MYH9* mRNA and improves muscle enhancement[138].

The effect of power training (moving resistance at higher speed) on function requires further investigation[289,290]. A pilot study of patients with sarcopenic obesity (defined using EWGSOP criteria for sarcopenia and BMI for obesity) were randomized to a strength and hypertrophy group or a high-speed circuit group for 15 weeks[289]. High-speed circuit training was associated with nonsignificant improvements between groups in short performance physical battery (mean difference 1.1, 95% CI–0.1 to 2.4; $P = 0.08$) and power (mean difference 158 W, 95% CI 2–315; $P = 0.01$). We note that while these trials enrolled patients with sarcopenic obesity in each arm, they are small, short-term studies.

Other exercise therapies, including tai chi or yoga, could potentially be beneficial; however, to our knowledge, no studies have evaluated these modalities in sarcopenic obesity. Tai chi and The Otago Exercise Programme (a home-based balance and strength fall prevention programme) have been shown to be effective at preventing falls and improving physical function, mobility and functional measures of lower extremity strength in older adults[291]. A meta-analysis of 18 trials ($n = 3,824$), including study participants greater than 65 years who participated in tai chi for a minimum of 4 weeks (range 1–12 months) 1–3 times per week, demonstrated a reduction in falls of 20% (relative risk (RR) 0.8, 95% CI 0.72–0.88)[292]. In addition, yoga has been shown to improve mobility in participants 60 years of age and older, with no restriction on their characteristics, whose follow-up ranged from 8 to 24 weeks (total duration 8–36 hours of yoga)[293]. A meta-analysis of 28 studies demonstrated a positive effect of aquatic exercises on physical functioning (RR 0.70, 95% CI 0.48–0.92) compared with no training (control group)[294]. Furthermore, the data suggested that aquatic exercises are as effective as land-based exercises (standardized mean difference 0.39, 95% CI 0.12–0.66). Finally, while training until failure might be an approach for muscle strengthening and endurance[295], we generally recommend exercising until fatigue rather than failure, as exercising until failure can increase the risk of musculoskeletal injury.

We advocate individualized exercise treatment for patients with sarcopenic obesity because of the associated medical comorbidity and disability. As previously described, the exercise programme[296] should begin at a fairly low-to-moderate intensity, duration and frequency to minimize injury and maximize adherence; this approach progressively induces exercise adaptations[246,247]. Aerobic activity should target ~65% of the peak heart rate, aiming to reach 70-–85% of peak heart rate over the duration of the exercise regimen. Resistance activities, on the other hand, should focus on 1–2 sets of 8–12 repetitions at ~65% of one repetition maximum, which is defined as the maximal amount of force a person generates in a single repetition, with the aim of advancing to a goal of 2–3 sets of 75% of one repetition maximum over time. These activities are recommended even for frail, older adults[246,247].

Calorie restriction and physical activity.

A trial of older adults with obesity[247] consisted of a hypocaloric diet with an energy deficit of 500–750 kcal per day on average, 1 g high-quality protein, plus either 60 min of progressive aerobic exercise and resistance training or 75–90 min of both aerobic exercise and resistance training, three times a week. The findings demonstrated increases in physical performance test scores (higher score equals higher level of function), more so in the combined aerobic and resistance exercise group (27.9 to 33.4 points (21% increase)) than in the aerobic (29.3 to 33.2 points (14% increase)) or resistance group (28.8 to 32.7 points (14% increase)) alone. Other activities for weight loss therapy in older adults reflect similar components and outcomes and have produced similar findings[250,297]. There are few multicomponent studies in patients with sarcopenic obesity. A meta-analysis showed that aerobic exercise and resistance were useful tools to preserve fat-free mass in adults aged ≥50 years who were engaged in a moderate energy restriction-induced weight loss programme[298]. Increased muscle mass and reduced total and visceral fat over an 8-week intervention were observed in predominantly female individuals, whose mean age was 69 years, with sarcopenic obesity engaged in resistance training[248]. A resistance programme of participants fulfilling the EWGSOP criteria for sarcopenia and obesity as defined by percentage body fat demonstrated reduced rates of sarcopenia and improved physical function following three training sessions weekly over a 12-week period compared with a control group receiving no intervention[297]. A combined treatment of diet and exercise improved physical function in frail older men with obesity aged ≥65 years for 1 year, despite resulting in a reduction in oestradiol levels and only a modest increase in testosterone levels[299].

Combining both diet and exercise can positively improve adipose markers of adiponectin and significantly reduce leptin levels. In response to a 6-month randomized diet and exercise intervention, levels of C-reactive protein and IL-6 decreased in older adults (age ≥65 years) with obesity (BMI ≥30 kg/m^2) compared with controls (−2.5 versus 0.8 mg/l ($P < 0.05$) and −2.4 versus 1.6 pg/ml ($P < 0.05$), respectively)[300]. Yet, the positive effects on circulating cytokines, adiponectin and TNF were due to diet and not exercise[301], which is consistent with the direct effect of exercise on or within muscle not being reflected in the circulation[133,134]. A study that investigated the effect of diet or diet and exercise interventions in individuals aged 50–79 years with overweight or obesity reported that levels of adiponectin increased in individuals with overweight or obesity compared with controls (diet resulted in 9.5% increase in adiponectin ($P < 0.001$), and diet and exercise resulted in a 6.6% increase in adiponectin ($P < 0.001$)). Furthermore, levels of leptin in individuals with obesity or overweight decreased by 27.1% in the diet group and 40.1% in the diet and exercise group[302].

Investigators in the LIFE pilot study reported that individuals in the physical activity group had reductions in IL-8 but no differences in other inflammatory markers[303]. A 12-week aerobic exercise regime in combination with a low glycaemic index diet or high glycaemic index diet resulted in reductions in leptin levels in two groups of participants who had elevated levels of adiponectin, suggesting that the reductions in leptin were a result of exercise training and independent of dietary glycaemic index[304]. Another study reported that

in postmenopausal women with overweight or obesity, adding aerobic activity to calorie restriction increased serum concentrations of adiponectin (6.9 μg/ml for individuals in the group without aerobic activity versus 8.5 μg/ml for individuals in the group with aerobic activity ($P < 0.001$))[305]. Levels of adiponectin were also elevated following a multicomponent, randomized lifestyle intervention study that investigated the mRNA expression of adiponectin and its receptor in skeletal muscle in adults with impaired glucose tolerance who were aged ≥60 years and had a BMI of 30–40 kg/m^2 (REF[306]). These data suggest that improved insulin sensitivity is due, in part, to the distribution of adiponectin across various tissues and an upregulation in the expression of its receptor. Other conflicting data suggest that in patients with knee osteoarthritis, weight training combined with walking three times a week for 1 hour does not have any significant effect on levels of TNF, IL-6 or C-reactive protein[307]. The addition of weight loss of 0.3 kg per week for 6 months to physical activity in older community-dwelling adults with obesity or overweight results in a greater reduction in serum levels of leptin and IL-6 than either physical activity alone or a successful ageing health education intervention[308].

