Sarcopenia

Alfonso J. Cruz-Jentoft, Avan A. Sayer

Servicio de Geriatría, Hospital Universitario Ramón y Cajal (IRYCIS), Madrid, Spain (Prof. AJ Cruz-Jentoft MD); **and AGE Research Group, Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK; National Institute for Health Research Newcastle Biomedical Research Centre, Newcastle upon Tyne Hospitals NHS Foundation Trust and Newcastle University, Newcastle upon Tyne, UK;** (Prof. AA Sayer PhD FRCP)

Correspondence to:
Alfonso J. Cruz-Jentoft, Servicio de Geriatría, Hospital Universitario Ramón y Cajal
Ctra. Colmenar km 9,1, 28034 Madrid, Spain
Phone/fax: +34 913368172
alfonsojose.cruz@salud.madrid.org

Unstructured summary

Sarcopenia is a progressive and generalised skeletal muscle disorder involving the accelerated loss of muscle mass and function that is associated with increased adverse outcomes including falls, functional decline, frailty and mortality. It occurs commonly as an age-related process in older people, influenced not only by contemporaneous risk factors but also by genetic and lifestyle factors operating across the life course. It can also occur in mid-life in association with a range of conditions. In recent years, sarcopenia has become the focus of intense research aiming to translate increased understanding about pathophysiology into improved diagnosis and treatment, with particular interest in the development of biomarkers, nutritional interventions, and drugs to augment the beneficial effects of resistance exercise. There is also interest in designing effective preventive strategies across the life course. It is likely that the diagnosis, treatment and prevention of sarcopenia will soon become part of routine clinical practice.

Fast facts / One page summary

- Sarcopenia is a progressive and generalised skeletal muscle disorder involving the accelerated loss of muscle mass and function that is associated with increased adverse outcomes including falls, functional decline, frailty and mortality.
- Diagnosis of sarcopenia relies on measuring muscle strength, muscle mass and physical performance, although different definitions and cut-off points have been proposed. Blood biomarkers are not yet available in clinical practice. The EWGSOP2 definition has been endorsed by several international societies.
- Case finding in patients with relevant symptoms (falls, weakness, slowness, functional impairments) is recommended. The SARC-F questionnaire can be used for screening in high prevalence settings.
- A syndromic approach is recommended to ascertain the underlying causes.
- Differential diagnosis has to be made with malnutrition, caquexia and frailty.
- The prevalence of sarcopenia increases with age and is higher in some care settings (acute hospital admission, nursing homes).
- Pathophysiology is complex and involves many pathways and systems.
- Guidelines recommend resistance exercise as the cornerstone for treatment of sarcopenia. Evidence on nutrition interventions is less consistent.
- There are no drugs approved for sarcopenia.
- Muscle strength and physical performance can be used to assess the effect of interventions in clinical practice.
- The prevention of sarcopenia is now a major area of research activity, using a life course perspective.
- An ICD-10 code for sarcopenia was announced in 2016. It is likely that the diagnosis, treatment and prevention of sarcopenia will soon become part of routine clinical practice.

Background

Sarcopenia is a term derived from the Greek 'poverty of flesh'. It was first described in the 1980s as an age-related decline in lean body mass affecting mobility, nutritional status and independence.[1] The definition has since evolved and there have been two recent milestones. The first was the introduction of muscle function into the concept in six consensus definitions since 2010.[2–7] This new focus on muscle function, usually defined by muscle strength but also by muscle power or physical performance, occurred because function was consistently shown to be a more powerful predictor of clinically relevant outcomes than muscle mass alone.[8–11] The second milestone was recognition of sarcopenia as an independent condition with an ICD-10 code in 2016.[12] Yet most clinicians remain unaware of the condition and the diagnostic tools needed to identify it.[13,14] This review describes recent progress and debate about a consensus definition, an approach to diagnosis and case finding, an overview of disease burden and pathophysiology, an outline of current treatment strategies, and future potential for prevention across the life course.

Definition

Sarcopenia has recently been defined as a progressive and generalised skeletal muscle disorder involving the accelerated loss of muscle mass and function that is associated with increased adverse outcomes including falls, functional decline, frailty and mortality.[15] When first coined, the word sarcopenia referred to an age-related loss of muscle mass and function.[1] However for decades it was used to describe muscle wasting (low muscle mass) alone without reference to function, and this concept is still used in some cancer and other disease-related sarcopenia research today. Nevertheless there has been some progress in recent years, and published consensus definitions by a range of expert groups from around the world now include muscle function in the concept of sarcopenia. Full agreement on the variables to be included and cut points has yet to be reached (Table 1). The most widely cited definition at this time is that proposed by the European Working Group on Sarcopenia in Older People (EWGSOP),[3] supported by the Asian Working Group

on Sarcopenia (AWGS)[6] and recently updated as EWGSOP2.[15] This is the only definition currently endorsed by a range of international scientific societies (EuGMS, ESPEN, ESCEO, IOF, IAGG-ER) for clinical practice and research.

