nature reviews disease primers

https://doi.org/10.1038/s41572-024-00550-w

Primer

Check for updates

Sarcopenia

Avan A. Sayer[1,2] ✉, Rachel Cooper[1,2], Hidenori Arai[3], Peggy M. Cawthon[4,5], Marie-Josiane Ntsama Essomba[6], Roger A. Fielding[7], Miranda D. Grounds[8], Miles D. Witham[1,2] & Alfonso J. Cruz-Jentoft[9]

Abstract

Sarcopenia is the accelerated loss of skeletal muscle mass and function commonly, but not exclusively, associated with advancing age. It is observed across many species including humans in whom it can lead to decline in physical function and mobility as well as to increased risk of adverse outcomes including falls, fractures and premature mortality. Although prevalence estimates vary because sarcopenia has been defined in different ways, even using a conservative approach, the prevalence is between 5% and 10% in the general population. A life course framework has been proposed for understanding not only the occurrence of sarcopenia in later life but also influences operating at earlier life stages with potentially important implications for preventive strategies. Harnessing progress in understanding the hallmarks of ageing has been key to understanding sarcopenia pathophysiology. Considerable convergence in approaches to diagnosis of sarcopenia has occurred over the last 10 years, with a growing emphasis on the central importance of muscle strength. Resistance exercise is currently the mainstay of treatment; however, it is not suitable for all. Hence, adjunctive and alternative treatments to improve quality of life are needed. An internationally agreed approach to definition and diagnosis will enable a step change in the field and is likely to be available in the near future through the Global Leadership Initiative in Sarcopenia.

Sections

Introduction

Epidemiology

Mechanisms/pathophysiology

Diagnosis, screening and prevention

Management

Quality of life

Outlook

[1]AGE Research Group, Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK. [2]NIHR Newcastle Biomedical Research Centre, Newcastle upon Tyne Hospitals NHS Foundation Trust, Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust and Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK. [3]National Center for Geriatrics and Gerontology, Obu, Japan. [4]California Pacific Medical Center, Research Institute, San Francisco, CA, USA. [5]University of California San Francisco, Department of Epidemiology and Biostatistics, San Francisco, CA, USA. [6]Department of Internal Medicine and Specialties, Faculty of Medicine and Biomedical Sciences, University of Yaounde I, Yaounde, Cameroon. [7]Nutrition, Exercise Physiology, and Sarcopenia Laboratory, Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA, USA. [8]Department of Anatomy, Physiology and Human Biology, School of Human Sciences, University of Western Australia, Perth, Western Australia, Australia. [9]Servicio de Geriatría, Hospital Universitario Ramón y Cajal (IRYCIS), Madrid, Spain. ✉e-mail: avan.sayer@newcastle.ac.uk

Introduction

Sarcopenia is "a progressive and generalized skeletal muscle disorder involving the accelerated loss of skeletal muscle mass and function"[1]. Sarcopenia is commonly, but not exclusively, associated with ageing and is observed across many species including humans[1,2]. The assignment of an International Classification of Diseases-10 clinical modification (ICD10-CM) code to sarcopenia in 2016 (ref. 3) reflects growing recognition of the clinical importance of this condition. A number of international groups of experts have played key roles in achieving this recognition aided by the increasingly robust evidence base that has emerged since the 1990s. This includes evidence demonstrating that sarcopenia can precipitate decline in physical function and mobility, detrimentally affect quality of life and result in increased risk of many other adverse outcomes including falls, fractures and premature mortality[4–8].

Since the term sarcopenia was first coined in the late 1980s[9,10], its definition has been evolving[11–13]. Over time many international groups have contributed to the development of conceptual and operational definitions of sarcopenia with a shift to incorporate empirical epidemiological evidence that complements and informs consensus-based approaches[2,14–21] (Fig. 1). This ongoing evolution of conceptual definitions of sarcopenia has resulted in the operationalization of several different definitions of sarcopenia within the literature and clinical practice. Although this has presented some challenges, considerable overlap exists between these definitions and all current definitions incorporate one or more of the following three components: low muscle mass (or low lean mass as an indicator of this), low muscle strength and low physical performance. Furthermore, a deeper analysis reveals striking similarities in diagnostic outcomes and in the specific cut-off points that are now endorsed. In addition, some differences in the cut-off points recommended by groups from different world regions should be expected given global variations in key components of sarcopenia and underlying drivers, such as body size and composition[22] (Fig. 2).

The establishment of the Global Leadership Initiative in Sarcopenia (GLIS) signals a promising move towards global consensus[23]. By explicitly defining commonly used terms to ensure their standardization[24] and creating the first global conceptual definition of sarcopenia[25], GLIS has undertaken the necessary groundwork for the development of a global operational definition suitable for application in both research and clinical settings worldwide.

The aetiology of sarcopenia is complex and many different underlying biological processes are implicated in its pathogenesis. In general, to distinguish sarcopenia from other muscle-wasting conditions, it has been suggested that the loss of muscle mass and strength could be referred to as primary sarcopenia when ageing is the only evident cause and as secondary sarcopenia when muscle loss is associated with a disease[15]. On this basis, primary sarcopenia is often detected by inferring age-related loss of muscle mass and strength if an individual's measured levels of these components fall below specified cut-off points and no specific cause is identified. This same approach is utilized to diagnose many other important health conditions including osteoporosis and hypertension, which are also detected by applying cut-off points to continuous measures of body structure and function.

In this Primer, we mainly focus on age-associated accelerated loss of skeletal muscle mass and function, that is, primary sarcopenia. We describe its epidemiology, mechanisms, diagnosis, prevention, management and the impact of sarcopenia on quality of life. We conclude by outlining those areas where further advancements in our understanding of this condition are soon expected, many of which could be transformative.

Epidemiology

Prevalence and incidence

To appreciate the impact and magnitude of sarcopenia, understanding its descriptive epidemiology, including the variation in its prevalence and incidence, by key population characteristics is important. However, the seemingly simple task of describing the distribution of sarcopenia within populations is currently complicated by the use of different operational definitions of sarcopenia that yield very different prevalence estimates[26–31]. One factor contributing to differences in prevalence relates to the components of muscle considered, with estimates generally higher when sarcopenia is defined using low lean mass only than when low muscle strength and/or physical function are also incorporated. As a consequence not only of the use of different sarcopenia definitions but also of differences in the characteristics of the populations being studied, the estimated prevalence of sarcopenia varies markedly. For example, two reviews of population-based studies across the world, one including adults ≥18 years of age[29] and one focused on community-dwelling adults ≥60 years of age[28], reported pooled prevalence estimates of sarcopenia that ranged between 5% and 22%[28,29,31]. These data confirm the variability in the prevalence of sarcopenia reported in an earlier systematic review of studies (published up to 2016) involving community-dwelling older adults (≥55 years of age). In this review, prevalence estimates of sarcopenia from 58 unique study populations from 26 countries were pooled and found to range between 10% and 40% depending on the definition utilized[27]. Taken together, even the most conservative estimates suggest that between 5% and 10% of the general population are living with sarcopenia.

Despite variation in estimates between studies, the proportion of older adults with sarcopenia is likely to be much higher as the prevalence of sarcopenia typically increases with age and is even higher among older institutionalized populations. Consistent with the observation that prevalence of sarcopenia increases with age are findings from longitudinal population-based studies that have estimated incidence of sarcopenia and shown that a considerable proportion of older adults develop sarcopenia over relatively short periods (that is, 4–8 years) of follow-up[32–34]. For example, analyses of the English Longitudinal Study of Ageing showed that 15% of community-dwelling adults (mean age 63 years) developed sarcopenia over 8 years of follow-up[32].

Sex differences in the prevalence of sarcopenia are inconsistent and may vary depending on the definition operationalized. This is exemplified by findings from a systematic review of 263 studies and meta-analyses of a subset of these studies that demonstrated a higher prevalence of sarcopenia in men than in women when using one set of European criteria, whereas the reverse was found when using American criteria, and there was no sex difference in prevalence when using Asian criteria[29]. Differences in the prevalence of sarcopenia between countries and world regions have also been reported. These regional differences cannot be easily summarized due in part to the limited availability of suitable data for estimating sarcopenia prevalence in some world regions (for example, Africa)[29,30]. However, evidence suggests that differences in the prevalence of sarcopenia can be attributed not only to variations in the definitions of sarcopenia utilized but also to the observed global variations in key components of sarcopenia, including grip strength[22] (Fig. 2).

Comorbidities

Many long-term health conditions share common pathological features with sarcopenia including systemic low-grade inflammation and oxidative damage[35]. As a result, a higher prevalence of sarcopenia is found

Fig. 1 | Key milestones in the development of a sarcopenia definition. Summary of some of the most important milestones in the development of a definition of sarcopenia. This includes the term 'sarcopenia' first being coined[9], and publication of the first definition of sarcopenia[10]; the European Society for Clinical Nutrition and Metabolism (ESPEN) consensus definition[14]; the European Working Group on Sarcopenia in Older People (EWGSOP) consensus definition[15]; the International Working Group on Sarcopenia (IWGS) consensus definition[2]; the Asian Working Group for Sarcopenia (AWGS) consensus definition[16]; the definition of the Foundations for the National Institutes of Health (FNIH) project on sarcopenia[17]; the European Working Group on Sarcopenia in Older People 2 (EWGSOP2) revised consensus definition[18]; the definition of the Sarcopenia Definitions and Outcomes Consortium (SDOC)[19]; the AWGS revised consensus definition[20]; the Australian and New Zealand Society for Sarcopenia and Frailty Research (ANZSSFR) Sarcopenia Diagnosis and Management Task Force recommendations[21]; and the Global Leadership Initiative in Sarcopenia (GLIS) conceptual definition of sarcopenia[25].

in specific patient groups compared with the general population[36]. In addition, marked differences are observed in the prevalence of sarcopenia between patient groups. For example, a 2023 review of studies conducted in different settings estimated a sarcopenia prevalence of 18% in patients with diabetes and 66% in patients with unresectable oesophageal cancer[31]. A higher prevalence of sarcopenia was also observed in patients with kidney and liver disease and in patients with different site-specific cancers than in other patient groups and the general population. In a systematic review published in 2023 of studies comparing sarcopenia prevalence in patients with cardiovascular diseases and the general population, the prevalence of sarcopenia was significantly higher in patients with acute decompensated heart failure (61%; 95% CI 49–72%), chronic heart failure (32%; 95% CI 23–41%) and cardiac arrhythmia (30%; 95% CI 25–35%) than in the general population[37]. Studies have also shown an increased prevalence of sarcopenia in patients with cancer[38], with sarcopenia associated with decreased progression-free survival in patients with metastatic cancers[39], which may in part be due to the potential overlap of sarcopenia with cachexia and malnutrition in people with cancer[40]. Sarcopenia has also been related to poor prognosis and complications in patients with liver cirrhosis[41]. A number of plausible mechanisms that may explain observed associations between sarcopenia and other health conditions have been proposed[39,41] but all require further investigation.

There has also been considerable interest in the relationships of both obesity and osteoporosis with sarcopenia, with the terms sarcopenic obesity and osteosarcopenia sometimes used to describe people living with these specific combinations of conditions, respectively. As these two conditions are often studied as outcomes in their own right, we refer readers to relevant reviews[42,43]. These highlight important evidence gaps and future research directions. Further research is also required to better understand respiratory sarcopenia[44] and sarcopenic dysphagia[45], and to elucidate the relationships between sarcopenia and other important age-associated conditions including dementia — relatively few studies have comprehensively examined sarcopenia among people living with dementia to date. A 2023 systematic review reported a significantly higher prevalence of sarcopenia in individuals with HIV infection compared with individuals without HIV[46]. Further investigation of this association is warranted, especially in low-income and middle-income countries where the combined impact of these conditions might lead to considerable disease and disability burden.