Risks of weight loss in older adults

Energy restriction with a hypocaloric diet with or without exercise results in the loss of approximately one-quarter of lean mass per unit weight, which could worsen sarcopenia and osteopenia[154]. A total of 33 intervention studies lasting 8–24 weeks reported that unopposed calorie restriction without resistance training leads to the loss of muscle mass and loss of handgrip strength of up to 4.6% and 1.7 kg, respectively[309]. Unopposed diet therapy without exercise in older frail adults ≥65 years with obesity (BMI ≥30 kg/m^2) led to a marked loss of lean mass at 6 months and 1 year (−3.5 kg and −3.2 kg, respectively) compared with the diet and exercise group, where the loss of lean mass was partially mitigated (−1.7 kg and −1.8 kg, respectively)[246]. In the Look AHEAD trial, total skeletal mass decreased in both of the intensive lifestyle groups and in the diabetes support and education group (−1.4 kg; $P < 0.001$). The researchers reported that patients in the intervention group regained appendicular lean mass during the second year and that weight loss was 5.2 kg less in the intervention group than in participants in the control group, whose weight did not markedly change after the second year[310]. A review of 52 studies reported that loss of fat-free mass as a proportion of overall weight was attenuated after combining exercise with calorie restriction[298].

Weight loss in younger adults (age 45–65 years) led to loss of lean mass after calorie restriction (4% reduction in lean mass; $P < 0.0001$), which was partially lessened by augmentation with aerobic activity (2% reduction in lean mass in participants who had augmented weight loss with aerobic activity; $P = 0.05$)[311]. One study evaluated the effectiveness of low-fat diets versus carbohydrate restricted diets with or without progressive resistance exercise on fat-free mass in 42 men with the metabolic syndrome whose age was 59 ± 7 years. Percent weight loss from appendicular lean mass dropped markedly more in the low-fat and no exercise group than in the other groups, suggesting that this intervention has a detrimental effect on appendicular lean mass[312].

Obesity is inversely related to BMD and fractures[313] but might increase the fracture risk through bone quality[314,315] or frailty[132,316] independent of BMD. Adipose tissue has been shown to be inversely associated with bone material strength and positively associated with cortical porosity, indicating an adverse effect of adipose tissue on bone microstructure[317]. Calorie restriction alters bone metabolism, resulting in the loss of BMD in the hip without effects on lumbar spine[318], even after a 4-month restriction[319]. Increases in bone markers such as osteocalcin and of carboxy-terminal telopeptide (C-telopeptide) and N-terminal telopeptide (N-telopeptide) oftype I collagen were observed. Levels of osteocalcin were increased in the diet-only group (36 ± 11.6%), yet its levels were no different than baseline in individuals on diet coupled with exercise; increased differences were reported in the disposition index (an index of insulin secretion after correction for insulin resistance) in the diet–exercise group (92.4 ± 11.4%) compared with the diet-only group (61.9 ± 15.3%) at 12 months[320]. Loss of BMD in older adults with obesity seems to continue during long-term lifestyle change in the opposite direction to the weight changes[321]. These findings suggest that BMD and markers of bone turnover following long-term calorie restriction show larger changes in patients than in healthy control participants advised to continue their current diet[322].

In one study, the authors reported that trabecular bone microarchitecture was no different in calorie- restricted participants (~35% less calories than controls) than in middle-aged individuals eating a Western diet[323]. Furthermore, trabecular geometry, cortical geometry and strength were no different in individuals undergoing intentional weight loss through calorie restriction or weight maintenance for 6 months[324], which suggests that calorie restriction has protective effects on bone quality. However, 2017 data from the Look AHEAD trial showed that long-term intentional weight loss was associated with a 39% increased risk of fragility fractures[325]. Very-low energy or protein-sparing diets to induce rapid weight loss are not recommended owing to potential loss of muscle mass, strength and bone and risks of dramatic fluid, electrolyte and water shifts owing to protein shifts; however, a preliminary, short-term study in a population of individuals ≥65 years of age suggests potential benefits[326]. Studies emphasize exercise training during calorie restriction to prevent an increase in bone turn-over[327] and an increase in serum levels of sclerostin[328], thus minimizing bone loss. Whether weight loss and exercise lower overall risk of falls and fractures despite the decline in BMD is unknown, suggesting the need for formal evaluation in future studies.

Supplementation with calcium and vitamin D.

Conventional strategies to minimize the effect of weight loss on bone metabolism, including up to 1,200 mg supplemental calcium per day and 800–1,000 international units (IU) per day of vitamin D_3, are needed to minimize the risk of weight loss-induced BMD reduction[329]. Oral calcium should be coupled with vitamin D to mitigate the potential risks of unopposed supplementation[330]. Supplementing vitamin D in patients with sarcopenic obesity can potentially influence and improve muscle function[331] and proximal muscle weakness[332] through the actions ofvitamin D metabolites[333]. Vitamin D deficiency is associated with an increased risk of falls and fractures, and reduced muscle mass and strength[334–338], independent of obesity. We agree with the American Geriatrics Society recommendation of

1,000 IU of vitamin D_3 per day with calcium among non-institutionalized adults aged ≥65 years[334], to maintain serum levels of vitamin D at ≥30 ng/ml.

Future directions and emerging therapies

We anticipate that a deeper understanding of sarcopenic obesity will emerge over the next decade, which will ultimately bridge the divide between clinical practice and research. Here, we outline the major gaps of knowledge and advancements needed to further the field (BOX 1).

Harmonizing a definition.

The most notable barrier to advancing the science in targeting this condition is the lack of a consistent definition for sarcopenic obesity. While the criteria for identifying and classifying subcutaneous or visceral adiposity are somewhat consistent, major progress is needed regarding the definition of sarcopenia. Advancing our understanding of the relative contributions of strength and muscle mass — as well as their differences — might help. The introduction in 2016 of an International Classification of Diseases 10 code for sarcopenia (M62.84) will permit clinical recognition and promote its diagnosis, classification and drug development[339,340]. Different populations, ethnicities and sexes require specific diagnostic thresholds; therefore, integrating highly accurate body composition measures into clinical settings will encourage clinical identification of sarcopenic obesity. The disparate classification has impeded progress in this field.