Table 1. Definitions of sarcopenia

Definition	Muscle mass	Muscle strength	Physical performance	Cut-offs defined	Comment
EWGSOP (2010)[3]	•	•	•		
IWGS (2011)[4]	•		•	•	
SSCWD (2011)[5]	•		•	•	Named "sarcopenia with limited mobility"
AWGS (2014)[6]	•	•	•	•	Same as EWGSOP but adds cutoffs for Asia
FNIH (2014)[7]	•	•		•	Uses physical performance as outcome
EWGSOP2 (2019)[15]	•	•	•	•	Physical performance used for severity

In clinical practice, the EWGSOP2 states that a person with low muscle strength and low muscle mass or quality will be diagnosed with sarcopenia. It may be best understood as

organ (skeletal muscle) failure or insufficiency.[16] As such, it may appear acutely (usually in the setting of an acute disease or sudden immobility, as during hospital admission) or have a more protracted (chronic) course. Muscle mass and strength (in parallel with bone mineral density) peak in young adulthood and, after a plateau, start decreasing gradually, with a faster decline in strength (figure 1).[17,18] The World Health Organization has recently shifted its paradigm from a disease-centered to a function-centered model, where intrinsic capacity (defined as a composite of all physical and mental capacities of an individual) interacts with the environment to determine functional ability. Muscle strength is included in the construct of intrinsic capacity that may merit lifelong monitoring.[19,20]

Clinicians may associate sarcopenia with leanness and not be aware that sarcopenia can also be present in obesity, leading to increased disability and mortality.[21] Sarcopenic obesity is usually identified when both low muscle mass and increased adiposity are present in an individual, but it may remain unnoticed when the focus of care is obesity, leading to adverse outcomes.[22] Sarcopenia and obesity share some underlying pathophysiological pathways.[23] Muscle loss may also increase the risks during weight loss in obese individuals.[24,25] However a consensus definition of sarcopenic obesity to date is lacking, and how muscle strength should be used to make a diagnosis in this setting remains unclear.[21,22,26] There is also a relationship between sarcopenia and dysphagia [27] (sarcopenic dysphagia) that merits a specific approach in clinical practice.[28]

Case finding

Most cases of sarcopenia go undiagnosed. Nevertheless, at this time, there is no evidence to support universal screening of sarcopenia as screening tools are not accurate [29–32] and the effect of such screening on relevant outcomes is far from proved.[33] Therefore, a case finding approach is current recommended practice.[15] This involves looking for sarcopenia when relevant symptoms are reported. These could include falling, weakness, slowness, self-reported muscle wasting, or difficulties carrying out the activities of daily living.[5,15] Case finding is particularly relevant in care settings where a higher prevalence of

sarcopenia may be expected such as acute hospitalisation, rehabilitation settings, or nursing homes.[34,35] The SARC-F is a commonly recommended case finding instrument with evidence to support its use.[33,36] It can be self-administered and has a low sensitivity but high specificity, so may be a good way to initiate identifying cases of sarcopenia in clinical practice (Table 2).[31,37]

Table 2. Components of the SARC-F screening test

This screening instrument has five questions addressing:
• Strength • Assistance in walking • Rise from a chair • Climb stairs • Falls

Diagnosis

The diagnosis of sarcopenia using any definition of sarcopenia is relatively straightforward. It requires measurement of a combination of muscle mass, muscle strength and physical performance (table 1). All definitions use at least two parameters but different cut points leading to lack of standardisation and poor application of these definitions in clinical practice[14]. The updated European Working Group on Older People (EWGSOP2) has proposed a stepwise approach (figure 2). It starts with a measure of muscle strength, usually grip strength which has a well validated protocol.[38] If grip strength is below the reference values for gender (table 3 or those proposed by the definitions listed in table 1), sarcopenia should be suspected. However, the differential diagnosis is wide and other potential causes for low muscle strength should be considered, for example hand osteoarthritis and neurological disorders. Nevertheless identifying low grip strength in the first instance is important because it is highly predictive of a range of adverse outcomes.[39–42]

The second step is measuring muscle mass. A number of techniques have been used to estimate muscle mass, but all have major limitations, including variability in the results, inconsistent use of cut points, and the weak relationship between muscle mass and adverse health outcomes.[39] Best agreement to date exists for the use of dual energy X-ray absorptiometry (DXA), which estimates lean mass, whilst bioimpedance absorptiometry (BIA), computerized tomography (CT) and magnetic resonance imaging (MRI) may have a role in some settings.[43] BIA is useful as a bedside test, but as BIA equations and cut points are population and device-specific there is a lack of standardisation that limits its accuracy.[44] CT and MRI are mostly used in research and also when needed for the follow-up of another condition, as in cancer patients.[45] Ultrasound has been recently been proposed as a simple alternative to measure muscle mass in clinical practice, but it is not standardised and does not have validated cut points yet.[46,47] Usually, appendicular lean mass (skeletal muscle in the extremities) is measured, and in most cases adjustment for height is used to define cut-off values. Unfortunately research focused on identifying cut points to define sarcopenia has led to a range of different values that are difficult to reconcile and introduce systematically.[48,49] For this reason, the EWGSOP2 definition has taken a pragmatic approach and opted for simple, easy to remember cut points exploiting relevant data where possible although this has sometimes been at the expense of consistency in how the cut points have been chosen. The primary aim is to encourage uptake using a standardised approach to identify sarcopenia in clinical practice, in much the same way cardiovascular risk factors have been introduced (table 3).[15]

Table 3. Reference values used to diagnose sarcopenia

Measure	Men	Women
Grip strength	<27 kg	<16 kg
Appendicular Skeletal Muscle Mass (ASM)/height^2	<7 kg/m^2	<5.5 kg/m^2
Gait speed	≤ 0·8 m/sec	
Timed Up and Go test	≥ 20 sec	

Based on those recommended by the EWGSOP2 [15]

Muscle quality is a term that is now used widely. However, it may refer to two different concepts: the relation between strength and mass, and observable characteristics of muscle such as inter- or intramuscular adiposity. It may well prove to be a more relevant concept to health than muscle mass but as yet is not sufficiently defined for use in clinical practice.[50]

