Sarcopenia is a major therapeutic challenge and a public health priority in both the US and Europe. More than two decades after the word was first used to define a distinct clinical condition, the definition of sarcopenia remains open for discussion, and its clinical relevance is still not fully understood. This book provides some answers. It is a valuable addition to the existing literature, providing a one-stop shop for state-of-the-art information on a topic of particular relevance for geriatricians and all those who care for the older population.

There are serious health consequences to sarcopenia in terms of frailty, disability, morbidity, and mortality. Identifying high risk groups of older people is straightforward, but making a diagnosis is more difficult. Having addressed the definition of sarcopenia the book therefore goes on to discuss current open questions that concern the clinical management of the condition. Chapters cover nosology, pathophysiology, clinical identification, and treatment: for example, is sarcopenia a normal part of the ageing process? When does it become a disease state? Is it only a morphologic or functional abnormality, or is it an age-related disease? Epidemiological, clinical, diagnostic and therapeutic aspects of sarcopenia are covered, as well as possible methods of prevention and treatment options.

- Defines and explains the clinical relevance of sarcopenia
- Covers all recent scientific evidence
- Discusses treatment options
- Considers ways of prevention

Written by experts in the field from both the US and Europe, this book will be of practical interest to geriatricians, clinicians and professionals working in nursing homes, nutrition and sport medicine. It is also a valuable and comprehensive reference work for professionals, post-graduates and researchers on age-related diseases, disability, nutrition and geriatric medicine.
Sarcopenia
Sarcopenia

Editors

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Preface

Over the past few years, sarcopenia has moved rapidly from being a concept used by a couple of academics to one that is widely explored in journals and scientific meetings. All aspects of sarcopenia, from basic science to clinical applicability, are now an extremely active area of research and clinical practice for those working in geriatric medicine, nutrition, epidemiology, basic biological research and many other disciplines. Its recent emergence, together with the conceptualization of frailty, is a step forward in the quest to identify and prevent the unwelcome disabilities that accompany many people in their last years of life.

Thus, the moment has come to summarize, to define where we are and where we are going, to stand on solid ground for the next step – or jump. This book is intended to be a clear and precise reference work for those physicians or researchers interested in having a global, yet detailed understanding of such a complex topic. Rooted in basic science and in the critical use of diagnostic tools, the book also covers clinical aspects, trying to identify the role of sarcopenia in the complex arena of age, disease, and physical disability.

To accomplish this task, we have carefully selected authors from both Europe and the United States, as the approach to sarcopenia differs slightly in each continent. This wide range of authors allows the reader a clearer picture of the issues involved. Of course, all of the authors, with no exception, are leading experts in the field. As editors we are extremely grateful for their enthusiastic acceptance to contribute to this book, the high quality of their submissions, and their patience in adapting their chapters to fit the book.

After describing the epidemiological challenge that sarcopenia brings to current geriatric care, and reviewing the definitions of the word, the first chapters, explore the biological aspects of muscle and the central nervous system and their relation with movement and function. Sarcopenia is then explored in the context of the individual, from a lifetime and a syndromic approach, looking at the adverse effects it has on health and function. An analysis of the intimate relations between sarcopenia, cachexia, frailty and bones opens the door to a description of the complexity of measuring different parameters linked to muscle mass and function. Finally, the door opens to intervention, from nutrition and exercise to drugs, ending with a difficult question: can sarcopenia (and thus disability) really be prevented?

We believe that we have produced a state-of-the-art textbook with a comprehensive approach to sarcopenia. We hope that it will be a valuable reference tool, not only for experts, but also for those who are interested in starting their own research in this area and those who wish to develop their own criteria about such a promising field within geriatric medicine.
CHAPTER 1

Epidemiology of Muscle Mass Loss with Age

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INTRODUCTION

The development of new body composition methods in the early 1970s and 1980s led to more research on this topic, including the study of differences in body composition between young and older persons. These initial studies were followed by much larger studies covering a wide age range investigating how body composition varied across the life span. Variations in lean body mass and fat-free mass were described between age groups. These studies served as the important scientific basis for developing the concept Sarcopenia. Sarcopenia was defined as the age-related loss of muscle mass [1]. The term is derived from the Greek words sarx (flesh) and penia (loss). The development of this concept further stimulated research in this specific body composition area. More recently, large-scale studies among older persons have included accurate and precise measurements of skeletal muscle mass. Moreover, these measurements have been repeated over time, enabling the sarcopenia process to be studied.