Risk factors

Many putative risk factors for sarcopenia have been described, some of which are acute and quickly lead to loss of muscle mass and function, whereas others accumulate over the life course and so take a longer time to impact sarcopenia. A systematic review and meta-analysis published in 2021 found that sociodemographic factors (for example, older age, being unmarried and living alone), being underweight, experiencing difficulties undertaking activities of daily living, smoking, alcohol intake, inactivity, disordered sleep, and several disease-related factors (such as diabetes mellitus, cognitive impairment, heart and respiratory disease, osteoporosis, osteoarthritis, depression, falls, anorexia, and anaemia) are associated with an increased likelihood of sarcopenia[47]. There was, however,

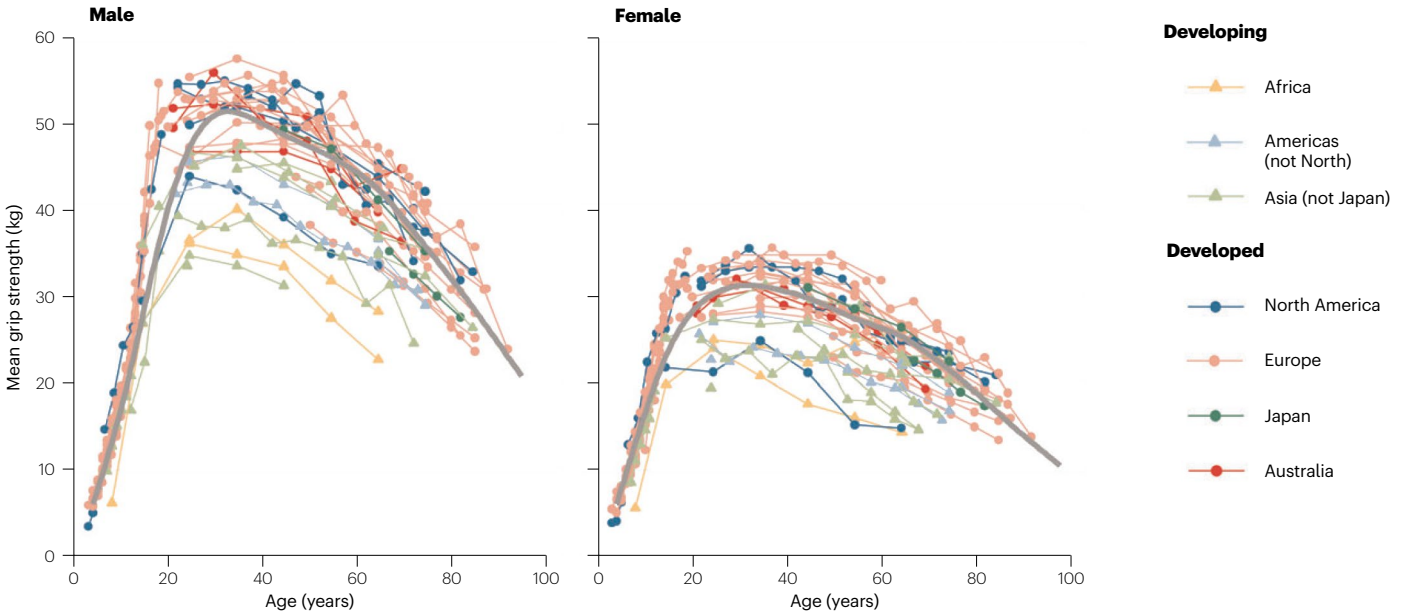

Fig. 2 | Grip strength by age, sex and UN world region. A total of 726 normative data items relating to 96,537 grip strength observations were extracted from 60 papers included in a systematic review[22]. Grip strength mean values from 63 different population-based samples reported in these 60 papers are shown. Each point represents the mean value of grip strength for each item of normative data, plotted against the mid-point of the age range it relates to. Values from the same sample are connected. Reprinted from ref. 22, CC BY 4.0.

considerable heterogeneity between studies and more consistent evidence of associations between some risk factors, such as inactivity and malnutrition, and sarcopenia than others. In addition, evidence regarding other factors, including sex and hypertension, and their association with sarcopenia was inconclusive[47].

Genetic risk factors. Research to identify potential genetic determinants of sarcopenia, has largely focused on specific components of sarcopenia definitions rather than sarcopenia per se. For example, several large genome-wide association studies (GWAS) have been undertaken to identify loci associated with lean body mass or grip strength. Although not all findings from individual GWAS have been replicated, single nucleotide variants in *TRHR*, *FTO*, *HSD17B11*, *VCAN*, *ADAMTSL3* and *IRS1* have been shown to be associated with lean mass, and variants in *BDNF*, *CPNE1* and *STC2* have been associated with grip strength[48]. In addition, data from the UK Biobank suggest that variants in HLA type are associated with sarcopenia, perhaps through inflammation[48].

Mechanisms/pathophysiology

Our current understanding of ageing skeletal muscle biology and the networks of cellular and molecular mechanisms that result in sarcopenia in humans is based on a wealth of data, the majority of which were obtained from preclinical animal studies, many using rodents. These studies have enabled the identification and investigation of various cellular components of skeletal muscle involved in normal maintenance of muscle mass and function. We summarize the cellular components involved in normal maintenance of muscle function to set the scene for the subsequent description of major age-related changes and processes that are thought to be implicated in the aetiology of sarcopenia.

Anatomy of skeletal muscle

Skeletal muscle structure and function (Fig. 3) is remarkably similar across species[49]. Skeletal muscle tissue represents ~40% of human body mass and there are ~600 different muscles that vary in size, architecture, and contractile and metabolic properties. These diverse muscles have vital roles in contraction to move different parts of the body, including breathing and eating, as well as regulation of metabolism and temperature[50]. Skeletal muscles are composed of highly specialized large multinucleated muscle fibres (myofibres) filled with many contractile proteins (such as myosin and actin) organized into sarcomeres. This contractile machinery is activated by electrical stimulation from a nerve (motor neuron) that connects to the myofibre surface membrane (sarcolemma) at the neuromuscular junction (NMJ). The sarcolemma is in close contact with a complexity of extracellular matrix (ECM) molecules via the adjacent specialized basal lamina on the myofibre surface rich in laminins, and a wealth of collagens and other molecules in the interstitial connective tissue. The ECM transfers and integrates the contractile force from the myofibres to the tendons to move parts of the skeleton. The interconnectivity between myofibres, NMJs, nerves, the ECM and a rich blood vessel network is critical for the maintenance of normal skeletal muscle function.

Types of muscle fibres. Skeletal muscles contain a spectrum of myofibres with very different properties, ranging from slow-twitch to fast-twitch contraction speeds (type 1 and type 2, respectively) identified by specific myosin isoforms and other contractile proteins[51,52]. The myofibre contraction uses ATP for energy, which is generated by different metabolic pathways and fuels. In general, type 1 fibres predominantly involve oxidation of lipids and type 2 fibres predominantly use glycogen or glucose[51,52]. In addition to the wide range of intrinsic (contractile and metabolic) properties, additional characteristics of slow and fast

myofibres that may be relevant to understanding mechanisms underlying the development of sarcopenia include: differential responses to exercise-induced muscle damage; susceptibility to atrophy; numbers of muscle precursors (satellite cells, required for regeneration); extrinsic influences of slow-twitch and fast motor neurons and different patterns of vasculature; and differential impacts of comorbidities and sexual dimorphism[52,53] (Fig. 4). Before extrapolating observations from a single muscle to different specialized muscles in the human body, the aforementioned variables in the context of ageing and the extent of manifestation of sarcopenia in different human muscles have to be taken into consideration[53]. In addition, differences between species when extrapolating preclinical data (for example, from rodents) to the human condition must be taken into account (Box 1).

Merits of preclinical studies

Diverse animal models provide fascinating insights into the mechanistic basis of ageing and longevity[54]. One powerful advantage of using laboratory rodents to investigate sarcopenia is that all tissues and entire muscles can be sampled at multiple ages across the entire lifespan. For example, a comprehensive transcriptomics study that compared data for three lower limb muscles and diaphragm from mice (both sexes) and rats (males), across seven ages (from 6 to 27 months), showed complex patterns of gene expression changes during ageing that differed between muscles, with more pronounced changes in rats, which more closely resemble humans, than mice[55]. Major pathways affected in sarcopenia often relate to increased NMJ denervation, inflammation, altered myofibre metabolism and the ECM[55]. Integration of such gene expression data with the complexity of information obtained (across species) using other powerful multiomics techniques including genomics, epigenomics, proteomics and metabolomics, along with the role of gut microbiota, provide new insights into the molecular mechanisms driving human sarcopenia[48]. Animal studies also allow easy genetic manipulation to determine the impact of specific molecules in ageing skeletal muscles, and to test interventions for potential clinical translation. To this end, dedicated mouse facilities now also model the genetic and biological complexity of human populations[56,57].

The challenge is to reconcile these extensive preclinical data where the focus is often on muscle mass, rather than function, with sarcopenia in humans where the reverse is true. As already emphasized, sarcopenia can be exacerbated by comorbidities (for example, cancer, obesity, diabetes, disuse and starvation) that can drive muscle atrophy preferentially in fast or slow myofibres involving very different mechanisms[52,58]. A further consideration is that many physiological studies of sarcopenia involve men only, with scarce data in older women, yet sexual dimorphism impacts many aspects of muscle biology[52,53].

Studies of muscle tissue in humans are limited, in part because muscle biopsies are invasive and can be hard to obtain, especially from older people. Biopsies are usually obtained from the vastus lateralis (or a few other limb muscles); the biopsy is very small and represents only a small portion of the entire muscle (and can vary in content depending on location and depth of sampling); thus extrapolation to all muscles can be problematic. However, human muscle biopsy analyses are very valuable to compare with the wealth of data obtained from animal studies. Fortunately, human blood samples can be relatively easily obtained to measure changes in many systemic molecules.

Pathobiology of sarcopenia

Myofibres are the central focus of sarcopenia; they are stable and long-lived with little evidence of intrinsic necrosis and regeneration in response to daily activities including exercise[52,53]. Maintenance of myofibre homeostasis requires a balance between protein synthesis and degradation (proteostasis), adequate nutrition and metabolism to

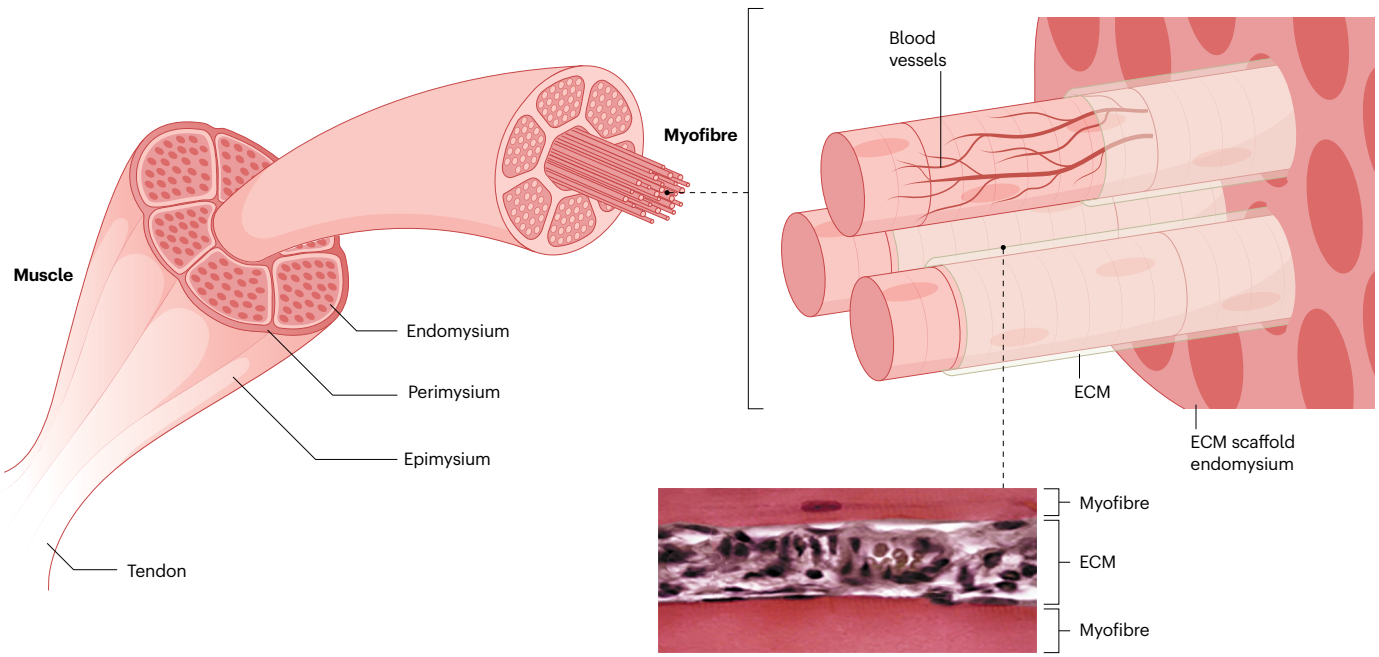

Fig. 3 | The overall structure of skeletal muscle tissue. The different layers of the extracellular matrix (ECM) in a whole muscle, and the complexity of ECM and cell interactions at the myofibre surface are illustrated. The image shows part of two myofibres (with pink sarcoplasm and myonuclei at the peripheral surface) adjacent to connective tissue (endomysium) that contains many cells including blood vessels. Adapted from ref. 149, Springer.