Physical performance is defined as the ability to carry out physical tasks in order to function independently in daily life. It involves function of the whole body as opposed to function of a single organ and depends not only on skeletal muscle but on an intact musculoskeletal system integrated with the central and peripheral nervous systems and involvement of a range of other body systems. It can be characterised using subjective or objective assessment of mobility, strength and balance, and commonly used single objective measures include gait speed and the 400 m timed walk. More complex composite measures such as the Short Physical Performance Battery (SPPB) and the Timed Up and Go (TUG) test) are also employed.[51,52] In recent years there has been discussion about whether physical performance should be part of the definition of sarcopenia [3,5] or be used as an outcome measure.[7] The latest EWGSOP2 definition suggests that physical performance should be considered a measure of the severity of sarcopenia.[15] Grading the severity of sarcopenia is important both to predict outcomes and to choose the intensity

of interventions. Emerging evidence for this comes from some recent clinical trials that have shown that interventions may have different effects in severe sarcopenia. For example it appears that a more intensive, multi-dimensional intervention that always includes exercise is needed for severe sarcopenia. [53,54]

Blood biomarkers of sarcopenia are not yet available in clinical practice. Research in this area has proved complex for a number of reasons, including only recent progress towards a consensus definition of sarcopenia; increasing recognition of acute and chronic sarcopenia; the existence of many interacting pathways involved in the pathophysiology; and the impact of related conditions.[55]

To date the most promising approach to measuring skeletal muscle mass is one based on the dilution of oral d3 creatine A. This is a non-invasive isotope dilution test that determines methyl-d3 creatine in fasting morning urine after an oral dose to calculate total skeletal mass. In a recent study, it was more strongly linked to outcomes such as physical performance and mobility in men than DXA lean mass.[56–58] In contrast, DXA is useful for quantifying body fat, which can impact on muscle function and going forward it is likely that multiple approaches rather than individual measures will be needed for the required diagnostic accuracy.[59–61]

Once sarcopenia has been confirmed, a systematic approach is recommended to ascertain the underlying causes.[3] The most frequent causes of sarcopenia are described in Table 4. Sarcopenia can occur in association with a range of long-term conditions in mid-life hence the growing interest from a range of medical and surgical specialties. However most older patients will have more than one associated condition. When no evident cause of a gradual onset sarcopenia is present in an older person, age-associated (primary) sarcopenia is diagnosed.

Table 4. Frequent underlying causes of sarcopenia

Nutritional	Low protein intake Low energy intake Micronutrient deficiency Malabsorption and other gastrointestinal conditions Anorexia (ageing, oral problems)
Inactivity-related	Bed rest / immobility / deconditioning Low activity / sedentary lifestyle
Disease	Bone and joint diseases Cardiorespiratory disorders including chronic heart failure and chronic obstructive pulmonary disease Metabolic disorders particularly diabetes mellitus Endocrine diseases particularly androgen deprivation Neurological disorders Cancer Liver and kidney disorders
Iatrogenic	Hospital admission Drug-related

Differential diagnosis

The three main conditions in the differential diagnosis of sarcopenia are malnutrition, cachexia and frailty.[62–64] Malnutrition has been the focus of a recent global effort to reach a consensus definition and this is changing understanding of both malnutrition and sarcopenia. The Global Leadership Initiative on Malnutrition (GLIM) has included reduced muscle mass as one of the three phenotypic criteria of malnutrition.[65] In parallel, the new EWGSOP2 definition of sarcopenia has put the focus on muscle function.[15] Thus, a finding of reduced muscle mass with normal muscle strength would be more suggestive of malnutrition than sarcopenia whereas reduced muscle mass with impaired muscle function would lead to a diagnosis of sarcopenia. Hence there has been a move away from

the original approach of defining sarcopenia purely in terms of low muscle mass. Studies of sarcopenia in the context of other conditions such as cancer that only consider muscle mass may therefore be characterising malnutrition or cachexia rather than sarcopenia, as muscle function is usually not explored.[66–68]

Cachexia is a term that has been used for decades to describe severe weight loss and muscle wasting associated with cancer, HIV and AIDS, or end-stage organ failure. Cachexia and sarcopenia may co-exist , and some aspects of the definition of sarcopenia, in particular low muscle mass, are included in modern definitions of cachexia.[2,69] Cachexia has a complex pathophysiology including excess catabolism and inflammation, endocrine and neurological changes, that are different to those described in sarcopenia.[70] The role of inflammation and cytokines seems to be more relevant in cachexia than in sarcopenia.[71] International consensus definitions of cachexia may guide clinical judgment.[2,69]

Frailty has been defined as a state of vulnerability to poor resolution of homoeostasis after a stressor event as a consequence of cumulative decline in many physiological systems.[72] Physical frailty is a subset of frailty characterised by the frailty phenotype involving unintentional weight loss, self-reported exhaustion, weakness (low grip strength), slow walking speed and low physical activity.[73] Physical frailty and sarcopenia are therefore closely related and sarcopenia has been described as the 'biological substrate of physical frailty' as summarised in figure 3.[74–79]

Disease burden

The disease burden from sarcopenia arises because it is relatively common and associated with adverse effects on current as well as future health. Estimates of disease frequency are becoming more precise with evolution of the definition. A recent systematic review explored the effect of definition on the prevalence of sarcopenia in older community dwelling populations. This highlighted that the original 2010 EWGSOP definition resulted in one of the lowest pooled prevalence estimates (12·9%, 95% confidence interval: 9·9–

15·5%) whereas the highest estimates (40·4%, 95% confidence interval: 19·5–61·2%) came from less current definitions that only used assessment of muscle mass.[35] Muscle mass cut points have a stronger influence on prevalence estimates than muscle function cut points.[80] Prevalence also depends on the setting, being more frequent in hospitalised patients, post-acute care settings, or in care homes than in the community.[34,81]

Studies determining the incidence of sarcopenia are relatively sparse although there is emerging evidence that it rises with age. There have been reports of an incidence of 1·6 % in European men and women aged 40-79 years using the EWGSOP definition;[82] 3·4% in a group of Chinese men and women mean age 72 years using the similar Asian Working Group definition;[83] and 3·6% in English men and women aged 85 years using the EWGSOP definition.[84]