Integrating methods for analysing body composition into clinical practice.

To promote the translation of methods for assessing body composition, including CT, MRI and DXA, into routine care, we acknowledge the need to remove regulatory and operational obstacles, particularly in the United States. For instance, DXA is routinely performed for screening and assessment of osteoporosis and is generally covered by insurance for this indication[341]. Older adults often receive gold standard imaging, which can accurately ascertain muscle and fat content, for indications other than sarcopenic obesity, such as abdominal pain or back pain[342,343]. Assessing muscle strength (using handgrip dynamometry) and muscle mass (using DXA, bioelectrical impedance or other modalities) can fill a clinical gap in identifying sarcopenic obesity. Widespread availability of DXA even in low-resource areas[344] permits this evaluation. Future studies should focus on dissemination and implementation strategies of using such diagnostics.

Epidemiology and clinical outcomes.

Further work is required to elucidate the descriptive epidemiology of sarcopenic obesity regarding important outcomes beyond weight loss, comorbidity and mortality. Though experts currently debate a unifying definition, one will ultimately become accepted, standardized and implemented. Until then, useful and cost-effective measures, including grip strength, gait speed, the short performance physical battery and/or bioelectrical impedance or DXA, should continue to be used in clinical and research arenas[345–347]. Focusing on patient-centred outcomes, including physical function and quality of life, is important. Additional trials in sarcopenic obesity can clarify the mechanisms underlying interactions

between fat, muscle and bone that explain alterations in short-term and long-term outcomes. Improved characterization of biological signalling will permit full comprehension of the differences between sarcopenia and sarcopenic obesity. The association of resource and cost data in health systems and third-party payers (insurers) will escalate the importance of sarcopenic obesity.

Dietary composition and restriction.

No specific interventions have tested diets for the treatment of sarcopenic obesity. While diets should be individualized, the composition of carbohydrates, fats and protein have differed in clinical trials. Adjusting these components might differentially affect muscle mass, strength and weight. Research should distinguish appropriate diets, the type of protein to administer (such as whey or casein) and potentially the timing of intake in relation to exercise, as well as whether recommendations should be based on ideal or total body weight. The specific composition of essential amino acids (for example, leucine or creatine) and vitamin D supplementation requires structured interventions to ascertain dosing and monitoring. For instance, leucine-rich protein can activate metabolic pathways involved in testosterone and IGF1 homeostasis[348–351]. Such elements will allow tailored dietary interventions.

Exercise and combined interventions.

While aerobic and resistance exercises are core components in the treatment of sarcopenic obesity, the specific frequency, intensity, time and types (aerobic, resistance or both) should be considered. The relationship of resistance exercises with respect to dietary composition requires evaluation. Longitudinal studies should verify whether weight loss plus combined aerobic and resistance training prolongs physical independence in sarcopenic obesity. Such studies might translate to older adults who have access to health membership benefits in community-based exercise centres[352]. Assessing aquatic therapies[353–355] or tai chi[356], in isolation or in tandem with other types of physical activities, might prove useful for treating patients with sarcopenic obesity. The addition of pharmacotherapy, such as testosterone supplementation, to progressive resistance training augmented the improvements in body composition, including reduced fat mass and improved lean mass[357]. However, whether or not physical activity should be combined with novel and promising treatments requires systematic and further investigation.

Periodization strategies.

Periodization, which is a systematic variation in physical training specificity, intensity and volume within periods, has emerged as a potential strategy to improve muscle performance[358]. Periodization is typically used in sports programmes aiming to achieve peak physical performance while minimizing overtraining risk. Linear periodization reduces training volume while increasing training intensity or load between cycles[359]. Periodized resistance training in older adults demonstrated equal efficacy in physical function and physiological outcomes when compared with non-periodized resistance training[360]. In patients with sarcopenic obesity (defined using handgrip strength and BMI), no differences were observed in strength, power or short performance physical battery following a 10-week periodization strategy of strength and endurance training with concentric and eccentric

movements[290]. Preliminary studies indicate that periodization results in increases in serum levels of irisin and decreases in IL-1β[361]. Leptin might also be reduced further with periodized resistance training[362]. While periodization could feasibly be prescribed in sedentary or frail older adults to improve physical function, it is premature to endorse this training as superior to non-periodized training[358]. Longer-term investigations in older populations with sarcopenic obesity are needed.

Whole-body vibration therapy.

Whole-body vibration therapy is a novel therapy that could increase muscle contraction efficiency and function with similar efficacy to resistance training, though data on its efficacy are mixed. This safe and convenient technique is associated with a low risk of injury[363,364]. Whole-body vibration therapy uses the transmission of mechanical stimuli through the person's body[365,366] to activate the primary ends of muscle spindles, which leads to neuromuscular activation[367–369]. The participant stands on a vibrating platform where electrical signals are delivered through the body, and thus primary endings of muscle spindles are activated.

Hengting Chen and colleagues[370] identified 10 randomized trials of whole-body vibration therapy showing its usefulness in younger adults (difference (d) = 0.35 (95% CI 0.05–0.64; $P = 0.02$)), but this usefulness was not seen in older adults (d = −0.04 (95% CI −0.28 to 0.21; $P = 0.78$)). The review included heterogeneous studies using different methodologies, training and vibration characteristics. Separately, Ricky Lau and colleagues[371] reviewed 13 trials of older adults and found significant treatment effects on knee extension dynamic strength (d = 0.63; $P = 0.006$), isometric strength (d = 0.57; $P = 0.003$) and functional measures such as sit-to-stand (d = 0.72; $P < 0.001$). Whole-body vibration therapy was as efficient as a fitness programme at increasing knee extension and lower leg muscle mass in non-institutionalized men aged 60–80 years old[372] and improved quality of life and functional measures[373].

Summative effects of the combination of whole body vibration therapy and resistance exercises[374–377] or of whole-body vibration therapy and vitamin D[367] are mixed. Others hypothesize that pathways contributing to weight loss as a result of whole-body vibration therapy could inhibit adipogenesis, increase energy expenditure and reduce muscle mass[378]. Augmenting existing squatting exercises with whole-body vibration therapy failed to improve muscle mass in younger men aged 18–30 years[379]. Future research should focus on type, frequency and duration of treatment[380].

Weight loss medications.