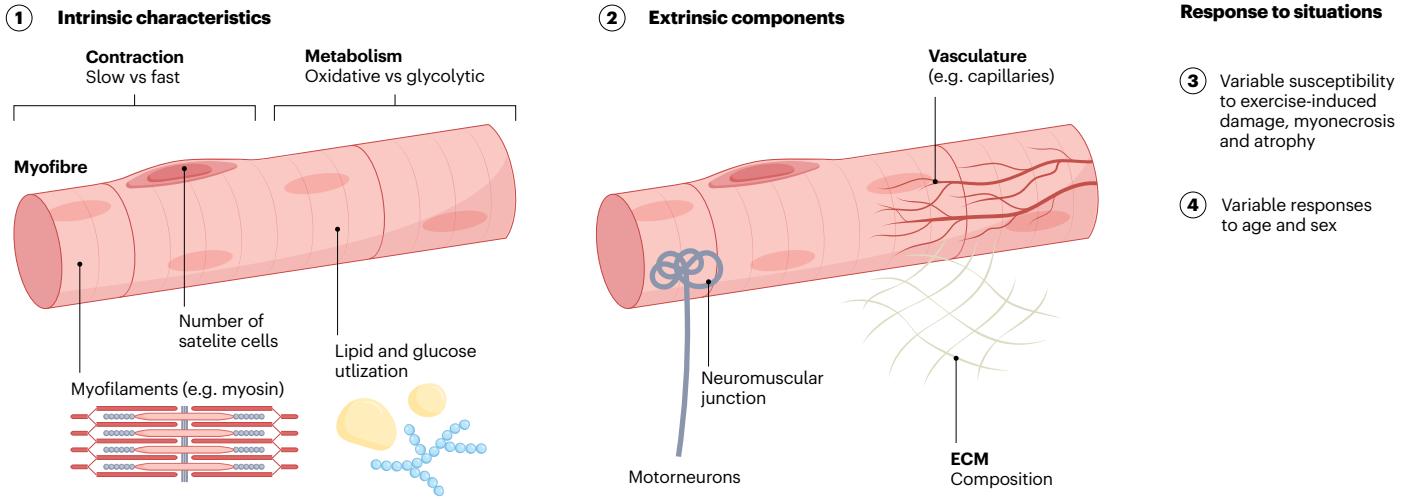

Fig. 4 | Differences between slow-twitch and fast-twitch myofibres. The great variability between the extent of sarcopenia in different human muscles is influenced, in part, by their composition of a range of slow-twitch and fast-twitch type myofibres, with many parameters influencing these differences in myofibre type. ECM, extracellular matrix. Adapted from ref. 52, CC BY 4.0.

generate energy (by mitochondria), a vascular supply to provide vital oxygen and nutrients, and innervation to stimulate contraction, involving a huge array of signalling and cellular interactions. These aspects are all altered during sarcopenia, along with ongoing age-related changes in the local ECM and systemic changes in hormones and the immune and inflammatory systems.

These and other major age-related molecular and cellular changes associated with biological ageing were originally described as nine hallmarks[59–61]. A review published in 2023 critically evaluated these nine hallmarks specifically in the context of sarcopenia and its pathophysiology, and highlighted five other hallmarks: altered inflammation, reduced vascular perfusion, neural dysfunction, ECM dysfunction and ionic dyshomeostasis[53]. The main age-related mechanisms and complex cellular interactions associated with sarcopenia are briefly summarized below. Detailed discussion and molecular aspects have been published elsewhere[48,53].

Changes to myofibres. Within the myofibre, alterations to DNA include epigenetic modifications that change patterns of gene transcription (involving signalling) accelerated by elevated oxidative stress. Age-related changes also occur in proteostasis (with reduced contractile proteins resulting in loss of muscle mass), influenced by altered mitochondria with increased oxidative stress and reduced (ATP) energy availability resulting in fatigue and impact on myofibre metabolism[53]. In intimate contact with the surface of myofibres are NMJs of the nerves that provide essential stimuli to initiate the complex events required for myofibre contraction; across the neuromuscular system there is extensive remodelling with age[52,53].

Vascular system. The vascular system with a dense dynamic capillary network surrounding myofibres is essential for muscle contraction and can rapidly increase in response to exercise to deliver oxygen and nutrients whilst removing waste products and heat. With ageing, there is reduced vascular perfusion, with decreased numbers of capillaries and fewer myofibre capillary contacts, and this reduces the capacity for muscle strength[53].

Neuronal system. Motor neurons and NMJ required for myofibre contraction, along with other aspects of the peripheral and central nervous system, change with ageing. Specifically, the vulnerability of fast motor neurons to oxidative damage results in denervation of fast myofibres and subsequent re-innervation by slow motor neurons converting fast to slow myofibres with reduced speed and reflexes[52,53]. In addition, there is also a loss of positional feedback from sensory neurons (in muscle spindles or proprioceptors) to motor neuron cell bodies in the spinal cord, with consequent decreased balance and gait[53].

ECM. General age-related fibrosis exacerbated by increased oxidative stress and crosslinking of collagen leads to increasing stiffness, which, in combination with changes in complexity of ECM interactions, have consequences for biomechanics and signalling[53].

Inflammation. Progressive age-related changes with a shift to a pro-inflammatory milieu with increased oxidative stress have a wide systemic impact, including responses to tissue damage and possible cellular senescence in skeletal muscle[53].

The precise sequence of these complex events, the extent of loss of muscle mass and function associated with each pathway, the life stages when people are most likely to be affected by each mechanism and those which may initiate and drive human sarcopenia remain unclear[48,53]. Many changes may be irreversible, although others can be ameliorated by exercise (or potentially by other interventions). Additional human data that will elucidate our understanding of the role of these different mechanisms in the aetiology of sarcopenia are anticipated in this emerging field.

Diagnosis, screening and prevention

Clinical presentation

Many people have low awareness of sarcopenia as a disease entity and the associated functional decline is instead perceived as an inevitable consequence of ageing[62]. Compounding the limited public awareness of sarcopenia is the finding that many clinical practitioners are

unaware of the diagnostic tools[63]. In addition, as the presentation of sarcopenia is often non-specific, it frequently goes undetected. However, sarcopenia should be suspected in people, who are, typically, older with impaired mobility (that is, slow or altered gait, difficulty rising from a chair or climbing stairs), perceived muscle weakness, progressive decline in physical function, unintentional weight loss or recurrent falls. Symptoms typically progress slowly over an extended period (from months to years), but sarcopenia can also develop quickly within days in acute clinical settings[64,65]. When left untreated, inability to walk and perform self-care activities of daily living (such as washing, dressing and feeding), falls and dependence may follow, with an increased risk of admission to a care home and premature death[66].

Although the focus of this review is age-related sarcopenia, it is important to acknowledge that sarcopenia is also common and should be suspected in a range of different clinical settings owing to malnutrition, inactivity or triggered by other long-term health conditions, such as heart failure, chronic obstructive pulmonary disease or cancer[1].

Case-finding. A wide variety of tools and instruments are available for case-finding sarcopenia, which reflects lack of agreement. Many of them, including the SARC-F questionnaire[67], the most widely used, show good specificity but low sensitivity in detecting sarcopenia[68,69]. These questionnaires are, therefore, not sufficient for diagnosis but may be used to identify people who would benefit from further assessment. Current consensus documents do not recommend population screening, as evidence to suggest a beneficial effect on any outcome of sarcopenia is lacking. Instead, a case-finding approach is suggested[18,20,21], either using the SARC-F questionnaire or clinical suspicion based on the symptoms described above. A positive case-finding test, or the presence of relevant symptoms, should prompt a diagnostic process to confirm or rule out the presence of sarcopenia.

Diagnosis

Diagnostic criteria. GLIS is in the process of establishing a global conceptual definition for sarcopenia[23,25]. GLIS aims to build on previous work of different organizations and consensus groups and align their criteria for the diagnosis of sarcopenia. This includes the criteria proposed by the European Working Group on Sarcopenia in Older People 2 (EWGSOP2) and endorsed by the Australia/New Zealand consensus[18,21], the 2019 version of the Asian Working Group for Sarcopenia consensus (AWGS 2019 (ref. 20)) and those published by the Sarcopenia Definitions and Outcomes Consortium (SDOC)[19]. Albeit not identical, the different groups recommend the measurement of at least one of three parameters — lean mass, muscle strength and physical performance — but with different recommended cut-off points for each parameter[1,23] (Table 1).

Muscle strength, a direct measure of muscle function, which is now a commonly accepted component of sarcopenia[25], is part of all three consensus definitions whereby a person may be considered to have probable sarcopenia when low muscle strength is found[18]. Once a diagnosis of sarcopenia is established, both the EWGSOP2 and the AWGS provide recommendations for defining the level of severity; however, other consensus definitions do not acknowledge differing severity levels. Sarcopenia is considered severe when both muscle strength and physical performance are impaired. The EWGSOP2 also classifies sarcopenia based on the aetiology (primary, that is age-related, or secondary, that is poor nutrition, inactivity or disease-related) and on its time course (acute, when it develops in <6 months, or chronic otherwise).

Muscle strength measurement. Muscle strength is at the forefront of the diagnosis of sarcopenia. Indeed, impaired muscle function characterized by low muscle strength is recognized as the most reliable skeletal muscle predictor of poor health outcomes including prolonged length of hospital stay, functional limitations, poor quality of life and

Box 1 | Important considerations when using animal models to investigate the mechanistic basis of sarcopenia in humans

Variability

Populations of humans are highly heterogeneous and considerable inter-individual variation exists in many factors across the life course, including lifestyle, genetics and long-term health conditions (for example, cancer and diabetes), which can exacerbate loss of muscle and complicate investigation of sarcopenia. By contrast, laboratory rodents are usually inbred and homogeneous, almost genetically identical and maintained under standard conditions across their lifespan, in strict specific pathogen-free conditions, to minimize variations and optimize scientific investigations. Humans and rodents also have markedly different lifespans. The healthy lifespan for normal laboratory rodents is ~2 years, and ageing occurs over ~9 months (from 15 to 24 months)[55]. This is a very short time frame compared with humans, where lifespan can extend to between 70 and 110 years, and ageing starts to manifest and progress over many decades before death.

Quantifying and defining sarcopenia

In rodents, sarcopenia is generally defined as normal age-related loss of mass (of dissected muscles) usually measured in hindlimb muscles. The transition to sarcopenia occurs from ~15 months of age (mature adult) and is pronounced by 24 months (this is usually not considered a pathology or disease). After 24 months, heterogeneity between individuals increases, with tumours and other comorbidities[55], and many animals are not in good health by ~30 months of age. Lifespan can vary between different colonies of animals and with their housing conditions.

Muscle function also declines in ageing rodents after ~15 months; for example, distance and speed for voluntary wheel running[150,151] and hindlimb gait[152]. However, such measurements in whole animals are time-consuming and rarely used as a routine readout of sarcopenia. By contrast, human muscle function is readily measured by a range of relatively simple different tasks, such as grip strength. Interestingly, regional manifestation of sarcopenia is similar in humans and rats; as human muscle mass declines more quickly with age in lower than in upper limbs, and sarcopenia (linked to neuromuscular dysfunction) is initially pronounced in hindlimbs of rats[152].