The link between low muscle strength and adverse health outcomes is long established. A study dating back to the 1980s demonstrated a link between low grip strength before hip fracture surgery and poor postoperative outcomes.[85] Two more recent linked systematic reviews have identified consistent relationships between low grip strength and increased mortality as well as some evidence for links between low grip strength and increased morbidity across the four domains of fracture, cognitive decline, cardiovascular disease and hospitalisation/ institutionalization.[86,87] It has also been convincingly linked to frailty.[88]

This literature now includes an increasing number of studies demonstrating the relationship between newer consensus definitions of sarcopenia and adverse health consequences including falls, functional decline, frailty, impaired quality of life, increased healthcare costs and mortality. A recent systematic review and meta-analysis showed consistent associations between EWGSOP defined sarcopenia and mortality with a pooled OR of 3·59 (95% CI 2·96–4·27) and a larger effect size in men and women aged 79 years and over.[89] The review also showed that sarcopenia was associated with functional decline, a higher rate of falls and hospitalisation although the evidence for a link to fractures and length of stay was less consistent. Findings from a recent systematic review

304 confirm that quality of life across domains is impaired in sarcopenia whether measured
305 using generic self-reported tools or disease-specific questionnaires.[90] Unsurprisingly, in
306 view of the link between sarcopenia and a range of adverse health outcomes, it has also
307 been associated with increased healthcare costs,[91] however the full extent of this has yet
308 to be elucidated.[92]
309
310 **Pathophysiology**
311 Ageing disturbs the homeostasis of skeletal muscle which requires balance between
312 hypertrophy and regeneration through complex and not yet fully understood mechanisms
313 and pathways (figure 4). Ageing appears to result in an imbalance between muscle protein
314 anabolic and catabolic pathways leading to overall loss of skeletal muscle. Cellular changes
315 in sarcopenic muscle include a reduction in the size and number of myofibres, particularly
316 affecting type II fibres. This is partly due to transition of muscle fibres from type II to type I
317 with age, together with intra- and intermuscular fat infiltration (myosteatosis) and a
318 decreased number of type II fibre satellite cells.[50,93–95] Recent findings suggest that
319 pathogenic inter-relationships between adipose tissue and muscle are important in
320 sarcopenia.[26] Mitochondrial integrity in myocytes is also altered.[96] Molecular changes in
321 sarcopenic muscle involve alterations to the complex signaling pathway that includes
322 insulin-like growth factor 1 (IGF-1), mTOR and FoxO transcription factors as well as other
323 interlinked pathways.[97] Neurologic signaling and control mechanisms also have an
324 important role in muscle function.[8,98] Deregulation in skeletal muscle gene expression,
325 probably mediated through epigenetic changes and modulated via microRNAs, has also
326 been described.[99]
327
328 Recent research suggests that there is cross-talk between muscle and bone through
329 endocrine factors such as myostatin, irisin, osteocalcin, and many others, although the
330 relevance of this communication in the pathogenesis of sarcopenia has not been well
331 established.[100] There is also preliminary evidence for an association between the age-
332 related decline in production of apelin, an endogenous peptide induced by muscle

contraction, and decreased muscle function through different pathways.[101] A detailed review of the pathophysiology of sarcopenia is beyond the scope of this seminar but a number of comprehensive reviews on this rapidly developing area are available.[102,103]

Treatment: non-pharmacological approaches

Understanding the pathophysiology of sarcopenia is key to developing effective new interventions and translational research in this area is growing rapidly. Recently, evidence-based clinical practice guidelines have been published that provide strong recommendations for physical activity as the cornerstone for treatment of sarcopenia.[33] There is compelling evidence for the benefits of resistance exercise in improving skeletal muscle strength [104] and mass [105] individually, and growing evidence for its benefit in sarcopenia defined as a combination of both strength and mass. Two recent systematic reviews of exercise interventions in older adults with sarcopenia showed evidence of significantly improved strength, mass and balance although the number of trials specifically recruiting participants with sarcopenia was small, and the training effect inconsistent due to heterogeneity in the mode, duration and intensity of exercise employed.[106,107] A more recent systematic review confirmed the effect of exercise in sarcopenic obesity.[108] There is an important gap in the evidence needed to recommend a specific exercise programme for sarcopenia and wide variation in clinical practice is the current norm.

The evidence on nutrition interventions is less consistent.[33] A number of studies have investigated the effects of exercise combined with nutrition to treat sarcopenia and a systematic review of non-pharmacological interventions for well characterised sarcopenia and physical frailty in older patients confirmed the effectiveness of exercise with or without nutritional supplementation to improve physical performance although the overall quality of the evidence was low.[107] Other reviews report variable findings although did not only include participants with sarcopenia.[109,110] Large scale trials are now underway to specifically address this area such as the European SPRINTT trial.[111,112]

The place of nutritional interventions without exercise for the treatment of sarcopenia is much less clear although overall there appears to be evidence for 'healthier' dietary patterns that are adequate in quality in terms of intakes of protein, vitamin D, antioxidant nutrients and long-chain polyunsaturated fatty acids.[113] However, many of the studies are observational in nature and high quality trials are less common. There remains debate about what constitutes an adequate intake of key nutrients such as protein as well as how they should be taken in terms of timing and distribution throughout the day.[114] Although most recent consensus documents recommend increasing protein intake in older people,[115,116] the only intervention trial comparing normal versus increased protein intake in mobility impaired (albeit not sarcopenic) participants was negative.[117]