None of the six FDA-approved medications for weight loss are approved for use in older adults aged over 65 years, and few have been evaluated in terms of changes in body composition. In nine older adults prescribed liraglutide, a weight decrease of 2.0 kg (−1.5 kg fat mass and −0.9% android fat) was observed, with a marginal improvement of 0.03 kg/m^2 in skeletal muscle index (absolute muscle mass normalized by height squared)[381]. Lorcaserin leads to more fat loss than placebo in patients with diabetes mellitus (−12.1% versus −5.9%; $P = 0.008$) and more trunk obesity (3.65% versus −0.36%). When compared

with controls, patients treated with lorcaserin had greater fat mass loss than lean mass loss[382]. Topiramate negatively affects BMD[383] but might not affect lean mass[384,385]. Phentermine minimally alters lean mass[386]. Bupropion can blunt olanzapine-associated weight gain without affecting bone metabolism[387] and in combination with naltrexone can lead to a reduction in fat mass without altering lean mass[388]. Orlistat promotes the weight loss via fat and visceral adipose tissue loss but minimally changes lean mass[389–391]. In carefully selected individuals, industry-sponsored trials should evaluate these agents in both older adults with obesity and patients with sarcopenic obesity.

Bariatric surgery.

Bariatric surgery improves weight and metabolic outcomes and reduces mortality. In carefully selected patients, this could be considered a treatment for sarcopenic obesity in older adults ≥65 years[392]. Its safety and efficacy in sarcopenic obesity is unknown other than one study that evaluated the influence of sarcopenic obesity on gastric bypass and sleeve gastrectomy results[393]. The population of participants had a mean age of 44 years, and no documented differences were observed in weight loss results or comorbidity resolution. Bariatric surgery leads to loss of fat mass[394], alters gut hormones[395] and can exacerbate weight loss-induced sarcopenia[396–398] and osteoporosis[399–402]. Carefully designed studies are needed before promoting this intervention.

Testosterone.

Obesity negatively affects serum levels of testosterone and disrupts the actions of testosterone by increasing its aromatization to oestrogen[403] and down regulating follicle-stimulating hormone and luteinizing hormone[404], thus exacerbating hypogonadotropic hypogonadism. Testosterone is an important regulator of body composition with ageing, as it increases muscle and bone mass, increases IGF1 levels, decreases inflammatory markers[405] and alters biomarkers of bone turnover in adults with hypogonadism. Testosterone deficiency can impair muscle adaptation to exercise owing to reduced expression of IGF1 and increased inflammatory cytokines. However, reductions in TNF and IL-6 observed in older men with hypogonadism can be reversed following testosterone treatment[406].

Supplementation with testosterone promotes IGF1 mRNA and protein expression, leading to increased lean mass through increased muscle protein synthesis[52]. Increases in IGF1 following testosterone administration might improve muscle mass and strength enhanced by exercise[52,56,406], and in men over 60 years with low testosterone, gains in lean mass following testosterone supplementation ranged from 1.6 kg to 6.20 kg (REF[407]). Androgen therapy also reduces fat mass (−1.78%). Therapy with testosterone and GH in older men aged 65–80 years with normal testosterone levels resulted in greater improvements in lean mass with both treatments than with either alone[56,408]. In select older men over the age of 60 years with testosterone deficiency and frailty, body composition and quality of life improved following supplementation with testosterone[409–411]. Three years of testosterone administration in patients with low levels of testosterone resulted in an increase in lean mass (0.9 kg, 95% CI 0.5–1.4; $P < 0.001$)[412]. Testosterone deficiency and treatment in older men have been reviewed elsewere[413].

There are conflicting data on the effect of testosterone supplementation on muscle strength and function[50,51,357,414]. In the 'Testosterone Trials', treatment with testosterone improved participants' results in the 6 min walk test compared with placebo (20.5% versus 12.6%; $P = 0.003$)[53]. Elsewhere, testosterone-associated increases in lean mass were accompanied by improvements in handgrip strength, knee extension and leg press and chest press exercises[415,416]. A meta-analysis of testosterone supplementation found effect sizes of 0.47 (95% CI 0.12–0.84) for upper and 0.63 (95% CI 0.03–1.28) for lower extremity strength[417], without sustained improvements in body composition[418]. Healthy men with reduced levels of testosterone had no improvements in muscle strength or mobility after 6 months of supplementation[350]. Another trial of testosterone treatment found improved stair-climbing power and strength[351].

Improvements in lean mass do not directly result in improved function after testosterone therapy[409]. With ageing, muscle strength often drops before muscle mass[73]. The nonlinear relationship between mass and function suggests that hypertrophy rather than muscle fibre hyperplasia materializes without neuronal plasticity. A reason for the observed significance in some studies might be a patient's intrinsic threshold for functional impairment. Frail older adults with testosterone deficiency could require minimal incremental gains in mass to realize benefit. Therefore, we suggest an individualized approach. Comorbidity and health status, small sample sizes, minimal changes in testosterone levels following treatment and the lack of practice sessions before initiating strength testing could have contributed to the negative findings. Areas of future research should identify responders to androgen supplementation in those with low lean mass or strength.

Testosterone potentially augments diet-induced loss of fat mass in individuals with BMI ≥30 kg/m^2 and low testosterone levels. Over 56 weeks, testosterone-treated participants (mean age 53 years) had greater reductions in fat mass (mean between-group difference 2.9 kg; $P = 0.04$) and visceral fat (−2,678 mm^2; $P = 0.04$) than controls. Testosterone-treated participants also had greater lean mass regain during weight maintenance (mean between-group difference 3.4 kg; $P = 0.002$) following the very-low-energy diet, suggesting that weight loss was exclusively fat mass[419]. As multicomponent interventions can attenuate lean mass losses, studies should evaluate whether testosterone replacement helps preserve muscle and bone mass during weight loss in patients with sarcopenic obesity.

Adverse events associated with testosterone supplementation include polycythemia[420], possible cardiovascular events[421], venous thromboembolism[422] and prostatism[423]. Those who favour supplementation cite a lack of credible evidence related to cardiovascular risk[424]. Future cost–benefit analyses should compare the relative benefits regarding body and bone composition with disability risk. To date, the American Association of Clinical Endocrinologists[187], the Endocrine Society[425] and the Obesity Society[186] have not recommended testosterone supplementation as a treatment for sarcopenia or obesity.

Selective androgen receptor modulators.