This chapter will discuss the results of epidemiological studies investigating the age-related loss of skeletal muscle mass. First, several cross-sectional studies will be presented comparing the body composition between younger and older persons. Then prospective studies will be discussed investigating the change in body composition with aging. The chapter will conclude with the results of more recent, prospective studies that precisely measured change in skeletal muscle mass in large samples of older persons.

MUSCLE MASS DIFFERENCES BETWEEN AGE GROUPS

Comparisons between young and older men and women with regard to muscle size have been made in several small studies. The results showed that healthy women in their 70s had a
33% smaller quadriceps cross-sectional area as obtained by compound ultrasound imaging compared to women in their 20s [2]. Using the same methodology and age groups, healthy older men had a 25% smaller quadriceps cross-sectional area [3]. In a study investigating thigh composition using five computed tomography scans of the total thigh, smaller muscle cross-sectional areas were observed in older men compared to younger men even though their total thigh cross-sectional area was similar. The older men had a 13% smaller total muscle cross-sectional area, 25.4% smaller quadriceps and 17.9% smaller hamstring cross-sectional area [4]. Using magnetic resonance imaging of the leg anterior compartment, muscle area was measured in young and older men and women [5]. The older persons had a smaller area of contractile tissue; 11.5% less in women and 19.2% less in men; compared to the young persons. These data, obtained by different body composition technologies, clearly showed a smaller muscle size in older persons compared to young persons. The observed differences in muscle size between age 20 and age 70 suggested a loss of skeletal muscle mass of about 0.26% to 0.56% per year.

The amount of non-muscle tissue within the muscle was also assessed using five computed tomography scans of the thigh in 11 elderly men and 13 young men [4]. Older men had 59.4% more non-muscle tissue within the quadriceps and 127.3% within the hamstring muscle. In a similar study, the amount of non-muscle tissue in older men was 81% higher in the plantar flexors as compared to young men [6]. Thus, apart from the smaller muscle size in old age, these studies suggested that the composition of the muscle also changed with aging, leading to less ‘lean’ muscle tissue in old age.

With the greater availability of body composition methods such as bioelectrical impedance and dual-energy x-ray absorptiometry over time, cross-sectional data on muscle size in large study samples including a broad age range have been collected. Examples of these studies using lean mass from DXA (the non-bone, non-fat soft tissue mass) and fat-free mass from bioelectrical impedance, presented by 10-year age groups of men, are presented in Figure 1.1 [7,8]. Older age groups had a lower total body fat-free mass, lower

![Figure 1.1](image-url)  
**Figure 1.1** Differences in fat-free mass and lean mass using different body composition methodologies between men of different age groups. BIA = bioelectrical impedance. DXA = dual-energy x-ray absorptiometry. Based on references 7 and 8.
Figure 1.2  Differences in muscle cross-sectional area and lean mass using different body composition methodologies between men and women of different age groups. DXA = dual-energy x-ray absorptiometry. CT = computed tomography. Anthrop. = anthropometry, using arm circumference and triceps skinfold. Based on references 9–11.

total body lean mass, and lower arm and leg lean mass. Figure 1.2 presents the differences in muscle size between 10-year age groups in men and women. With increasing age group, the data suggested a lower whole body lean mass and leg lean mass as assessed by DXA [9], a smaller arm muscle cross-sectional area (from anthropometric measures [10]) and a smaller calf muscle cross-sectional area (from peripheral quantitative computed tomography [11]). These cross-sectional data derived from samples from Italy, Australia, India, Japan, and the USA consistently suggested a decline in muscle size with aging. These data also suggested a steeper decline in muscle size with aging in men compared to women.

Cross-sectional data from a sample of 72 women aged 18 years to 69 years suggested a strong correlation between age and the amount of low density lean tissue as assessed by a computed tomography scan of the mid-thigh. The density of muscle tissue as assessed by computed tomography is indicative of the amount of fat infiltration into the muscle [12]. Higher age was associated with greater amounts of low density lean tissue (correlation coefficient = 0.52 [13]). This result again suggested a greater fat infiltration into the muscle with increasing age.