Table 1 | Criteria recommended for defining sarcopenia by different international consensus groups

Low lean mass			Low grip strength		Low physical performance	
Measure	**Gender**	**Recommended cut-off point**	**Gender**	**Recommended cut-off point[a]**	**Measure**	**Recommended cut-off point**
EWGSOP2 (ref. 18)[b]						
ALM	Male	<20 kg	Male	<27 kg	Gait speed	≤0.8 m/s
	Female	<15 kg	Female	<16 kg	SPPB score	≤8
ALMI	Male	<7.0 kg/m^2			TUG	≥20 s
	Female	<5.5 kg/m^2			400 m walk test	Non-completion or ≥6 min
					Five chair stands time	>15 s
AWGS[20]						
ALMI	Male	<7.0 kg/m^2 with DXA or BIA	Male	<28 kg	Gait speed	<1.0 m/s
	Female	<5.4 kg/m^2 with DXA; <5.7 kg/m^2 with BIA	Female	<18 kg	SPPB score	<9
					Five chair stands time	≥12 s
SDOC[19]						
Not used			Male	<35.5 kg	Gait speed	<1.0 m/s
			Female	<20 kg		

The definitions of these three working groups are presented as they reflect the most up to date consensus for Europe, Asia and the USA at the time of publication, and it is the recommendations of these working groups that have been most commonly operationalized in studies synthesized in published systematic reviews of sarcopenia prevalence[27–29]. ALM, appendicular lean mass; ALMI, appendicular lean mass index (= ALM/height^2, where height is in metres); AWGS, Asian Working Group for Sarcopenia; BIA, bio-electrical impedance analysis; DXA, dual-energy X-ray absorptiometry; EWGSOP2, European Working Group on Sarcopenia in Older People 2 (note that this definition has also been adopted by the Australian and New Zealand Society for Sarcopenia and Frailty Research Sarcopenia Diagnosis and Management Task Force[21]); SDOC, Sarcopenia Definitions and Outcomes Consortium; SPPB, short physical performance battery; TUG, timed up-and-go. [a]These are the cut-off points for absolute grip strength. SDOC highlights that adjustments of strength for body mass index, body fat or arm lean mass are also acceptable. [b]EWGSOP2 defines confirmed sarcopenia as the presence of low muscle strength and low muscle quantity (lean mass). Low physical performance is then used to define severity of sarcopenia.

death[70–74]. Muscle strength is usually measured by hand grip strength using a hand-held dynamometer (typically a Jamar hydraulic or electronic device), which is widely considered to be an adequate marker of overall limb strength[75]. It is important to standardize the way grip strength is measured using a validated protocol[76,77]. The person being assessed is asked to sit on a chair with the elbow flexed at 90° and the maximum grip strength of the dominant hand is measured. Different sex-specific cut-off points have been proposed in different regions, to account for differences in populations and settings[22]. Although other reasons for impaired muscle strength exist (for example, poor motivation or hand osteoarthritis), low muscle strength is often indicative of sarcopenia and is predictive of adverse functional outcomes, and its detection is a good reason to consider intervention[18].

Muscle mass measurement. No reliable method of measuring full body muscle quantity, that can be feasibly applied cost-effectively at scale across multiple settings, is available. To date, CT imaging is one of the gold standard techniques for quantifying muscle mass in sarcopenia[78]. Indeed, CT imaging gives precise estimations of skeletal muscle mass with the most common metrics being skeletal muscle area (SMA), skeletal muscle index (SMI) and muscle radiation attenuation (MRA), which is a measure of fat infiltration in the muscle. Although it provides reliable data, the use of CT imaging in daily practice is limited owing to its cost and the risk of radiation-related adverse effects. Additionally, no normative population data to define cut-off points are available. MRI can also be used but its use is limited owing to its high cost, several contraindications, such as implants, and limited availability in various settings[78,79].

Dual-energy X-ray absorptiometry (DXA) and bio-electrical impedance analysis (BIA) are alternative methods of estimating muscle quantity. DXA involves using a scanner to pass two low-dose X-rays through the body (either the whole body or specific regions). These X-rays are absorbed differently by bone and soft tissues and, therefore, data from the scans can be used to quantify bone mineral density, fat mass and lean mass. BIA involves using scales, which pass small electrical currents around the body. As these currents pass at different speeds through different body tissues owing to variation in their water content, with fat mass causing greater impedance due to its lower water content than lean mass, readings from BIA can be used to estimate whole-body fat and lean mass.

Recommended cut-off points for low lean mass provided in consensus definitions usually refer to DXA and/or BIA (Table 1), as reference data for lean mass assessed using these methods are more widely available. However, their use is controversial because of concerns about the accuracy of the measures of lean mass they provide and how adequately these measures correlate with muscle mass. DXA provides an indirect estimate of the skeletal muscle mass that may be adjusted for body size[18,20]. In addition, DXA is not always available, has high equipment costs, and is not strongly linked to outcomes[19]. BIA has been widely used as it is a cheap, fast and easy-to-use method of estimating body composition without any radiation exposure. However, accuracy is limited because measurements depend on several physical assumptions and may be influenced by parameters such as oedema, skin temperature, sweat and bladder filling. In addition, no standard set of equations are available to estimate lean mass from physical electrical conduction parameters and equations that do exist are specific to particular

populations and types of BIA machine, which may not be generalizable to other populations and devices.

Another method of measuring muscle quantity is ultrasonography, which is widely available and is used in daily practice to support muscle mass point-of-care assessment[18,80]. Indeed, ultrasonography has been shown to have good validity in estimating muscle mass of older adults, including those with comorbidities, when compared with DXA, MRI and CT[80,81]. Standardized anatomical landmarks and measuring points have been proposed in consensus statements, although further validation studies are needed especially as the technique requires practice to be accurate and reproducible[82].

An alternative to imaging is the D3-creatine (D3-Cr) dilution method for estimating total-body skeletal muscle mass, and interest in its use is growing[83]. However, a number of methodological concerns and practical considerations still need to be addressed before it or any other biomarker can be widely adopted[84].

Physical performance. Low physical performance is a component of some definitions of sarcopenia and a method of assigning severity in others[18–20]. Physical performance is a multidimensional concept, which provides an overview of muscle function, locomotion and balance. Many measures of physical performance are described in various settings, but four are widely used to assess the severity of sarcopenia: timed up-and-go, gait speed, chair stand performance, and the short physical performance battery[4] (which is a composite score based on gait speed, chair stand performance and standing balance)[18,77]. Of these measures, gait speed is probably the most widely used in sarcopenia research and is recommended by SDOC because it is strongly linked to functional outcomes. Time to walk 400 m has also been used in some major sarcopenia studies, with the inability to complete it in <15 min being considered a walking disability. The usefulness of the chair stand test is debated. It can be used as an indicator of physical performance and the EWGSOP2 has proposed it as an alternative to grip strength for identifying low muscle strength. However, there is some evidence that these two parameters are not equivalent[85,86].

Differential diagnosis

The main differential diagnosis includes other causes of low muscle mass because sarcopenia and low muscle mass, although overlapping, are different conditions[36]. Indeed, low muscle mass (also referred to as muscle wasting) can occur at any age, in the context of acute or chronic conditions including malnutrition[80]. Most current definitions of sarcopenia, malnutrition and cachexia all include low muscle mass as a criterion. As a consequence, when low muscle mass is found, all three conditions (that is, sarcopenia, malnutrition and cachexia) should be considered, as they may coexist. Guidance on how these conditions are distinguished is available elsewhere[23,40].

Prevention

Evidence from longitudinal population-based studies suggests that a life course approach to the prevention of sarcopenia may be beneficial. For example, pooled data on grip strength measured in 12 different UK studies at different ages show that grip strength increases to a peak in early adult life followed by a maintenance phase, prior to decline with increasing age[87]. On this basis, interventions during different periods of life may influence the risk of developing sarcopenia in later life through effects on both peak strength achieved and subsequent rates of decline[88]. However, evidence for the long-term effectiveness of interventions over the life course for prevention of sarcopenia is, as yet, limited.

Among various interventions that can be implemented, nutrition and physical activity seem to be the most promising[89]. Growing evidence suggests that the nutritional approach is a key component of improving lean body mass in adulthood[89,90]. However, evidence on specific nutrients that are effective for preventing the development of sarcopenia is more limited. Concerning physical activity, the implementation of early preventive strategies during adolescence is of particular interest. Indeed, exercise interventions implemented during this period are likely to be beneficial as part of a long-term strategy to delay the onset of poor health outcomes[91,92]. Regarding adult life, there are cumulative benefits of physical activity across adulthood on physical performance in midlife[93,94]. Some groups advocate for person-centred approaches to physical and dietary interventions in those at high risk of sarcopenia[21]. Whether treatments for conditions, such as hypertension, diabetes mellitus or dyslipidaemia, can prevent sarcopenia is currently unclear.

Management

The goals of treatment for sarcopenia are to reverse or stabilize the loss of muscle strength (and ideally also muscle mass), and thereby preserve or enhance quality of life and the ability to undertake activities of daily living. Currently, few management options exist with good randomized controlled trial (RCT) evidence for the treatment of sarcopenia. Nevertheless, this is an active area of research with promising emerging therapies and the management of sarcopenia is likely to see rapid changes in the next few years.

Resistance exercise

Resistance exercise is effective in improving muscle strength and muscle mass in people with or at risk of sarcopenia[95,96] and current evidence from RCTs supports offering resistance exercise to all those diagnosed with sarcopenia. Established principles of exercise prescription, namely specificity, overload and progression should be used to deliver an effective exercise dose[95,97] (Box 2). The optimum duration, frequency and intensity of training are still debated, but studies have shown improvements with one or two training sessions per week and with intensities as low as 50% of one-repetition maximum (that is, the maximum muscle strength that an individual can exert for a single repetition of an exercise) in older people with sarcopenia[95]. However, higher intensities and frequencies (up to 70–85% of one-repetition maximum two or three times per week) may be required to produce optimal gains[98]. Mixed modality exercise programmes (including resistance exercise, but also aerobic and balance exercise) are also recommended to manage comorbidities and age-associated conditions, such as cardiorespiratory disease and falls, which frequently accompany sarcopenia[99]. For example, large trials such as the SPRINTT project, involving individuals with physical frailty and sarcopenia, have demonstrated that such interventions can reduce the incidence of mobility disability[100].

Nutritional interventions

Protein. Current evidence suggests that protein supplementation is effective in improving muscle strength and muscle mass when used as an adjunct to resistance exercise training[101]. The evidence for protein supplementation as a standalone intervention for sarcopenia is less clear[102], and debate continues as to the most appropriate protein source (for example, animal or dairy versus plant)[103], timing of ingestion (especially relative to exercise) and the amount required. Current guidance on adequate protein intake varies significantly across different

Box 2 | Example prescription for resistance exercise training in people with sarcopenia

Training frequency
- Two sessions per week

Exercise selection
- Lower body
  - Squat or leg press
  - Knee extension
  - Leg curl
  - Calf raise
- Upper body
  - Chest press
  - Seated row
  - Pull down

Exercise intensity
- Repetition continuum-based prescription:
  - 40–60% 1RM progressing to 70–85% 1RM
- RPE-based prescription:
  - RPE 3–5 on ten point scale progressing to RPE 6–8

Exercise volume
- 1–3 sets of 6–12 repetitions

Rest periods
- Within session
  - 60–120 s between sets; 3–5 min between exercises
- Between sessions
  - At least 48 h

1RM, one-repetition maximum; RPE, rating of perceived exertion. Box 2 reprinted with permission from ref. 95, Oxford University Press.

guidelines, some of which focus on healthy older people and some of which focus on older people living with sarcopenia[21,104–106]. Many of these guidelines are based on observational data and further RCTs are needed to establish whether increased protein intake improves outcomes for people living with sarcopenia in the absence of resistance exercise training[90]. Although current guidelines for patients with chronic kidney disease (CKD) suggest reducing protein intake[107], any possible benefit of this reduction on renal function must be weighed against potential deleterious effects on skeletal muscle, particularly owing to an increased risk of sarcopenia in patients with CKD[108].

Vitamin D. Current evidence for the effectiveness of vitamin D as an intervention for sarcopenia is limited. Systematic reviews have suggested either a small beneficial effect on muscle strength and mass, no effect on, or even possible worsening of, muscle strength and physical performance[109–111] and increased risk of falls, particularly at very high doses[112]. The relationship between the frequency or dose of vitamin D supplementation and outcomes is unclear, but individuals with low baseline 25-hydroxyvitamin D concentrations may be more likely to benefit[113]. On the basis of existing evidence, vitamin D supplementation seems unlikely to provide substantial improvements in muscle strength or function, although vitamin D supplementation may still be indicated for coexisting conditions (for instance, as an adjunct to antiresorptive therapy in osteoporosis)[114].

Other interventions. A range of other nutritional interventions are currently under study. These interventions include leucine, hydroxymethyl butyrate, and ω-3 fatty acids as well as nutraceuticals with effects on inflammation, mitochondrial function and cellular senescence[115]. Current data on these interventions are mixed and many of them have not been tested specifically in populations with sarcopenia. Further studies focusing on populations with sarcopenia are required to establish their role in sarcopenia treatment.