Selective androgen receptor modulators (SARMs) target androgen receptors on muscle and bone but do not activate androgenic effects elsewhere. SARMs indirectly affect nonmuscle androgen receptor pathways mediated by muscle fibroblasts[426]. Enobosarm, a non-steroidal

SARM, successfully increased muscle mass and physical function in patients without cancer and in those with advanced lung, colorectal or breast cancer or lymphoma[427–429]. Other studies showed increases in lean mass without improvements in strength or physical performance in patients with sarcopenia[428,430]. Early trials demonstrated a greater total lean mass of 1.3 kg ($P < 0.001$), better physical function as measured by reduced stair climb time ($P = 0.013$), a trend towards lower blood levels of glucose of 6.9 ± 2.5 mg/dl ($P = 0.052$) and lower insulin sensitivity (−27.5% versus 2.6%; $P = 0.013$) with 3 mg per day of GTx-024 (an orally bioavailable nonsteroidal SARM) than with placebo[429]. Enobosarm significantly increased lean mass compared with baseline (1.0 kg, 95% CI −4.8 to 11.5; $P = 0.046$) versus controls (0.02 kg, 95% CI −5.8 to 6.7; $P = 0.88$). SARM treatment in older women with low lean mass, a self-reported mobility disability and a short physical performance battery score between 4 and 9 provided improvements in muscle mass without benefits of improved strength[430]. SARMs that have been developed in the past 5 years have not demonstrated adverse effects[431] and have restored cortical and trabecular bone in orchidectomized mice[432]. Transdermal SARMs could emerge in the future[433]. A review of SARMs has been conducted elsewhere[434], but they could be of benefit to patients with sarcopenic obesity who require muscle mass improvements rather than strength. However, conclusive evidence is still needed.

Anamorelin.

Anamorelin, an oral ghrelin analogue, is effective for improving appetite in patients with cancer cachexia and might hold promise in patients with sarcopenic obesity. Its anti-inflammatory and anabolic properties might counter the negative nitrogen balance observed in sarcopenia. Anamorelin is safe, well tolerated and stimulates appetite by promoting expression of GH, IGF1 and IGF-binding protein 3 (REFS[435,436]), which reverses muscle atrophy in mice[437]. A meta-analysis of 1,641 patients with cancer demonstrated improved total body weight, lean mass and quality of life (1.78, 95% CI 1.28–2.28, $P < 0.001$; 1.10, 95% CI 0.35–1.85, $P = 0.004$; 0.19, 95% CI 0.08–0.30, $P = 0.0006$, respectively)[438]. A review of four studies demonstrated high heterogeneity with improved symptom scores, and in three studies, improved lean mass was shown[439]. Anamorelin improved lean mass in patients with cancer cachexia compared with placebo (2.09 kg, 95% CI 0.94–3.25; $P = 0.0006$)[440] but failed to improve muscle power or handgrip strength in patients with inoperable nonsmall-cell lung cancer[441]. Lack of functional improvements were also observed in patients with unresectable non-small-cell lung cancer[442]. Adverse effects are no different than with placebo. It is unclear whether the improved lean mass observed in patients treated with anamorelin has differential effects on intramuscular fat in patients with sarcopenic obesity. As no studies have established improved function or strength, further evaluation is needed, particularly in the subset of patients with sarcopenic obesity who have low lean mass with intact muscle strength.

Myostatin inhibitors.

Individuals with sarcopenia have elevated levels of myostatin[443], a negative regulator of skeletal muscle growth development[444]. Myostatin is also expressed in adipose tissue and is inversely related to insulin resistance[445]. In vitro trials demonstrate that myostatin inhibitors increase muscle mass and strength[446], suppress irisin, downregulate inflammatory cytokines

and improve insulin resistance[447]. Its expression drops following weight loss because it directly influences adipocyte metabolism[448], and myostatin inhibitors can directly inhibit muscle loss. Myostatin inhibitors reduce expression of myostatin in both aerobic and resistance exercise[449] and might be beneficial in treating sarcopenic obesity. Early data suggest improved physical function in patients with non-small-cell lung cancer[427]. Interventions should directly measure changes in levels of myostatin and corresponding changes in muscle mass, strength, function and insulin sensitivity.

Vitamin K.

Vitamin K might have a role in mitigating bone loss following intentional weight loss by inhibiting bone resorption[450] and osteoclast formation[451]. Its deficiency has been associated with increased risk of fragility fractures[452–455], particularly in patients who are malnourished[456,457]. Vitamin K supplementation can restore serum levels of the vitamin[458,459] and might increase bone resorption markers[460]. Conflicting data exist; in some studies, vitamin K antagonists demonstrate no differences in BMD or fracture rates[461], while other data suggest lessening of steroid-induced BMD[462] and sex-specific improvements in insulin sensitivity[463]. One study[464] reported that over 3 years vitamin K supplementation was not implicated in the age-related changes in skeletal muscle or adipose tissue mass in older community-dwelling adults. Our understanding of the complex relationship between vitamin K and weight loss-induced effects on bone, muscle and fat in sarcopenic obesity is currently in its infancy[465].

Mesenchymal stem cells.

Muscle, bone and cartilage derived from mesenchymal cells share common precursor mesenchymal stem cells. In mice, transplantation of satellite cells into damaged muscle leads to self-renewal and muscle regeneration[466,467]. An early human study suggests a role for mesenchymal stem cells in managing frailty[468]. The cost, regulatory constraints and potential ethical barriers of applying such technology into clinical settings need to be addressed further.

Conclusions

The growing challenges associated with sarcopenic obesity will probably worsen with the changing demographic distribution of our ageing population. Effective evidence based therapies can be helpful for improving physical function in older adults. We encourage further agreement on defining sarcopenic obesity within both research and clinical settings. In our opinion, a lack of a consensus definition is one of the greatest limitations to advancing the science. Without being able to accurately identify populations of patients, there will be continued difficulties in targeting further obesity subtypes. Clarifying the mechanisms that contribute to sarcopenic obesity might elucidate novel therapies to improve function, quality of life and prevent institutionalization. A number of novel therapies independently hold promise or could be considered adjunctively for those who have struggled with a lifetime of reduced motivation. These potential strategies should be key research questions in future work.

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Glossary

Sarcopenia
The loss of muscle mass, strength or physical function with age.

Oxidative capacity
The maximal ability of muscle to utilize oxygen per g of muscle per hour.

Thermic effect of food
The amount of energy expended owing to the body's processing and storage of food.

Fat-free mass
A term interchangeably used with muscle mass and lean mass; it refers to the mass of all visceral organs, muscles (smooth and skeletal), bones, ligaments and tendons but does not include fat that is present in the marrow of bones or internal organs.

Waist circumference
An anthropometric measure of central obesity (subcutaneous and visceral) measured at the level of the iliac crest.

Visceral fat
A measurement of the adiposity located among organs within the abdominal cavity; it is associated with inflammation and increased cardiometabolic risk.