High protein oral nutritional supplements may be more effective on some outcomes in the more specific context of sarcopenia with malnutrition.[54,118] There is also considerable interest in the value of individual nutrients such as the essential amino acid leucine and its metabolite beta-hydroxy beta-methylbutyric acid (HMB) which have shown some effects in improving muscle mass and function,[119,120] as has fish oil-derived n-3 (omega-3) polyunsaturated fatty acid (PUFA) therapy which increased muscle mass and function in one study of healthy older adults.[121]

Treatment: pharmacological approaches

At this time, there are no drugs approved for sarcopenia. A recent umbrella review has brought together systematic reviews and meta-analyses focusing on pharmacological interventions to improve muscle mass, strength and physical performance in older people.[122] Interestingly very few studies identified baseline sarcopenia status, so the findings could only be generalised to older people rather than to people with sarcopenia. The umbrella review identified seven systematic reviews or meta-analyses involving ten pharmacological interventions: vitamin D, combined oestrogen-progesterone, dehydroepiandrosterone (DHEA), growth hormone, growth hormone-releasing hormone,

391 combined testosterone-growth hormone, insulin-like growth factor-1, pioglitazone,
392 testosterone, and angiotensin-converting enzyme inhibitors. There appeared to be a
393 beneficial effect of vitamin D on strength and physical performance in women with low
394 baseline levels (<25 nmol/l). An effect of testosterone on muscle mass more than strength
395 or function, in men with low serum levels (<200–300 ng/dl), was also reported although
396 findings from the high profile Testosterone Trials suggest limited benefit of testosterone
397 for physical function, particularly in those with a slow walking speed, and caution
398 regarding the cardiovascular side effect profile.[123]
399
400 There is major research activity focused on developing new drugs for sarcopenia although
401 progress has not been straightforward. Initial interest in selective androgen receptor
402 modulators (SARMs) from mainly small phase I and II trials [124,125] has not been followed by
403 convincing results from larger studies. There is early evidence that myostatin inhibition
404 may prove beneficial, consistent with recognition that myostatin acts as a brake on muscle
405 differentiation, hypertrophy and protein synthesis. Results to date have not always been
406 consistent but positive findings include those from a phase II proof of concept trial that
407 reported that a myostatin antibody was associated with increased muscle mass and
408 improvement in some measures of physical performance in older, weak patients with a
409 history of falling (but not diagnosed sarcopenia). [126] Another phase II randomised
410 controlled proof of concept study of bimagrumab for sarcopenia found an increase in
411 thigh muscle volume and increased gait speed in those slow at baseline.[127]
412
413 **Assessing the effect of interventions in research and clinical practice**
414 Assessment of the effect of interventions in research and clinical practice is required to
415 enable them to be targeted appropriately. Unfortunately, there is still no clear consensus
416 on what intermediate measures should be used either in research settings [128] or in clinical
417 guidelines.[33] In the absence of an established regulatory pathway for the development of
418 interventions to date, the European Medicines Agency is using the SPRINTT trial to identify
419 standard outcome measures that may be used in future drug research.[111]

At present, there is a case for using the same muscle strength and physical performance measures as utilised at the initial assessment. Improvements in the short physical performance battery (SPPB) of 1 point or gait speed over 0.1 m/s are recognised as of clinical relevance.[129] In contrast minimum significant change has not been well defined for grip strength. Improvement in activities of daily living or in the number of falls may be even more relevant but not so straightforward to determine. However, there is increasing interest in developing Patient Reported Outcome Measures (PROMs) for sarcopenia.[130] Additionally, the SarQoL questionnaire, a sarcopenia-specific quality of life measure, can be used to understand the impact of the intervention on the global status of the patient.[131]

Looking ahead

The prevention of sarcopenia is a major area of research activity and observational epidemiological studies have identified important risk factors such as older age and low socioeconomic status as well as modifiable influences including low physical activity and poor diet,[132] although the direct effects of alcohol consumption and cigarette smoking are less clear.[133] The focus of preventive strategies to date has been to modify these risk factors in later life, particularly to increase levels of physical activity,[134,135] but more recently there has been consideration of the role of influences operating much earlier in the life course.

Birth cohort studies have proved invaluable in this area and findings from the Hertfordshire Ageing Study [136] and Hertfordshire Cohort Study [137] provided the first evidence that small size at birth was linked with lower grip strength 60 or 70 years later, with confirmation in a subsequent systematic review.[138] These findings have been explained by a life course approach to sarcopenia where it is proposed that muscle mass and function in older people depend not only on the rate of decline in later life and the

448 influences operating then, but also on the peak reached in young adulthood which is in
449 turn determined by factors operating earlier in life.[139]
450
451 Normative data for grip strength across the life course from UK studies (figure 5) [18] and
452 from global grip strength data [140] are now available. They not only confirm the concept
453 underlying a life course approach to sarcopenia - that skeletal muscle strength rises to a
454 peak in early adulthood, then plateaus, before starting to decline - but have also provided
455 a data driven approach to deriving cut points for low grip strength. For example, it has
456 been proposed that a grip strength of 2·5 standard deviations or more below the young
457 normal mean indicates low grip strength. This approach is analogous to that used to
458 define osteoporosis in terms of low bone mineral density relative to a young normal
459 mean.
460
461 The importance of mid-life influences is also becoming increasingly apparent. For
462 example, a study using data from the British National Survey of Health and Development
463 (the 1946 birth cohort) has shown evidence of cumulative benefits of increased life time
464 physical activity (LTPA) across mid-life on grip strength at the age of 60–64 years in men
465 and women. This demonstrated that those in the upper third of LTPA score had a mean
466 grip strength 2·11 kg (95% CI: 0·88-3·35) greater than those in the lower third after
467 adjustment.[141]
468
469 The life course approach to prevention is an important area going forward because it
470 extends the opportunity for intervention from late old age to young old age, mid-life and
471 before, when lifestyle changes such as regular physical activity and optimising diet may be
472 easier to put into place.[142] This also has the potential to enable public health messages to
473 younger people encouraging lifestyle modification such as increasing levels of physical
474 activity, to refer not only to immediate but also to lifelong benefits for skeletal muscle
475 health. However the evidence to date supporting this approach is largely observational
476 and trials of life course interventions are needed using efficient methodologies such as

trials within birth cohorts.[143] Linking a life course approach to understanding the underlying cellular and molecular mechanisms of sarcopenia has the potential to become a particularly powerful way to develop targeted treatment and preventive strategies.[144]