There is some evidence that combined interventions (for instance, whey protein, amino acids and vitamin D) are effective in improving muscle mass and strength in people with sarcopenia[116]. The role of weight loss therapies (via diet or via pharmacological agents such as GLP1 agonists) in people with a combination of sarcopenia and obesity (sarcopenic obesity) requires further study. Although weight loss has the potential to improve physical function, it may also lead to further loss of lean mass in people with sarcopenia[117], and adjunctive exercise may be essential to mitigate loss of muscle.

Exercise mimetics such as electrostimulation and whole-body vibration provide potentially attractive alternatives to exercise for people limited by joint pain or recent surgery. Initial findings suggest that electrical stimulation can prevent the loss of muscle mass after major surgery and can improve muscle mass and strength when used for short courses[118–120]. Whether electrostimulation therapies can improve muscle strength and physical function over the longer term is unclear and further trials are required to define the place of these therapies in the overall treatment of sarcopenia.

Drugs

No drugs have yet been shown to have unequivocal benefits for the treatment of sarcopenia in humans. However, many different drug classes are currently being researched to establish proof-of-concept or efficacy for the treatment of sarcopenia; both novel agents and repurposed compounds are under investigation[121]. A number of drug classes have failed to demonstrate efficacy, including angiotensin-converting enzyme inhibitors and angiotensin receptor blockers[122], spironolactone and allopurinol. Some classes of medication may have beneficial effects but are limited by adverse effects; for example, testosterone and growth hormone[121]. Considerable effort has gone into the development of myostatin pathway inhibitors (either by targeting myostatin itself or the activin receptor complex). Myostatin is a naturally occurring myokine that binds to the activin II receptor, initiating a cascade of downstream signalling that inhibits satellite cell and myoblast proliferation and mature myofibre hypertrophy — effects that can be reversed by myostatin pathway inhibitors[123]. These agents are effective in improving lean mass in selected groups but accompanying improvements in muscle strength or physical function have been equivocal[124].

Classes of therapeutics under active exploration include selective androgen receptor modulators[125], NAD analogues (for example, trigonelline[126]), and senolytic and senostatic agents (including metformin)[127]. Agents targeting mitochondrial dysfunction (for example, urolithin A) have shown initial promise in small RCTs[128]. A range of other therapies including anti-inflammatories and Mas receptor agonists are also being investigated (Table 2). Additional classes of drugs, such as troponin activators and ryanodine receptor modulators, which

Table 2 | Example medication classes under investigation for sarcopenia

Medication class	Drugs
Myostatin pathway inhibitors	Bimagrumab
Senolytics and senostatics	Dasatinib in combination with quercetin, fisetin
Anti-inflammatories	JAK-2 inhibitors (e.g. tofacitinib), ibuprofen
mTOR modulation	Metformin, rapamycin
NAD analogues	Nicotinamide riboside, acipimox
Agents to improve mitochondrial function	Urolithin A, Renamezin
Antioxidant/redox pathway modulators	Allopurinol
Renin–angiotensin–aldosterone system modulators	Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, spironolactone, Mas (angiotensin 1-7 receptor) agonists
Androgen receptor agonists	Testosterone, selective androgen receptor modulators
Ghrelin analogues	Anamorelin

JAK, Janus kinase; mTOR, mechanistic target of rapamycin.

are currently being studied for other myopathies, are also likely to be considered for study in sarcopenia in the future.

Holistic assessment

Sarcopenia rarely occurs as an isolated medical condition, and effective management requires a holistic approach to improve the health of the individual. In younger adults, this approach should comprise a comprehensive medical history, examination and investigations to rule out alternative diagnoses, particularly progressive neurological conditions. Older people with sarcopenia are likely to benefit from comprehensive geriatric assessment. This multidisciplinary, evidence-based process of multidomain assessment and management serves to address other medical conditions, medication use, pain control and psychological state, optimizes functional abilities and ensures appropriate social support[129]. Comprehensive geriatric assessment has been shown to improve a range of outcomes including independence, return home from hospital and reduced short-term death rates[130,131]. All of these aspects are relevant and important in the management of older people living with sarcopenia.

The key step in management is to deliver resistance exercise training via supervised, tailored programmes with adequate intensity and progression, with protein supplementation as a potential adjunctive therapy (Fig. 5). Other therapies should be offered only as part of RCTs, pending more robust evidence of their efficacy, safety and feasibility. Older people (who constitute the majority of people with sarcopenia) are often under-served by research, and recruitment to sarcopenia trials has been challenging historically. Efforts to develop the evidence base for sarcopenia treatments have been complicated by a focus on skeletal muscle function in healthy people, and offering trial participation to people with sarcopenia is necessary to build a relevant evidence base for future treatment of sarcopenia.

Quality of life

The growing body of evidence highlighting the adverse effects of sarcopenia on individuals, their families and communities is one of the driving forces behind increasing efforts to raise awareness of sarcopenia, improve its diagnosis and identify effective management strategies for its prevention and treatment. This includes evidence of increased risk of many adverse outcomes including falls, fractures and premature mortality[4–8], as well as increased health-care use[132]. However, the outcome that arguably best captures lived experience is quality of life.

In one of the first studies to examine a key component of sarcopenia, muscle weakness, in relation to health-related quality of life (HRQOL)[133], cross-sectional associations between lower grip strength and reduced HRQOL were reported in a sample of ~3,000 older community-dwelling men and women participating in the Hertfordshire Cohort Study. Consistent with this are subsequent findings from longitudinal analyses in which weaker grip strength and slower chair rise, walking and timed up-and-go speeds at baseline were associated with lower positive mental wellbeing scores 4–10 years later in the Hertfordshire Cohort Study and four other British population-based studies[134].

Since the publication of these early studies, a number of reviews of the associations between sarcopenia, its key components and HRQOL have been undertaken[135–138]. In systematic reviews published in 2016 and 2017 (refs. 136,137), evidence of associations between sarcopenia (or lower levels of its components) and reduced HRQOL were found in included studies (n = 20 and n = 6, respectively). However, both sets of review authors called for additional high-quality studies with greater standardization of assessments of sarcopenia and HRQOL. Findings from a systematic review published in 2023 suggest that researchers have responded to this call[138]: this later review identified 43 observational studies (most published between 2018 and 2023) that had examined the association between sarcopenia and quality of life in adults ≥60 years of age living in the community or assisted living facilities. These studies were conducted in 24 countries with a greater concentration in Europe than other continents but with some representation from all world regions. The meta-analysis of individual study results provided evidence of a statistically significant association between sarcopenia and lower HRQOL. Caution is required in the interpretation of the overall scale of the association estimated owing to a high degree of heterogeneity between studies. Nonetheless, this review provided compelling evidence that in observational studies of

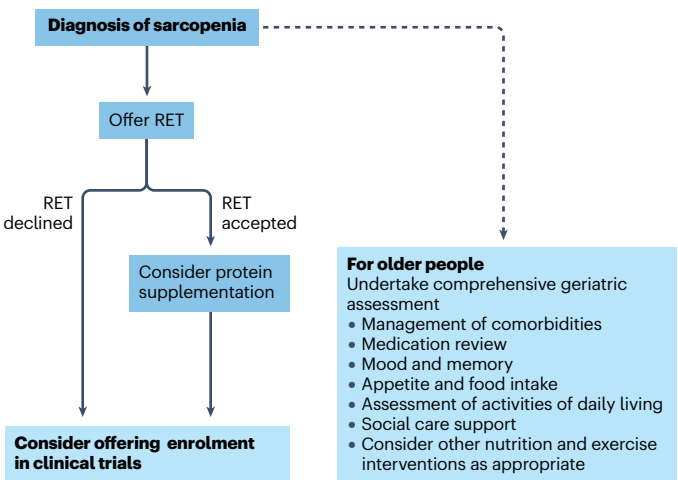

Fig. 5 | Algorithm for management of sarcopenia. This algorithm outlines the different management strategies that may currently be followed after sarcopenia is diagnosed dependent on whether or not resistance exercise training (RET) is offered and the age of the person diagnosed.

Box 3 | Patient experience

In 2023, 11 older people (six men and five women) who had experienced age-related decline in muscle function were identified via Patient and Public Involvement and Engagement events led by the Ageing, Sarcopenia and Multimorbidity theme within the National Institute for Health and Care Research (NIHR) Newcastle Biomedical Research Centre, UK. These people were each asked a standard set of questions to help inform future research on sarcopenia. The participants were asked about changes in their strength and physical function over time, the impacts of these changes on their daily lives, and how this made them feel. With their consent, anonymized excerpts from their responses are quoted below.

Changes in muscle strength and ability to do physical everyday tasks

- I've noticed I've become weaker for example walking up and down stairs. I've found getting up and out of a chair harder and noticed my upper body strength has got weaker.
- I can't walk as far as I used to, can now only manage to walk the length of a football pitch and back. Bending down and gardening is harder and I have to push up off the floor. I've noticed my grip isn't as strong as it used to be and I find it harder to reach for things.
- I've definitely noticed changes. It's trickier to get out of a chair now and my feet wobble. I'm much slower at doing my job. Climbing the stairs is also harder. I'm a lot slower than I used to be and I have to grab the banister.

Impacts on daily life, and how these impacts made people feel

- They [changes in strength and function] have had a big impact. I can't walk the dog as far as I used to and I only go on shorter walks now. I get frustrated that I can't do what I used to be able to do.
- Was easy to carry two full coal buckets, now it's down to one. Found holding my arm out to the side to pick up a full glass hard, had to hold my right arm to help with kettle holding. Feel despondent, annoyed and determined to get strength back.
- I used to be in a walking group but now I can't keep up with the pace. I feel sad that I had to stop going.
- I'm now limited in what I can do. I've had to get a gardener to help with the garden. I'm also very independent so found it hard on my mental wellbeing to ask for help. It upsets me that I can't do the things I used to and I sometimes get frustrated.

older adults, most of whom were community-dwelling, those participants classified as living with sarcopenia typically have lower HRQOL than those without sarcopenia. Reports of similar associations in specific patient groups (for example, people with colorectal cancer[139] or Parkinson disease[140]) serve to highlight that the impacts of sarcopenia on quality of life are likely to be wide-reaching, extending beyond the community to clinical settings, with potential to exacerbate the impacts of other diseases on HRQOL.

A noteworthy finding in the systematic review published in 2023 (ref. 138) is that stronger associations between sarcopenia and lower HRQOL were observed when a condition-specific rather than generic HRQOL measure was used. The condition-specific instrument used was the Sarcopenia Quality of Life questionnaire (SarQoL). Since its development in 2015 (ref. 141), SarQoL has been translated into 35 languages and multiple validation studies have demonstrated the ability of this 55-item instrument to detect differences in HRQOL between older people living with and without sarcopenia[138]. Although the team who developed SarQoL have identified further research required on the psychometric properties of this instrument, evidence for its utility as a patient-reported outcome measure in clinical trials is emerging[142].

Associations between sarcopenia and lower HRQOL are likely to be at least partly explained by the detrimental impacts of sarcopenia on people's mobility, independence and ability to carry out the physical tasks of daily living (Box 3), all of which have been shown to be important facets of quality of life that are highly valued by people as they age[143]. Further work to understand these associations and elucidate novel opportunities to mitigate the adverse impacts of sarcopenia on quality of life will be facilitated by the assessment of HRQOL, using a condition-specific instrument, in people living with or at high risk of developing sarcopenia in different settings and by the incorporation of HRQOL assessments in studies of interventions designed to prevent or treat sarcopenia.

Outlook

Sarcopenia is a topic whose time has come and a number of factors have contributed to this[23]. First, although sarcopenia is a relatively newly recognized clinical condition, it is common, occurs globally, and is increasingly perceived as a major problem by patients and healthcare providers[144]. Second, an effective treatment exists in the form of resistance exercise training that can be implemented now. Third, the potential for advances in the field is immense with great progress being made in understanding the underlying skeletal muscle biology and an increasing focus on how these findings can be translated into improving the diagnosis, treatment and prevention of sarcopenia across the life course. A particularly exciting feature of the field is the opportunity for scientists and clinicians from a range of disciplines to contribute, and biomedical science has a particularly important role to play.

Epidemiology

Despite variation in estimates of prevalence resulting from the use of different approaches to definition, it is clear that sarcopenia is common. GLIS is likely to bring about international consensus in the conceptual definition of sarcopenia and in standard approaches to its operationalization and diagnosis in different world regions, with recognition that different populations may still require different cut-off points. This in turn will improve the consistency of prevalence estimates not only in the general population (including older people) but also in patient groups with specific long-term health conditions.