Intramyocellular lipids
Fat depositions within the muscle structure.

Myostatin
A transforming growth factor-related protein that is synthesized and secreted in skeletal muscle and negatively regulates muscle mass and function.

VO2 max
The maximal amount of oxygen used per kg of body weight during maximal exercise.

Lean mass
A term that refers to the mass of all visceral organs, muscles (smooth and skeletal), bones, ligaments and tendons but excludes fat from bone.

Appendicular lean mass
Muscle mass consisting of the sum of the upper and lower limbs.

Grip strength
A measurement used in the ascertainment of upper extremity strength; it is assessed using the dominant hand with a hand-held dynamometer.

Knee extensor strength
A measure of lower extremity strength. The test is performed using a dynamometer with the participant sitting with hips and knees flexed at 90°; the participant extends his or her knee and pushes against a resistance pad — the results are measured in kilograms or pounds.

Quadriceps muscle area
Cross-sectional 2D area at the level of the quadriceps muscle of the lower limb.

Skeletal muscle index
Absolute muscle mass (in kg) normalized for height (muscle mass in kg divided by height (in m)).

Absolute muscle mass
Muscle mass consisting of all limbs and muscle from visceral organs.

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Key points

- Body composition changes that occur with the ageing process can lead to sarcopenic obesity, an increasingly prevalent disorder owing to the increased prevalence of obesity in an ageing population.
- Hormonal, inflammatory and myocellular mechanisms impact underlying biological processes that promote fat deposition and loss of lean mass and strength.
- Definitions of sarcopenia and obesity can vary considerably, prompting difficulties in the diagnosis and epidemiological understanding of sarcopenic obesity as well as the development of treatment strategies for this disease.
- Lifestyle interventions including calorie restriction and physical activity consisting of aerobic and resistance exercises are the cornerstones of therapy.
- Clinicians and researchers need to be aware of weight loss-induced sarcopenia and osteopenia.
- Novel, promising therapies, including weight loss medications, bariatric surgery, whole-body vibration therapy, periodization (a systematic variation in physical training specificity, intensity and volume within periods), testosterone, selective androgen receptor modulators, anamorelin, myostatin inhibitors, vitamin K and mesenchymal stem cells, require further investigation.

Box 1 |

Emerging therapies in sarcopenic obesity

Anamorelin

A ghrelin analogue used in cancer cachexia that could promote appetite and enhance lean mass with anti-inflammatory and anabolic properties.

Bariatric surgery

The safety and efficacy of different procedures (Roux-en-Y, gastric band and gastric sleeve) are currently unknown but can be considered in carefully selected older adults aged 65 years and older.

Mesenchymal stem cells

Shared precursors of muscle, bone and cartilage that hold promise in the regeneration of muscle tissue. Barriers exist but these cells may play a promising role in the future management of sarcopenia.

Myostatin inhibitors

A treatment type with biological plausibility for improving physical function by enhancing skeletal muscle growth development. This class of therapy can directly inhibit muscle loss, with data suggesting improvements in physical function in patients with cancer.

Neuromuscular activation

Whole-body vibration therapy (using electrical stimuli) or tai chi can enhance muscle contraction efficiency and function.

Periodization strategies

Systematic variation in training specificity, intensity and volume used in sports programmes to achieve peak physical performance. May be feasibly prescribed in sedentary, frail, older adults to improve function but it is premature to endorse these strategies.

Testosterone and selective androgen receptor modulators

Important regulators of body composition that increase muscle and bone mass by increasing insulin-like growth factor 1 (IGF1) and decreasing inflammatory markers. Data on their impact on muscle strength and function are conflicting. Selective androgen receptor modulators (that is, enobosarm) preferentially target androgen receptors on muscle and bone, sparing the androgenic impact elsewhere in the body. Early efficacy studies demonstrate improved lean mass and function in patients with cancer.

Weight loss therapies

Anti-obesity medications (liraglutide, lorcaserin, phentermine, topiramate, bupropion and orlistat) are approved for use in non-geriatric populations with weight loss as an

indication. Their use is restricted to off-label use for weight loss, and few data exist on their safety and efficacy in this population.

Vitamin K

Inhibits bone resorption and osteoclast formation and may be helpful in mitigating bone loss following intentional weight loss. Supplementation may increase bone resorption markers, although conflictive data exist on its effect on BMD and fractures.