Conclusions

Sarcopenia is a progressive and generalised skeletal muscle disorder involving the accelerated loss of muscle mass and function that is associated with adverse health outcomes. It is increasingly recognised not only as an age-related problem, but one associated with a range of long-term conditions. Several recent new consensus definitions have advanced the field in the last decade. Experimental medicine is focusing on translating understanding of pathophysiology into advances in the diagnosis, treatment and prevention of sarcopenia and a life course approach may provide a useful framework. Important research areas to be addressed include increasing understanding of underlying cellular and molecular mechanisms, the development of biomarkers, improved accuracy of diagnostic tests, and the design of effective strategies for sarcopenia across the life course.

Search strategy and selection criteria

We developed a structured search strategy in Pubmed for publications in English using the search term “sarcopenia” in combination with one of the following keywords: “definition”, “screening”, “diagnosis”, “muscle mass”, “strength”, “frailty”, “malnutrition”, “cachexia”, “outcomes”, “disability”, “mortality”, “pathophysiology”, “life course”, “treatment”, and “exercise”. We focused on clinical trials, meta-analysis and review articles. Only articles published after 2010 (when most definitions of sarcopenia were published) were searched, but we did not exclude major contributions published before. We referenced articles judged to be relevant to this Seminar. When many similar articles were available, the most recent were used. Additional papers were identified from personal libraries and the reference lists of retrieved articles. Review articles are used to provide useful details and references on specific areas that cannot be covered in depth in this Seminar.

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Contributors

Both authors planned the manuscript, did the literature search, contributed to the tables and figures, and wrote, edited, and approved the manuscript.

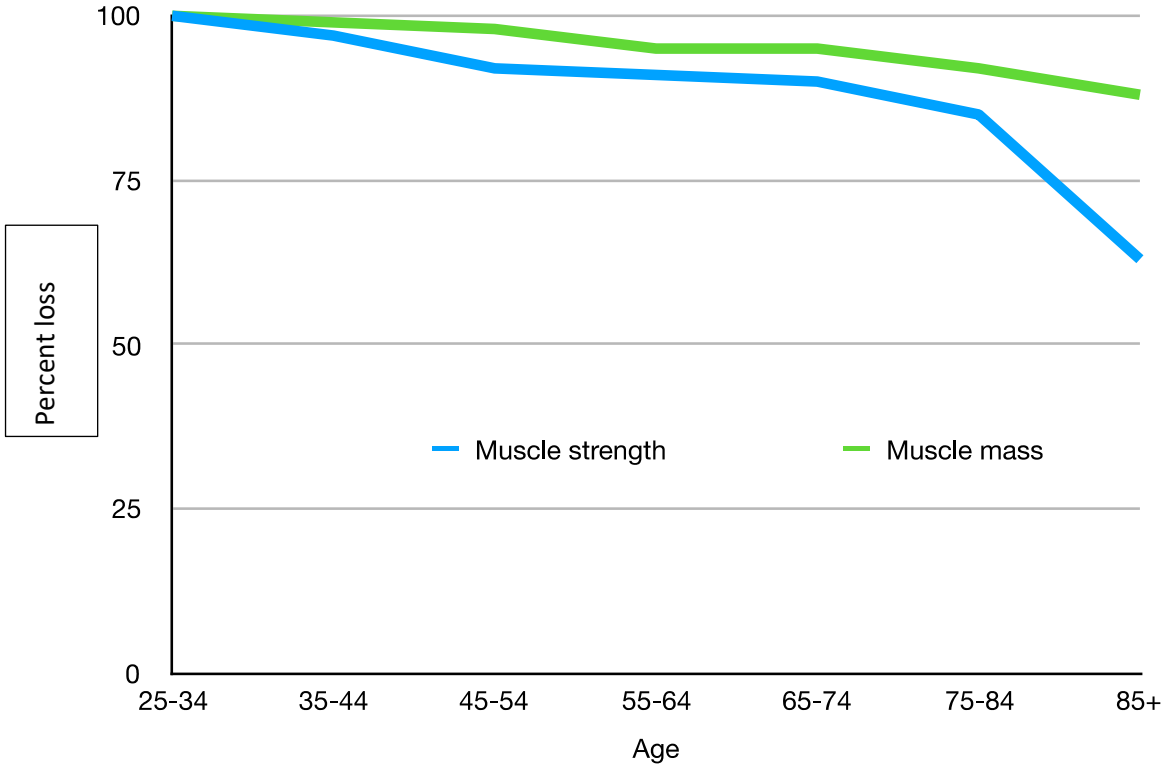
Conflicts of interest

ACJ has received speaker fees from Abbott Nutrition, Fresenius, Nestlé, Nutricia, Sanofi-Aventis; is a member of advisory boards for Abbott Nutrition, Nestlé and Pfizer; and has worked on research projects with Abbott Nutrition and Nutricia.

AAS received speaker fees from Abbott Nutrition 2011 and 2012.