Mechanisms and pathophysiology

Some of the most exciting developments in the sarcopenia field are currently happening in ageing skeletal muscle biology, and harnessing progress in understanding the hallmarks of ageing has been key. Hallmarks are biological mechanisms characterized by being associated with age and also with the potential to be experimentally manipulated

to both accelerate and slow ageing. The number of ageing hallmarks has increased from nine to 12 in a review of this field in 2019 (ref. 61), and applying the original nine to the context of skeletal muscle has delineated those most likely to be relevant in sarcopenia[53]. In addition, five novel hallmarks have been proposed for ageing skeletal muscle (altered inflammation, reduced vascular function, neural dysfunction, ECM dysfunction and ionic dyshomeostasis), and these should be the focus of research, for example, to identify pathophysiological causes resulting in a common phenotype. Studies that include women as well as men will also be crucial.

Diagnosis, screening and prevention

In the past 10 years, there has been considerable convergence in approaches to sarcopenia diagnosis, with a growing emphasis on the central importance of muscle strength. GLIS will provide impetus for an internationally agreed definition in the near future[23]. Existing evidence demonstrates that adopting a standard definition of sarcopenia can support required organizational changes to clinical practice[145], improve awareness and case-finding and lead to local service improvements that benefit people living with sarcopenia[146], suggesting that GLIS will enable a step change in both research and clinical practice at a global level. Case-finding remains the approach of choice as there is no evidence to date that screening is effective. The evidence for preventive strategies is currently limited, although a life course approach to understanding sarcopenia is advocated. With deep phenotyping of skeletal muscle being embedded increasingly widely in longitudinal epidemiological studies of women and men[147,148], important insights are likely to accrue.

Management

Resistance exercise training is currently the mainstay of treatment for sarcopenia, and recognizing the importance of guidance on how to prescribe appropriate exercise has been an important step forward[95]. However, exercise is not suitable for all people living with sarcopenia, so discovering both adjunctive and alternative treatments is imperative. Nutritional supplementation seems to have a role, particularly if nutritional status is suboptimal. By contrast, drug development is proving challenging and there are no licensed drugs for sarcopenia to date. However, drug development is an area of considerable interest and breakthroughs are likely to be enabled by close collaboration between those working in preclinical and human ageing skeletal muscle biology and those working in experimental medicine to translate the mechanistic understanding into first-in-human intervention studies.

Quality of life

One of the most important features of sarcopenia is its adverse effect on people's quality of life. This has not always been captured consistently in human studies to date but is an increasing focus for both observational and intervention studies and trials going forward.

Global perspectives

Important advances have been made in sarcopenia research in the past 25 years and the field is now ready for a step change, with an internationally agreed approach to the definition and diagnosis likely to be available in the near future. GLIS is central to this but, despite ensuring for the first time in an international sarcopenia initiative the involvement of researchers from all world regions, considerable imbalance remains in researchers, funding and findings from continents such as Africa, and South America. This is hampering progress, and sustained support, for example, to encourage international research collaboration initiatives across continents, could enable sarcopenia to be recognized, understood and managed across all areas of the world and, therefore, be transformative.

Published online: 19 September 2024

References

1. Cruz-Jentoft, A. J. & Sayer, A. A. Sarcopenia. *Lancet* **393**, 2636–2646 (2019).
This is a state of the art seminar paper on sarcopenia with a clinical focus.
2. Fielding, R. A. et al. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International Working Group on Sarcopenia. *J. Am. Med. Dir. Assoc.* **12**, 249–256 (2011).
This is one of two substantive consensus definitions for sarcopenia developed and published almost simultaneously in 2010/2011 (see Cruz-Jentoft et al. (2010) for the other). This definition was developed by investigators in the USA under the leadership of the International Working Group on Sarcopenia (IWGS).
3. Anker, S. D. et al. Welcome to the ICD-10 code for sarcopenia. *J. Cachexia Sarcopenia Muscle* **7**, 512–514 (2016).
4. Guralnik, J. M. et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J. Gerontol.* **49**, M85–M94 (1994).
5. Visser, M. & Schaap, L. A. Consequences of sarcopenia. *Clin. Geriatr. Med.* **27**, 387–399 (2011).
6. Zhang, X. et al. Sarcopenia as a predictor of all-cause mortality among older nursing home residents: a systematic review and meta-analysis. *BMJ Open.* **8**, e021252 (2018).
7. Cawthon, P. M. et al. Putative cut-points in sarcopenia components and incident adverse health outcomes: an SDOC analysis. *J. Am. Geriatr. Soc.* **68**, 1429–1437 (2020).
8. Xu, J. et al. Sarcopenia is associated with mortality in adults: a systematic review and meta analysis. *Gerontology* **68**, 361–376 (2022).
9. Rosenberg, I. H. Summary comments. *Am. J. Clin. Nutr.* **50**, 1231–1233 (1989).
This is widely believed to be the first publication to use the term 'sarcopenia'.
10. Evans, W. J. & Campbell, W. W. Sarcopenia and age-related changes in body composition and functional capacity. *J. Nutr.* **123**, 465–468 (1993).
11. Bijlsma, A. Y. et al. Chronology of age-related disease definitions: osteoporosis and sarcopenia. *Ageing Res. Rev.* **11**, 320–324 (2012).
12. Cawthon, P. M. Recent progress in sarcopenia research: a focus on operationalizing a definition of sarcopenia. *Curr. Osteoporos. Rep.* **16**, 730–737 (2018).
13. Coletta, G. & Phillips, S. M. An elusive consensus definition of sarcopenia impedes research and clinical treatment: a narrative review. *Ageing Res. Rev.* **86**, 101883 (2023).
14. Muscaritoli, M. et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". *Clin. Nutr.* **29**, 154–159 (2010).
A paper by the Special Interest Group (SIG) of the European Society for Clinical Nutrition and Metabolism (ESPEN) that emphasized the need for a clear clinical definition of sarcopenia to enable the application of effective diagnostic and treatment approaches.
15. Cruz-Jentoft, A. J. et al. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. *Age Ageing* **39**, 412–423 (2010).
This is one of two substantive consensus definitions for sarcopenia developed and published almost simultaneously in 2010/2011 (see Fielding et al. (2011) for the other). This definition was developed by investigators in Europe under the leadership of the European Working Group on Sarcopenia in Older People (EWGSOP).
16. Chen, L. K. et al. Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. *J. Am. Med. Dir. Assoc.* **15**, 95–101 (2014).
17. Studenski, S. A. et al. The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. *J. Gerontol. A Biol. Sci. Med. Sci.* **69**, 547–558 (2014).
18. Cruz-Jentoft, A. J. et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* **48**, 16–31 (2019).
This is an updated sarcopenia definition produced by the European Working Group on Sarcopenia in Older People 2 (EWGSOP) that has replaced their earlier definition (Cruz-Jentoft et al. (2010)).
19. Bhasin, S. et al. Sarcopenia definition: the position statements of the Sarcopenia Definition and Outcomes Consortium. *J. Am. Geriatr. Soc.* **68**, 1410–1418 (2020).
A paper outlining the position statements of the Sarcopenia Definitions and Outcomes Consortium (SDOC), which provides an evidence-based definition of sarcopenia.
20. Chen, L. K. et al. Asian Working Group for Sarcopenia: 2019 Consensus update on sarcopenia diagnosis and treatment. *J. Am. Med. Dir. Assoc.* **21**, 300–07.e2 (2020).
This paper outlines a definition of sarcopenia proposed by the Asian Working Group for Sarcopenia (AWGS).
21. Zanker, J. et al. Consensus guidelines for sarcopenia prevention, diagnosis and management in Australia and New Zealand. *J. Cachexia Sarcopenia Muscle* **14**, 142–156 (2023).
This paper outlines consensus recommendations for sarcopenia developed by the Australian and New Zealand Society for Sarcopenia and Frailty Research (ANZSSFR) Sarcopenia Diagnosis and Management Task Force.