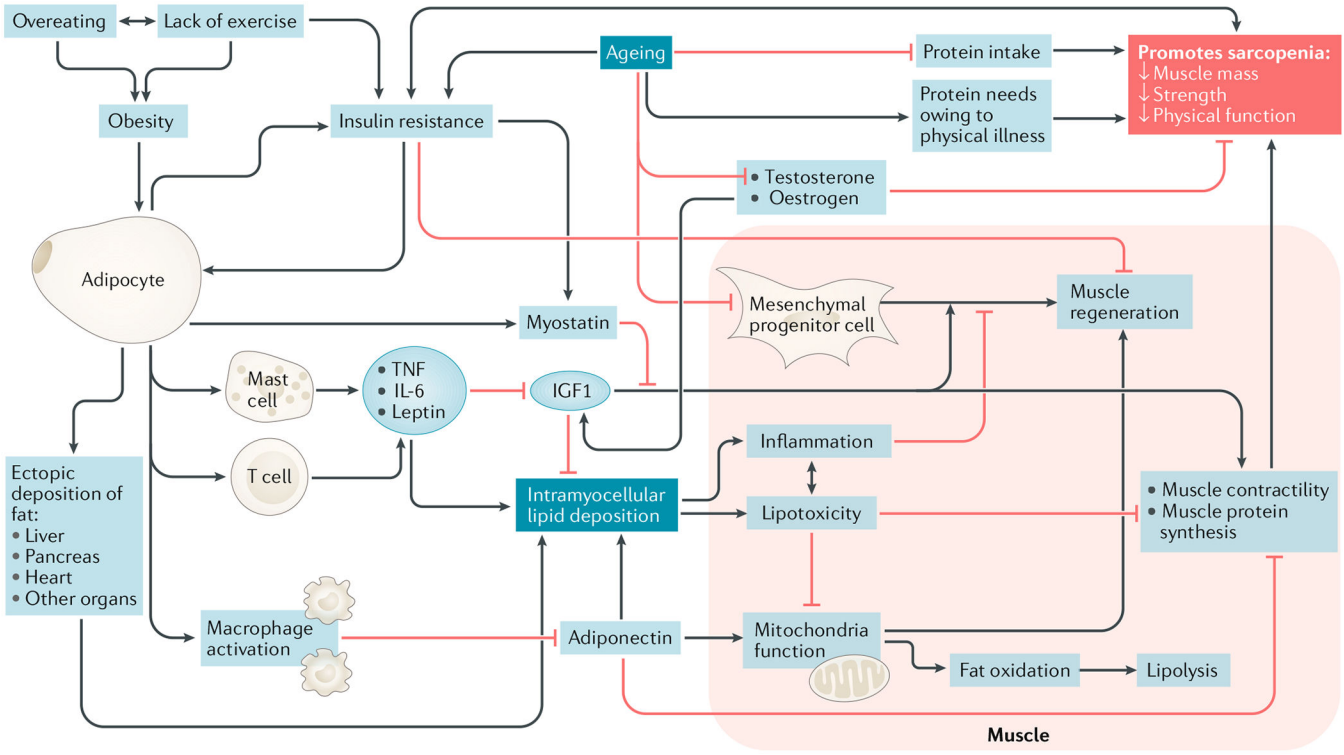

Fig. 1 |. A proposed model of mechanisms leading to sarcopenic obesity.

The proposed interplay between adipose and muscle tissue, which is believed to contribute to the development of sarcopenic obesity, is shown. The black lines are stimulatory, while red lines with flat ends indicate inhibition. IGF1, insulin-like growth factor 1; TNF, tumour necrosis factor.

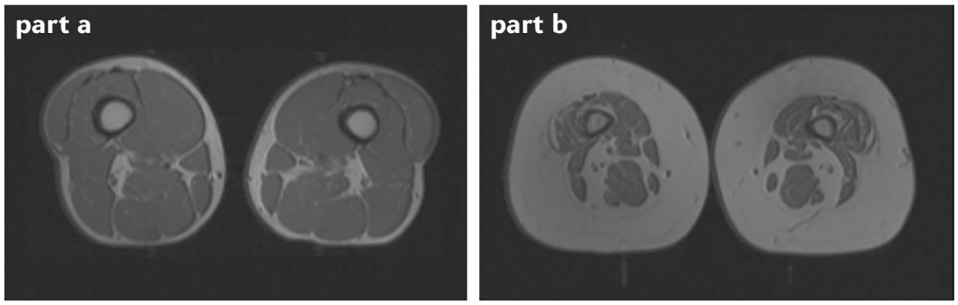

Fig. 2 |. MRi of individuals with and without obesity.

Cross-sectional MRI of the quadriceps area of an individual without obesity with normal muscle characteristics (part **a**) and an individual with obesity with small muscles and infiltration by adipose tissue (part **b**) is shown. More muscle tissue is visible in part **a** than in part **b**, and the higher intensity signals seen in part **b** indicate fat infiltration of the muscle. Images courtesy of Edward Weiss, St Louis University School of Medicine, St Louis, MO, USA.

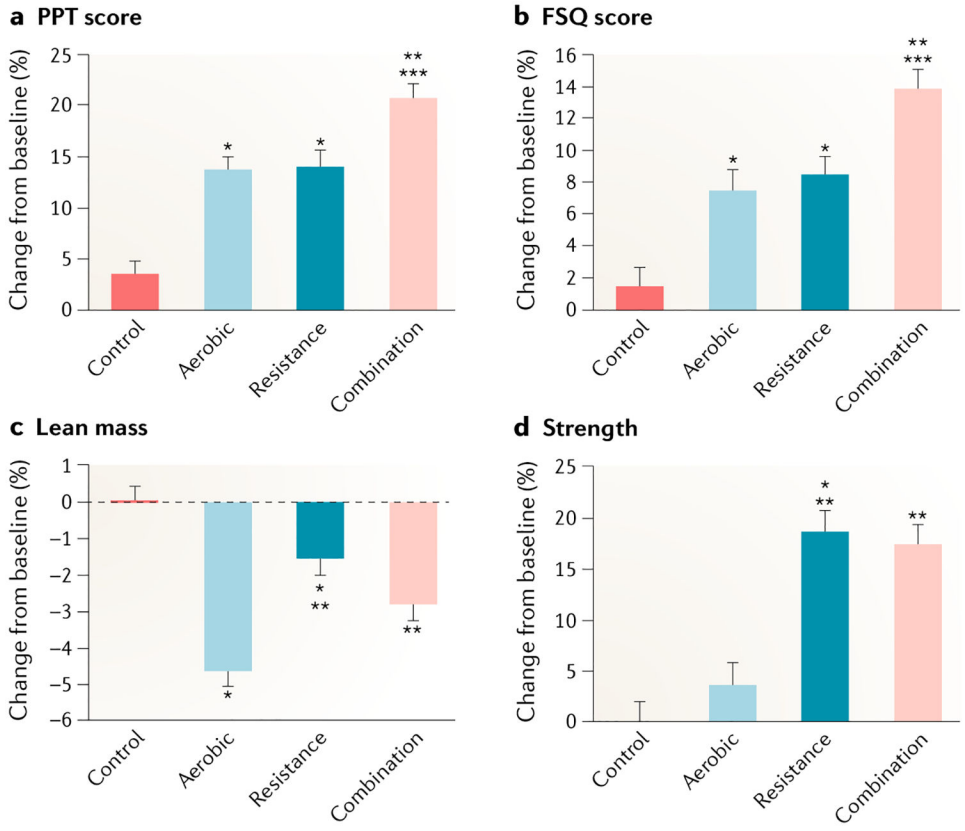

Fig. 3 |. Mean percentage changes in physical function and lean mass during the weight loss interventions.

Measures used included a physical performance test (PPT) (scores range from 0 to 36, with higher scores indicating better functional status) (part **a**); the Functional Status Questionnaire (FSQ) (scores range from 0 to 36, with higher scores indicating better functional status) (part **b**); lean mass (part **c**); and strength (measured as total one repetition maximum (that is, the total of the maximum weight a participant can lift, in one attempt, in the bicep curl, bench press, seated row, knee extension, knee flexion and leg press)) (part **d**). Scores on the PPT were used as an objective measure of frailty (primary outcome), and scores on the FSQ were used as a subjective measure of frailty. Percentage changes are presented as least-squares-adjusted means; T bars indicate standard errors. **P* < 0.05 for the comparison with the control group. ***P* < 0.05 for the comparison with the aerobic group. ****P* < 0.05 for the comparison with the resistance group. Figure adapted with permission from REF[247], New England Journal of Medicine, Villareal, D. T. et al. Aerobic or resistance exercise, or both in dieting obese older adults, **376**, 1943–1955 Copyright © (2017) Massachusetts Medical Society. Reprinted with permission.