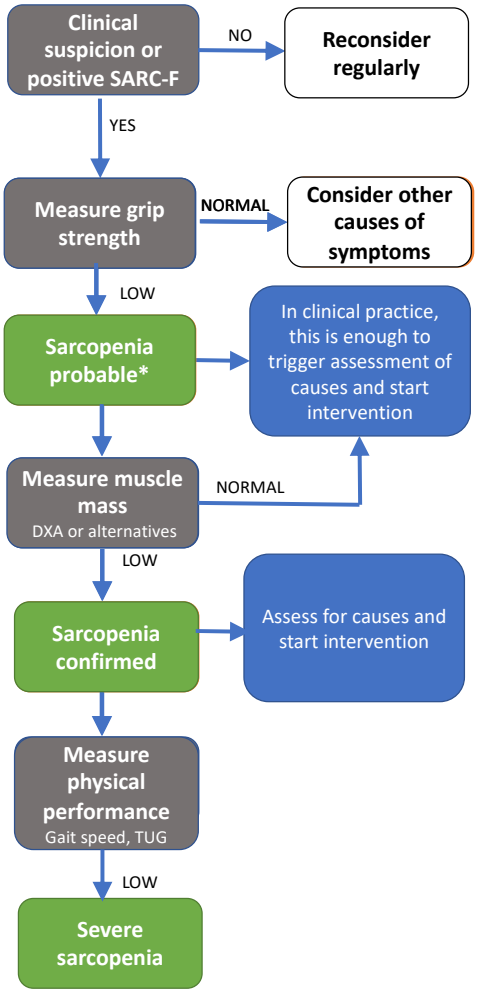
Figures:

Figure 1. Percent loss of muscle mass and muscle strength with age in men.



Adapted from Ferrucci L et al.[17]

531 Figure 2. A simple algorithm to diagnose sarcopenia in clinical practice



*Always consider other reasons for low muscle strength (e.g., depression, stroke, balance disorders, peripheral vascular disorders)

532

533 Adapted from EWGSOP2.[15]

534

535 Figure 3. Relationship between sarcopenia, physical frailty and general frailty
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537