22. Dodds, R. M. et al. Global variation in grip strength: a systematic review and meta-analysis of normative data. *Age Ageing* **45**, 209–216 (2016).
23. Sayer, A. A. & Cruz-Jentoft, A. Sarcopenia definition, diagnosis and treatment: consensus is growing. *Age Ageing* **51**, afac220 (2022).
24. Cawthon, P. M. et al. Defining terms commonly used in sarcopenia research: a glossary proposed by the Global Leadership in Sarcopenia (GLIS) Steering Committee. *Eur. Geriatr. Med.* **13**, 1239–1244 (2022).
25. Kirk, B. et al. The conceptual definition of sarcopenia: Delphi consensus from the Global Leadership Initiative in Sarcopenia (GLIS). *Age Ageing* **53**, afae052 (2024).
This paper reports on the first global conceptual definition of sarcopenia that has been created by the Global Leadership Initiative in Sarcopenia (GLIS) using a Delphi consensus process.
26. Shafiee, G. et al. Prevalence of sarcopenia in the world: a systematic review and meta-analysis of general population studies. *J. Diabetes Metab. Disord.* **16**, 21 (2017).
27. Mayhew, A. J. et al. The prevalence of sarcopenia in community-dwelling older adults, an exploration of differences between studies and within definitions: a systematic review and meta analyses. *Age Ageing* **48**, 48–56 (2019).
28. Carvalho do Nascimento, P. R., Bilodeau, M. & Poitras, S. How do we define and measure sarcopenia? A meta-analysis of observational studies. *Age Ageing* **50**, 1906–1913 (2021).
29. Petermann-Rocha, F. et al. Global prevalence of sarcopenia and severe sarcopenia: a systematic review and meta-analysis. *J. Cachexia Sarcopenia Muscle* **13**, 86–99 (2022).
30. Mballa Yene, B. V. et al. Prevalence of sarcopenia in Africa: a systematic review. *Clin. Interv. Aging* **18**, 1021–1035 (2023).
31. Yuan, S. & Larsson, S. C. Epidemiology of sarcopenia: prevalence, risk factors, and consequences. *Metabolism* **144**, 155533 (2023).
This is a comprehensive review that summarizes evidence from 130 studies that have examined the risk factors and consequences of sarcopenia.
32. Yang, L., Smith, L. & Hamer, M. Gender-specific risk factors for incident sarcopenia: 8-year follow up of the English Longitudinal Study of Ageing. *J. Epidemiol. Community Health* **73**, 86–88 (2019).
33. Sallfeldt, E. S. et al. Sarcopenia prevalence and incidence in older men – a MrOs Sweden study. *Geriatr. Nurs.* **50**, 102–108 (2023).
34. Zhou, S. et al. Longitudinal association between uric acid and incident sarcopenia. *Nutrients* **15**, 3097 (2023).
35. Lang, T. et al. Sarcopenia: etiology, clinical consequences, intervention, and assessment. *Osteoporos. Int.* **21**, 543–559 (2010).
36. Cruz-Jentoft, A. J., Gonzalez, M. C. & Prado, C. M. Sarcopenia ≠ low muscle mass. *Eur. Geriatr. Med.* **14**, 225–228 (2023).
37. Zuo, X. et al. Sarcopenia and cardiovascular diseases: a systematic review and meta-analysis. *J. Cachexia Sarcopenia Muscle* **14**, 1183–1198 (2023).
38. Surov, A. & Wienke, A. Prevalence of sarcopenia in patients with solid tumors: a meta-analysis based on 81,814 patients. *JPEN J. Parenter. Enter. Nutr.* **46**, 1761–1768 (2022).
39. Luo, L. et al. Sarcopenia as a risk factor of progression-free survival in patients with metastases: a systematic review and meta-analysis. *BMC Cancer* **23**, 127 (2023).
40. Bullock, A. F. et al. Malnutrition, sarcopenia and cachexia: exploring prevalence, overlap, and perceptions in older adults with cancer. *Eur. J. Clin. Nutr.* **78**, 486–493 (2024).
41. Kim, G. et al. Prognostic value of sarcopenia in patients with liver cirrhosis: a systematic review and meta-analysis. *PLoS ONE* **12**, e0186990 (2017).
42. Prado, C. M. et al. Sarcopenic obesity in older adults: a clinical overview. *Nat. Rev. Endocrinol.* **20**, 261–277 (2024).
43. Fagundes Belchior, G. et al. Osteosarcopenia: beyond age-related muscle and bone loss. *Eur. Geriatr. Med.* **11**, 715–724 (2020).
44. Sato, S. et al. Respiratory sarcopenia: a position paper by four professional organizations. *Geriatr. Gerontol. Int.* **23**, 5–15 (2023).
45. Wakabayashi, H. et al. Diagnosis and treatment of sarcopenic dysphagia: a scoping review. *Dysphagia* **36**, 523–531 (2021).
46. SeyedAlinaghi, S. et al. A systematic review of sarcopenia prevalence and associated factors in people living with human immunodeficiency virus. *J. Cachexia Sarcopenia Muscle* **14**, 1168–1182 (2023).
47. Gao, Q. et al. Associated factors of sarcopenia in community-dwelling older adults: a systematic review and meta-analysis. *Nutrients* **13**, 4291 (2021).
48. Liu, J. C. et al. Multi-omics research in sarcopenia: current progress and future prospects. *Ageing Res. Rev.* **76**, 101576 (2022).
49. Rai, M. et al. Skeletal muscle degeneration and regeneration in mice and flies. *Curr. Top. Dev. Biol.* **108**, 247–281 (2014).
50. Frontera, W. R. in *DeLisa's Physical Medicine and Rehabilitation: Principles and Practice* 6th edn (ed Frontera, W. R.) 69–88 (Lippincott Williams and Wilkins, 2019).
51. Schiaffino, S. & Reggiani, C. Fiber types in mammalian skeletal muscles. *Physiol. Rev.* **91**, 1531 (2011).
52. Lloyd, E. M. et al. Slow or fast: implications of myofibre type and associated differences for manifestation of neuromuscular disorders. *Acta Physiol.* **238**, e14012 (2023).
53. Granic, A. et al. Hallmarks of ageing in human skeletal muscle and implications for understanding the pathophysiology of sarcopenia in women and men. *Clin. Sci.* **137**, 1721–1751 (2023).
This comprehensive review evaluates how each of the nine original hallmarks of ageing (see Lopez-Otin et al. (2013)) contributes to the pathophysiology of sarcopenia. It also proposes five novel hallmarks of skeletal muscle ageing and considers their clinical relevance.
54. Holtze, S. et al. Alternative animal models of aging research. *Front. Mol. Biosci.* **8**, 660959 (2021).
55. Shavlakadze, T. et al. Age-related gene expression signatures from limb skeletal muscles and the diaphragm in mice and rats reveal common and species-specific changes. *Skelet. Muscle* **13**, 11 (2023).
56. Korstanje, R. et al. The Jackson Laboratory Nathan Shock Center: impact of genetic diversity on aging. *Geroscience* **43**, 2129–2137 (2021).
57. Moaddel, R. et al. Proteomics in aging research: a roadmap to clinical, translational research. *Aging Cell* **20**, e13325 (2021).
58. Ciciliot, S. et al. Muscle type and fiber type specificity in muscle wasting. *Int. J. Biochem. Cell Biol.* **45**, 2191–2199 (2013).
59. Lopez-Otin, C. et al. The hallmarks of aging. *Cell* **153**, 1194–1217 (2013).
A seminal paper in ageing research that proposes nine cellular and molecular hallmarks of ageing that contribute to the ageing process and influence age-related phenotypes: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication.
60. Schmauck-Medina, T. et al. New hallmarks of ageing: a 2022 Copenhagen Ageing Meeting summary. *Aging* **14**, 6829–6839 (2022).
61. López-Otín, C. et al. Hallmarks of aging: an expanding universe. *Cell* **186**, 243–278 (2023).
62. Van Ancum, J. M. et al. Lack of knowledge contrasts the willingness to counteract sarcopenia among community-dwelling adults. *J. Aging Health* **32**, 787–794 (2020).
63. Guralnik, J. M. et al. Limited physician knowledge of sarcopenia: a survey. *J. Am. Geriatr. Soc.* **71**, 1595–1602 (2023).
64. Welch, C. et al. Acute sarcopenia secondary to hospitalisation – an emerging condition affecting older adults. *Aging Dis.* **9**, 151–164 (2018).
65. Montero-Errasquín, B. & Cruz-Jentoft, A. J. Acute sarcopenia. *Gerontology* **69**, 519–525 (2023).
66. Beaudart, C. et al. Health outcomes of sarcopenia: a systematic review and meta-analysis. *PLoS ONE* **12**, e0169548 (2017).
67. Malmstrom, T. K. et al. SARC-F: a symptom score to predict persons with sarcopenia at risk for poor functional outcomes. *J. Cachexia Sarcopenia Muscle* **7**, 28–36 (2016).
68. Bahat, G., Erdoğan, T. & İlhan, B. SARC-F and other screening tests for sarcopenia. *Curr. Opin. Clin. Nutr. Metab. Care* **25**, 37–42 (2022).
69. Huang, L. et al. The accuracy of screening instruments for sarcopenia: a diagnostic systematic review and meta-analysis. *Age Ageing* **52**, afad152 (2023).
70. Cooper, R. et al. Objectively measured physical capability levels and mortality: systematic review and meta-analysis. *BMJ* **341**, c4467 (2010).
71. Cooper, R. et al. Physical capability in mid-life and survival over 13 years of follow-up: British Birth Cohort Study. *BMJ* **348**, g2219 (2014).
72. Koopman, J. J. et al. Handgrip strength, ageing and mortality in rural Africa. *Age Ageing* **44**, 465–470 (2015).
73. Leong, D. P. et al. Prognostic value of grip strength: findings from the Prospective Urban Rural Epidemiology (PURE) study. *Lancet* **386**, 266–273 (2015).
74. Celis-Morales, C. A. et al. Associations of grip strength with cardiovascular, respiratory, and cancer outcomes and all cause mortality: prospective cohort study of half a million UK Biobank participants. *BMJ* **361**, k1651 (2018).
75. Bohannon, R. W. et al. Grip and knee extension muscle strength reflect a common construct among adults. *Muscle Nerve* **46**, 555–558 (2012).
76. Roberts, H. C. et al. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. *Age Ageing* **40**, 423–429 (2011).
This paper outlines a standardized protocol for the assessment of hand grip strength.
77. Beaudart, C. et al. Assessment of muscle function and physical performance in daily clinical practice: a position paper endorsed by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO). *Calcif. Tissue Int.* **105**, 1–14 (2019).
78. Sanchez-Rodriguez, D., Marco, E. & Cruz-Jentoft, A. J. Defining sarcopenia: some caveats and challenges. *Curr. Opin. Clin. Nutr. Metab. Care* **23**, 127–132 (2020).
79. Mijnarends, D. M. et al. Validity and reliability of tools to measure muscle mass, strength, and physical performance in community-dwelling older people: a systematic review. *J. Am. Med. Dir. Assoc.* **14**, 170–178 (2013).
80. Compher, C. et al. Guidance for assessment of the muscle mass phenotypic criterion for the Global Leadership Initiative on Malnutrition diagnosis of malnutrition. *JPEN J. Parenter. Enter. Nutr.* **46**, 1232–1242 (2022).
81. Nijholt, W. et al. The reliability and validity of ultrasound to quantify muscles in older adults: a systematic review. *J. Cachexia Sarcopenia Muscle* **8**, 702–712 (2017).
82. Perkisas, S. et al. Application of ultrasound for muscle assessment in sarcopenia: 2020 SARCUS update. *Eur. Geriatr. Med.* **12**, 45–59 (2021).
83. Pagano, A. P. et al. Estimating muscle mass using D_3-creatine dilution: a narrative review of clinical implications and comparison with other methods. *J. Gerontol. A Biol. Sci. Med. Sci.* **79**, glad280 (2024).
84. McCarthy, C. et al. D_3-creatine dilution for skeletal muscle mass measurement: historical development and current status. *J. Cachexia Sarcopenia Muscle* **13**, 2595–2607 (2022).
85. Verstraeten, L. M. G. et al. Handgrip strength rather than chair stand test should be used to diagnose sarcopenia in geriatric rehabilitation inpatients: REStORing health of acutely unwell adulTs (RESORT). *Age Ageing* **51**, afac242 (2022).