Table 1 |

Selected definitions of sarcopenia with or without obesity

Author, year and study name (when applicable)	Sarcopenia component	Measurement modality (cut-off points)	Obesity component (cut-off points)	Validated population
Newman, 2003 (ref.[469])	ALM divided by height squared	DXA (men <7.23kg/m^2; women <5.67kg/m^2)	BMI (≥30kg/m^2)	New Mexico Elder Health Survey
	ALM divided by height and fat mass	DXA (lowest twentieth percentile of residuals (sex-specific))	BMI (≥30kg/m^2)	Health ABC study
Baumgartner, 2000 (ref.[470])	ALM divided by height squared	DXA (men <7.26kg/m^2; women <5.45kg/m^2)	Body fat (men >27%; women >38%)	New Mexico Aging Process Study
Baumgartner, 2004 (ref.[191])	ALM divided by height squared	DXA (men <7.26kg/m^2; women <5.45kg/m^2)	Body fat (men ≥28%; women ≥40%)	New Mexico Elder Health Survey
Villareal, 2005, ASN–TOS[186]	ALM divided by height squared	ALM (<5.45kg/m^2, sex is not specified)	BMI (≥30kg/m^2)	Young healthy population
Bouchard, 2009 (ref.[188])	ALM divided by height squared	DXA (men <8.51kg/m^2; women <6.29kg/m^2)	Body fat (men ≥28%; women ≥35%)	Nutrition as a Determinant of Successful Aging study
Fielding, 2011, IWGSP[180]	Physical function	Gait speed (<1m/s)	NA	NA
	Lean mass	DXA (less than the twentieth percentile healthy adults, ALM divided by height squared: men ≤7.23kg/m^2; women ≤5.67kg/m^2)	NA	Health ABC
Cruz-Jentoft, 2010, EWGSOP[156]	ALM divided by height squared	DXA (men ≤7.26kg/m^2; women ≤5.50kg/m^2)	NA	Rosetta study
		DXA (men ≤7.25kg/m^2; women ≤5.67kg/m^2)	NA	Health ABC study
		DXA (men ≤7.23kg/m^2; women ≤5.67kg/m^2)	NA	Health ABC study
	Residuals	DXA (ALM (fat mass divided by height), men: −2.29; women: −1.73)	NA	Health ABC study
	SMI divided by height squared	BIA (men ≤8.87kg/m^2; women ≤6.42kg/m^2)	NA	Taiwanese population
	ALM divided by height squared	(men: severe ≤8.50kg/m^2, moderate 8.51–10.75kg/m^2. Women: severe ≤5.75kg/m^2; moderate 5.76–6.75kg/m^2)	NA	NHANES III study
	Muscle strength	Handgrip strength (men <30kg; women <20kg)	NA	InCHIANTI study
	Muscle strength based on BMI category	Handgrip strength (males: BMI <24 kg/m^2: <29.0kg; BMI 24.1–26.0 kg/m^2: <30.0kg; BMI 26.1–28.0 kg/m^2: <30.0kg; and BMI >28 kg/m^2: <32.0kg; females: BMI <23 kg/m^2: <17.0kg; BMI 23.1–26.0 kg/m^2: <17.3kg; BMI 26.1–29.0 kg/m^2: <18.0kg; and BMI >29 kg/m^2: <21.0kg)	NA	Cardiovascular Health Study
	Physical performance	SPPB (≤8)	NA	EPESE study
		Gait speed over 6m (<1m/s)	NA	Health ABC study
		Gait speed over 6m (<1.175m/s)	NA	Health ABC study

Author, year and study name (when applicable)	Sarcopenia component	Measurement modality (cut-off points)	Obesity component (cut-off points)	Validated population
		Gait speed over 15 ft (men ≤1.73m: <0.65m/s; and >1.73m: <0.76m/s; women: ≤1.59m: <0.65m/s; and >1.59m: <0.76m/s)	NA	Cardiovascular Health Study
		Gait speed over 4m (<0.8m/s)	NA	InCHIANTI study
Studenski, 2014, FNIH[182]	Weakness	Handgrip strength (men <26kg; women <16kg)	NA	Multiple study cohorts
		Handgrip strength:BMI (men <1.0; women <0.56)	NA	Multiple study cohorts
	ALM	Men <19.75kg; women <15.02kg	NA	Multiple study cohorts
	ALM:BMI	Men <0.789; women <0.512	NA	Multiple study cohorts
Asian Working Group for Sarcopenia, 2014 (ref.[185])	ALM divided by height squared	DXA (men <7.0kg/m^2; women <5.4kg/m^2)	NA	NA
		BIA (men <7.0kg/m^2; women <5.7kg/m^2)	NA	NA
	Strength	Handgrip strength (men <26kg; women <18kg)	NA	NA
	Performance	Gait speed over 6m (<0.8m/s)	NA	NA

ABC, Ageing, Body and Body Composition; ALM, appendicular lean mass; ASN, American Society of Nutrition; BIA, bioelectrical impedance; DXA, dual-energy X-ray absorptiometry; EPESE, Established Populations for the Epidemiologic Study of the Elderly; EWGSOP, European Working Group on Sarcopenia in Older People; FNIH, Foundation for the National Institutes of Health; IWGSP, International Working Group on Sarcopenia; NA, not applicable; NHANES, National Health and Nutrition Examination Survey; SMI, skeletal muscle index; SPPB, short performance physical battery; TOS, The Obesity Society.

Table 2 |

Potential approved therapies in sarcopenic obesity

component	goal	Suggested approach
Calorie restriction	Lose body fat and improve physical function	500–1,000kcal per day
		~0.5kg per week aiming for 8–10% weight loss at 6 months followed by weight loss maintenance
		No specific diets are proven in this population
Aerobic exercises	Improve cardiorespiratory fitness	150 min per week of moderate to vigorous aerobic exercise
Resistance exercises	Improve muscle strength and mass; attenuate loss of muscle and bone during weight loss efforts	60–75 min of resistance training 3 times weekly, separated by one day focusing on strength, balance and flexibility
Protein supplementation	Mitigate loss of muscle mass and strength	1.0–1.2g/kg per day of protein in divided doses (25–30g daily)
		2.5–2.8g leucine daily
Calcium supplementation	Prevent potential disturbances in bone metabolism	1,200 mg per day of supplemental calcium, preferably through dietary measures
Vitamin D supplementation	Prevent potential disturbances in bone metabolism	1,000 IU vitamin D per day, ideally maintaining blood levels ≥30 ng/ml

IU, international units.