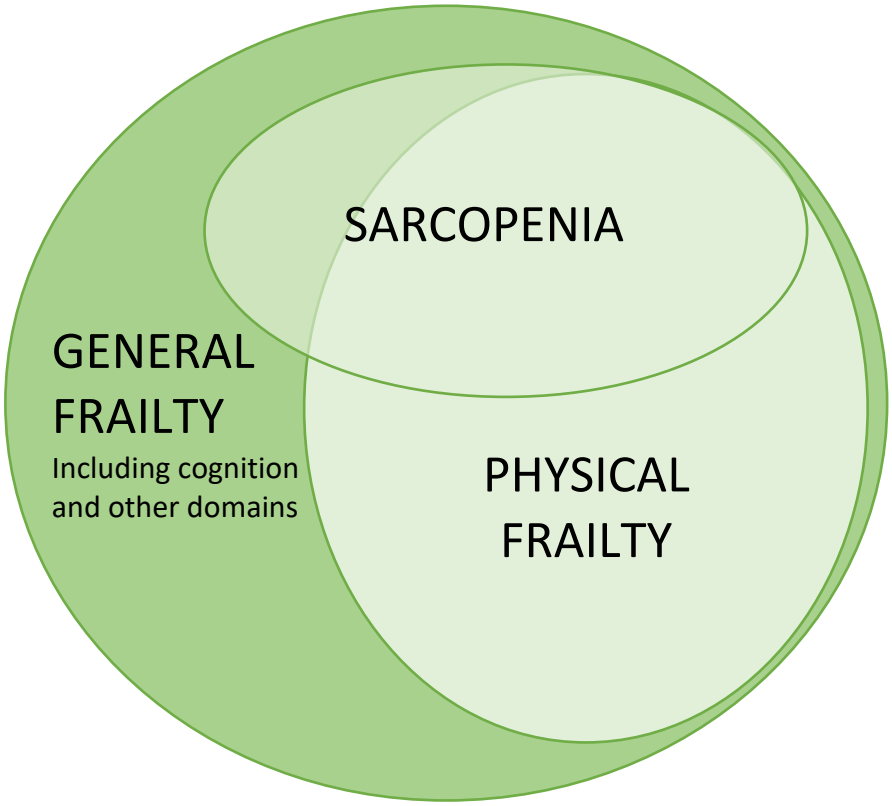


Figure 4. The multifactorial aetiology of sarcopenia

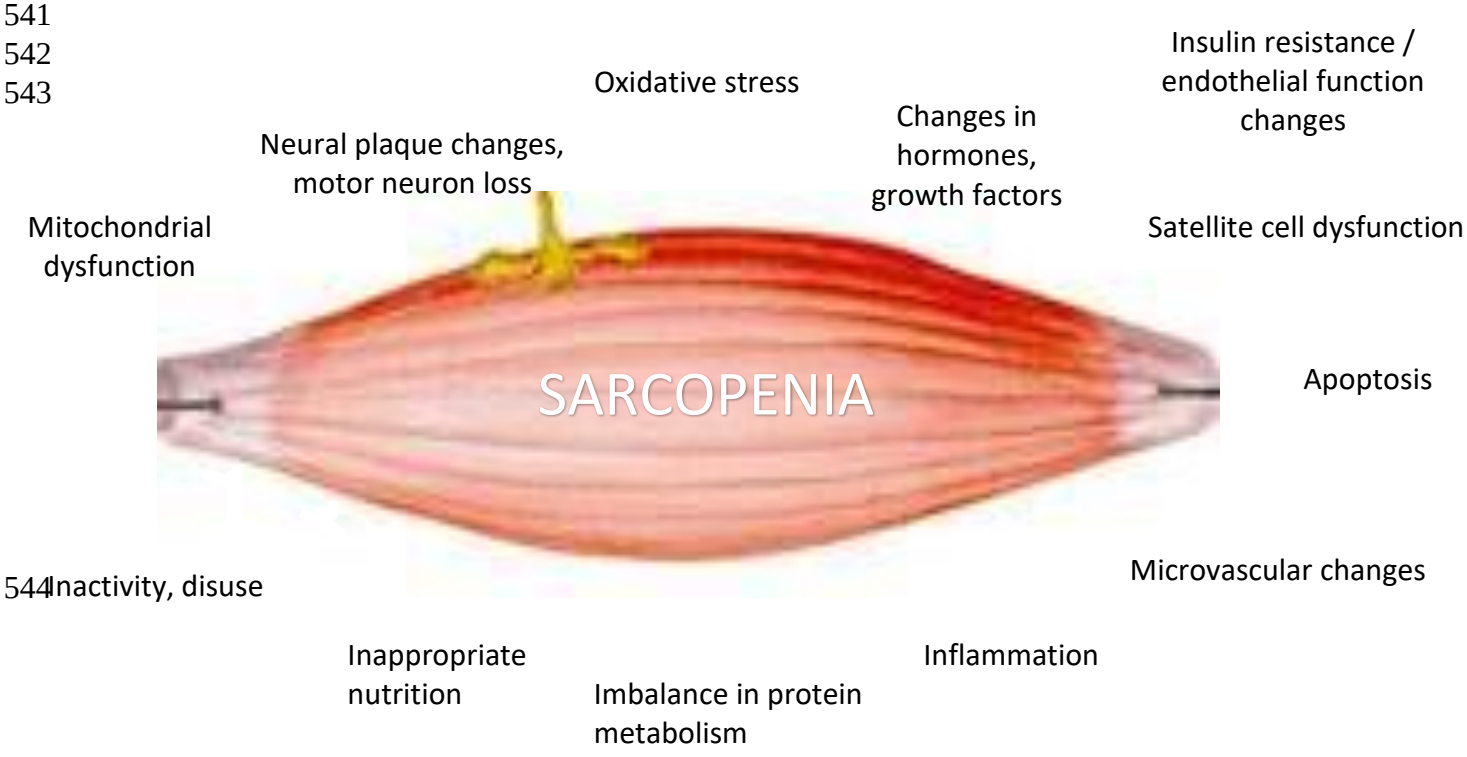
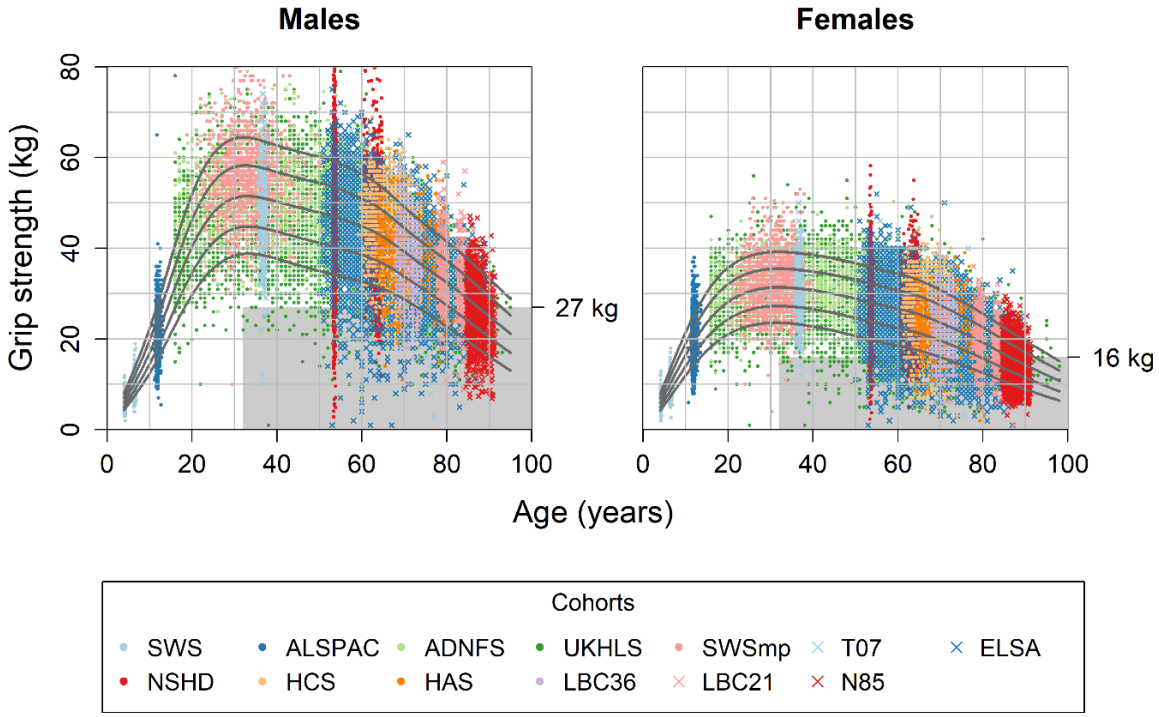


Figure 5. UK Normative data for grip strength across the life course



Centiles shown are 10th, 25th, 50th, 75th and 90th. Cut-points based on T-score of ≤ -2.5 are shown for males and females (≤ 27 and 16kg, respectively).

ADNFS Allied Dunbar National Fitness Survey, ALSPAC Avon Longitudinal Study of Parents and Children, ELSA English Longitudinal Study of Ageing, HAS Hertfordshire Ageing Study, HCS Hertfordshire Cohort Study, LBC1921 and LBC1936 Lothian Birth Cohorts of 1921 and 1936, N85 Newcastle 85+ Study, NSHD Medical Research Council National Survey of Health and Development, SWS Southampton Women's Survey, SWSmp mothers and their partners from the SWS, T-07 West of Scotland Twenty-07 Study, UKHLS Understanding Society: the UK Household Panel Study.

Adapted from Dodds R et al.[11]

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