86. Johansson, J. et al. Comparing associations of handgrip strength and chair stand performance with all-cause mortality – implications for defining probable sarcopenia: the Tromso Study 2015-2020. *BMC Med.* **21**, 451 (2023).
87. Dodds, R. M. et al. Grip strength across the life course: normative data from twelve British studies. *PLoS ONE* **9**, e113637 (2014).
By pooling data from 12 British population-based studies this paper presents empirical data that demonstrate how mean levels of grip strength change across life and provides compelling evidence of the need for a life-course approach to the study of sarcopenia. The data presented in this paper have been used to identify cut-off points for low grip strength in the European Working Group on Sarcopenia in Older People 2 revised consensus definition for sarcopenia (see Cruz-Jentoft et al. (2019)).
88. Azzolino, D. et al. Musculoskeletal changes across the lifespan: nutrition and the life-course approach to prevention. *Front. Med.* **8**, 697954 (2021).
89. Kulkarni, B., Hills, A. P. & Byrne, N. M. Nutritional influences over the life course on lean body mass of individuals in developing countries. *Nutr. Rev.* **72**, 190–204 (2014).
90. Robinson, S. et al. The role of nutrition in the prevention of sarcopenia. *Am. J. Clin. Nutr.* **118**, 852–864 (2023).
91. Santos, L., Elliott-Sale, K. J. & Sale, C. Exercise and bone health across the lifespan. *Biogerontology* **18**, 931–946 (2017).
92. Bull, F. C. et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *Br. J. Sports Med.* **54**, 1451–1462 (2020).
93. Cooper, R., Mishra, G. D. & Kuh, D. Physical activity across adulthood and physical performance in midlife: findings from a British birth cohort. *Am. J. Prev. Med.* **41**, 376–384 (2011).
94. Dodds, R. et al. Physical activity levels across adult life and grip strength in early old age: updating findings from a British birth cohort. *Age Ageing* **42**, 794–798 (2013).
95. Hurst, C. et al. Resistance exercise as a treatment for sarcopenia: prescription and delivery. *Age Ageing* **51**, afac003 (2022).
This paper outlines the principles of effective resistance exercise prescription and proposes a resistance exercise programme that can be used as a resource for clinicians and exercise practitioners treating older adults with sarcopenia.
96. Shen, Y. et al. Exercise for sarcopenia in older people: a systematic review and network meta analysis. *J. Cachexia Sarcopenia Muscle* **14**, 1199–1211 (2023).
97. Fragala, M. S. et al. Resistance training for older adults: position statement from the National Strength and Conditioning Association. *J. Strength. Cond. Res.* **33**, 2019–2052 (2019).
98. Liu, C. J. & Latham, N. K. Progressive resistance strength training for improving physical function in older adults. *Cochrane Database Syst. Rev.* **2009**, Cd002759 (2009).
99. Dodds, R. M. et al. Sarcopenia, long-term conditions, and multimorbidity: findings from UK Biobank participants. *J. Cachexia Sarcopenia Muscle* **11**, 62–68 (2020).
100. Bernabei, R. et al. Multicomponent intervention to prevent mobility disability in frail older adults: randomised controlled trial (SPRINTT project). *BMJ* **377**, e068788 (2022).
101. Kirwan, R. P. et al. Protein interventions augment the effect of resistance exercise on appendicular lean mass and handgrip strength in older adults: a systematic review and meta-analysis of randomized controlled trials. *Am. J. Clin. Nutr.* **115**, 897–913 (2022).
102. Nunes, E. A. et al. Systematic review and meta-analysis of protein intake to support muscle mass and function in healthy adults. *J. Cachexia Sarcopenia Muscle* **13**, 795–810 (2022).
103. Granic, A. et al. Myoprotective whole foods, muscle health and sarcopenia: a systematic review of observational and intervention studies in older adults. *Nutrients* **12**, 2257 (2020).
104. Bauer, J. et al. Evidence-based recommendations for optimal dietary protein intake in older people: a position paper from the PROT-AGE Study Group. *J. Am. Med. Dir. Assoc.* **14**, 542–559 (2013).
105. Chen, L. K. et al. Roles of nutrition in muscle health of community-dwelling older adults: evidence-based expert consensus from Asian Working Group for Sarcopenia. *J. Cachexia Sarcopenia Muscle* **13**, 1653–1672 (2022).
106. Deutz, N. E. et al. Protein intake and exercise for optimal muscle function with aging: recommendations from the ESPEN Expert Group. *Clin. Nutr.* **33**, 929–936 (2014).
107. Ikizler, T. A. et al. KDOQI clinical practice guideline for nutrition in CKD: 2020 update. *Am. J. Kidney Dis.* **76**, S1–S107 (2020).
108. Duarte, M. P. et al. Prevalence of sarcopenia in patients with chronic kidney disease: a global systematic review and meta-analysis. *J. Cachexia Sarcopenia Muscle* **15**, 501–512 (2024).
109. Beaudart, C. et al. The effects of vitamin D on skeletal muscle strength, muscle mass, and muscle power: a systematic review and meta-analysis of randomized controlled trials. *J. Clin. Endocrinol. Metab.* **99**, 4336–4345 (2014).
110. Cheng, S. H. et al. The optimal strategy of vitamin D for sarcopenia: a network meta-analysis of randomized controlled trials. *Nutrients* **13**, 3589 (2021).
111. Prokopidis, K. et al. Effect of vitamin D monotherapy on indices of sarcopenia in community dwelling older adults: a systematic review and meta-analysis. *J. Cachexia Sarcopenia Muscle* **13**, 1642–1652 (2022).
112. Sanders, K. M. et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. *JAMA* **303**, 1815–1822 (2010).
113. Pinto Pereira, S. M. et al. Linear and nonlinear associations between vitamin D and grip strength: a mendelian randomization study in UK Biobank. *J. Gerontol. A Biol. Sci. Med. Sci.* **78**, 1483–1488 (2023).
114. Kirk, B., Zanker, J. & Duque, G. Osteosarcopenia: epidemiology, diagnosis, and treatment – facts and numbers. *J. Cachexia Sarcopenia Muscle* **11**, 609–618 (2020).
115. Bagherniya, M. et al. The beneficial therapeutic effects of plant-derived natural products for the treatment of sarcopenia. *J. Cachexia Sarcopenia Muscle* **13**, 2772–2790 (2022).
116. Bauer, J. M. et al. Effects of a vitamin D and leucine-enriched whey protein nutritional supplement on measures of sarcopenia in older adults, the PROVIDE study: a randomized, double blind, placebo-controlled trial. *J. Am. Med. Dir. Assoc.* **16**, 740–747 (2015).
117. Sargeant, J. A. et al. A review of the effects of glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter 2 inhibitors on lean body mass in humans. *Endocrinol. Metab.* **34**, 247–262 (2019).
118. Wu, S. et al. Effects of vibration therapy on muscle mass, muscle strength and physical function in older adults with sarcopenia: a systematic review and meta-analysis. *Eur. Rev. Aging Phys. Act.* **17**, 14 (2020).
119. de Oliveira, T. M. D. et al. Effects of whole-body electromyostimulation on health indicators of older people: systematic review and meta-analysis of randomized trials. *J. Bodyw. Mov. Ther.* **31**, 134–145 (2022).
120. Hardy, E. J. et al. Post-operative electrical muscle stimulation attenuates loss of muscle mass and function following major abdominal surgery in older adults: a split body randomised control trial. *Age Ageing* **51**, afac234 (2022).
121. Rolland, Y. et al. Current and investigational medications for the treatment of sarcopenia. *Metabolism* **149**, 155597 (2023).
122. Achison, M. et al. Effect of perindopril or leucine on physical performance in older people with sarcopenia: the LACE randomized controlled trial. *J. Cachexia Sarcopenia Muscle* **13**, 858–871 (2022).
123. Lee, S. J. Targeting the myostatin signaling pathway to treat muscle loss and metabolic dysfunction. *J. Clin. Invest.* **131**, e148372 (2021).
124. Lee, S. J. et al. Challenges and future prospects of targeting myostatin/activin A signaling to treat diseases of muscle loss and metabolic dysfunction. *J. Gerontol. A Biol. Sci. Med. Sci.* **78** (Suppl. 1), 32–37 (2023).
125. Fonseca, G. et al. Selective androgen receptor modulators (SARMs) as pharmacological treatment for muscle wasting in ongoing clinical trials. *Expert. Opin. Investig. Drugs* **29**, 881–891 (2020).
126. Membrez, M. et al. Trigonelline is an NAD^+ precursor that improves muscle function during ageing and is reduced in human sarcopenia. *Nat. Metab.* **6**, 433–447 (2024).
127. Witham, M. D. et al. New horizons in cellular senescence for clinicians. *Age Ageing* **52**, afad127 (2023).
128. Liu, S. et al. Effect of urolithin A supplementation on muscle endurance and mitochondrial health in older adults: a randomized clinical trial. *JAMA Netw. Open.* **5**, e2144279 (2022).
129. Parker, S. G. et al. What is Comprehensive Geriatric Assessment (CGA)? An umbrella review. *Age Ageing* **47**, 149–155 (2018).
130. Ellis, G. et al. Comprehensive geriatric assessment for older adults admitted to hospital. *Cochrane Database Syst. Rev.* **9**, Cd006211 (2017).
131. Ambagtsheer, R. C. et al. Does CGA improve health outcomes in the community? An umbrella review. *J. Am. Med. Dir. Assoc.* **24**, 782–789.e15 (2023).
132. Norman, K. & Otten, L. Financial impact of sarcopenia or low muscle mass – a short review. *Clin. Nutr.* **38**, 1489–1495 (2019).
133. Sayer, A. A. et al. Is grip strength associated with health-related quality of life? Findings from the Hertfordshire Cohort Study. *Age Ageing* **35**, 409–415 (2006).
134. Cooper, R. et al. Physical capability and subsequent positive mental wellbeing in older people: findings from five HALCyon cohorts. *Age* **36**, 445–456 (2014).
135. Rizzoli, R. et al. Quality of life in sarcopenia and frailty. *Calcif. Tissue Int.* **93**, 101–120 (2013).
136. Woo, T., Yu, S. & Visvanathan, R. Systematic literature review on the relationship between biomarkers of sarcopenia and quality of life in older people. *J. Frailty Aging* **5**, 88–99 (2016).
137. Tsekoura, M. et al. Sarcopenia and its impact on quality of life. *Adv. Exp. Med. Biol.* **987**, 213–218 (2017).
138. Beaudart, C. et al. Measuring health-related quality of life in sarcopenia: summary of the SarQoL psychometric properties. *Aging Clin. Exp. Res.* **35**, 1581–1593 (2023).
The Sarcopenia Quality of Life questionnaire (SarQoL) was developed in 2015 to assess health-related quality of life as it relates to sarcopenia. This review summarizes all available published evidence on the utility of the SarQoL up to January 2023.
139. Barbosa, M. V. et al. Association between functional aspects and health-related quality of life in patients with colorectal cancer: can handgrip strength be the measure of choice in clinical practice? *Support. Care Cancer* **31**, 144 (2023).
140. da Costa Pereira, J. P. et al. Sarcopenia and dynapenia is correlated to worse quality of life perception in middle-aged and older adults with Parkinson's disease. *Nutr. Neurosci.* **27**, 310–318 (2023).
141. Beaudart, C. et al. Development of a self-administrated quality of life questionnaire for sarcopenia in elderly subjects: the SarQoL. *Age Ageing* **44**, 960–966 (2015).
142. Witham, M. D. et al. Performance of the SarQoL quality of life tool in a UK population of older people with probable sarcopenia and implications for use in clinical trials: findings from the SarcNet registry. *BMC Geriatr.* **22**, 368 (2022).
143. Molzahn, A. et al. The importance of facets of quality of life to older adults: an international investigation. *Qual. Life Res.* **19**, 293–298 (2010).
144. Pinedo-Villanueva, R. et al. Health care costs associated with muscle weakness: a UK population-based estimate. *Calcif. Tissue Int.* **104**, 137–144 (2019).
145. Offord, N. J. et al. Current practice in the diagnosis and management of sarcopenia and frailty – results from a UK-wide survey. *J. Frailty Sarcopenia Falls* **4**, 71–77 (2019).

146. Caulfield, L. A., et al. The Benchmarking Exercise Programme for Older People (BEPOP): design, results and recommendations from the first wave of data collection. *J. Frailty Sarcopenia Falls* www.jfsf.eu/accepted/JFSF-23M-11-037.pdf (2024).
147. Dodds, R. M. et al. Advancing our understanding of skeletal muscle across the lifecourse: protocol for the MASS_Lifecourse study and characteristics of the first 80 participants. *Exp. Gerontol.* **166**, 111884 (2022).
148. Cummings, S. R. et al. The Study of Muscle, Mobility and Aging (SOMMA): a unique cohort study about the cellular biology of aging and age-related loss of mobility. *J. Gerontol. A Biol. Sci. Med. Sci.* **78**, 2083–2093 (2023).
149. Grounds, M. D. in *Skeletal Muscle Repair and Regeneration* (eds Schiaffino, S. & Partridge, P. A.) 269–302 (Springer, 2008).
150. McMahon, C. D. et al. Lifelong exercise and locally produced insulin-like growth factor-1 (IGF-1) have a modest influence on reducing age-related muscle wasting in mice. *Scand. J. Med. Sci. Sports* **24**, e423–e435 (2014).
151. Soffe, Z. et al. Effects of loaded voluntary wheel exercise on performance and muscle hypertrophy in young and old male C57Bl/6J mice. *Scand. J. Med. Sci. Sports* **26**, 172–188 (2016).
152. Pannérec, A. et al. A robust neuromuscular system protects rat and human skeletal muscle from sarcopenia. *Aging* **8**, 712–729 (2016).

Acknowledgements

The authors thank H. Atkinson (Patient and Public Involvement and Engagement Manager for the Ageing, Sarcopenia and Multimorbidity Theme within the National Institute for Health and Care Research Newcastle Biomedical Research Centre) and the 11 people who shared their experiences of sarcopenia for contributing to the patient experience box. A.A.S., R.C. and M.D.W. acknowledge support from the National Institute for Health and Care Research (NIHR) Newcastle Biomedical Research Centre (reference NIHR203309). R.C. also receives support as part of a generous donation made by the McArdle family to Newcastle University for research that will benefit the lives of older people in the UK. R.A.F. acknowledges support from the US Department of Agriculture, under agreement no. 58-1950-4-003.

Author contributions

Introduction (R.A.F. and R.C.), Epidemiology (P.M.C., H.A., M.-J.N.E. and R.C.), Mechanisms (M.D.G.), Diagnosis, screening and prevention (A.J.C.-J., H.A. and M.-J.N.E.), Management (M.D.W., H.A. and M.-J.N.E.), Quality of life (R.C.), Outlook (A.A.S.), overview of the Primer (A.A.S. and R.C.).

Competing interests

A.A.S. reports research grant funding from the National Institute for Health and Care Research UK, UK Research and Innovation, a research collaboration agreement with Regeneron Pharmaceuticals and a previous Pfizer Investigator Initiated Research Grant. R.C. reports research grant funding from the National Institute for Health and Care Research UK and UK Research and Innovation. H.A. has no funding or other conflicts of interest to disclose. P.M.C. is a consultant to and owns stock in Myocorps. M.-J.N.E. has no funding or other conflicts of interest to disclose. R.A.F. reports grants from the National Institutes of Health and USDA Agricultural Research Service; grants and personal fees from Axcella Health, Juvicell, Inside Tracker and Biophytis; and personal fees from Amazentis, Nestle, Pfizer, Rejuvenate Biomed, Embion and Hevolution Foundation, outside the submitted work. M.G. has no funding or other conflicts of interest to disclose. M.D.W. reports research grant funding from the National Institute for Health and Care Research UK and UK Research and Innovation. A.J.C.-J. has no funding to disclose. A.J.C.-J. has received honoraria for lectures or for organizing independent educational events from Abbott Nutrition, Danone-Nutricia, Nestlé Health Science and Fresenius-Kabi, and consulting fees from Akros Pharma, Chugai Pharmaceutical, Rejuvenate Biomed, Reneo Pharmaceutical and Toray Industries.

Informed consent

The authors affirm that all contributors to the patient experience box provided informed consent for publication of their experiences.

Additional information

Peer review information *Nature Reviews Disease Primers* thanks S. von Haehling; N. Martinez-Velilla, who co-reviewed with A. Cedeno-Veloz; D. Scott; and H. Wakabayashi, for their contribution to the peer review of this work.

Disclaimer The views expressed in this publication are those of the authors and do not necessarily reflect the views of the National Institute for Health and Care Research, the Department of Health and Social Care, the McArdle family or the US Department of Agriculture.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.