These cross-sectional data, however, should be interpreted carefully as cohort and period effects, and not aging per se, may have caused the observed differences in muscle size and muscle composition between the age groups. For example, well-known cohort differences in body height, a strong determinant of muscle size, may partly explain the lower muscle mass in older persons compared to younger persons. In addition, period differences in lifestyle (e.g. sports participation and diet) and job demands may have differentially affected muscle size and muscle composition between age groups. Therefore, prospective data are preferred to investigate the change in muscle mass with aging.
Forbes was among the first researchers to report prospective data on the age-related decrease in lean body mass in a small group of adults using potassium\(^{40}\) counting data [14]. The reported decline was \(-0.41\)% per year as obtained in 13 men and women aged 22–48 years.

Many prospective studies followed using body composition techniques such as bioelectrical impedance, isotope dilution, skinfolds and underwater weighing to study change in fat-free body mass and total body water with aging [15–21]. However, due to the body composition methodologies used in these studies, no precise measurement of skeletal muscle mass could be obtained because fat-free mass and total body water also include lean, non-muscle tissue such as the visceral organs and bone. Therefore, these studies only provide a crude estimate of the sarcopenia process with aging.

More recent prospective studies have measured the decline in appendicular skeletal muscle mass using DXA [22–25], the decline in total body skeletal muscle mass using 24-h urinary creatinine excretion [26], and the decline in muscle cross-sectional area by CT in older persons [27,28]. The characteristics of these studies are presented in Table 1.1. From these studies a precise and accurate estimation of the sarcopenia process can be obtained. The relative annual decline in skeletal muscle mass was estimated to be between \(-0.64\) and \(-1.29\) \% per year for older men and between \(-0.53\) and \(-0.84\) \% per year for older women (Figure 1.3). In older persons the absolute as well as the relative decline of skeletal muscle mass with aging was larger in men compared to women.

### Table 1.1 Characteristics of prospective studies investigating the age-related change in skeletal muscle mass in older men and women

<table>
<thead>
<tr>
<th>Reference</th>
<th>N and sex</th>
<th>Age (mean (SD) or range (y))</th>
<th>Mean follow-up time (y)</th>
<th>Body composition method</th>
<th>Muscle measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>27</td>
<td>12 men</td>
<td>71.1 (5.4)</td>
<td>8.9</td>
<td>CT</td>
<td>Mid-thigh total anterior muscle cross-sectional area</td>
</tr>
<tr>
<td>28</td>
<td>813 men</td>
<td>70–79</td>
<td>5</td>
<td>CT</td>
<td>Mid-thigh muscle cross-sectional area</td>
</tr>
<tr>
<td></td>
<td>865 women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>26 women</td>
<td>75.5 (5.1)</td>
<td>2.0</td>
<td>DXA</td>
<td>Leg skeletal muscle mass</td>
</tr>
<tr>
<td>24</td>
<td>1129 men</td>
<td>70–90</td>
<td>5</td>
<td>DXA</td>
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<tr>
<td></td>
<td>1178 women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>24 men</td>
<td>60–90</td>
<td>4.7</td>
<td>DXA</td>
<td>Appendicular skeletal muscle mass</td>
</tr>
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<td></td>
<td>54 women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>62 men</td>
<td>71.6 (2.2)</td>
<td>5.5</td>
<td>DXA</td>
<td>Appendicular skeletal muscle mass</td>
</tr>
<tr>
<td></td>
<td>97 women</td>
<td>71.4 (2.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>52 men</td>
<td>60.4 (7.9)</td>
<td>9.7</td>
<td>24-h urinary creatinine excretion</td>
<td>Total body skeletal muscle mass</td>
</tr>
<tr>
<td></td>
<td>68 women</td>
<td>60.4 (7.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SD = standard deviation, CT = computed tomography, DXA = dual-energy x-ray absorptiometry
Figure 1.3  Annual decline (%) in skeletal muscle mass in older men and women from prospective studies with follow-up times from 2 to 9.7 years.

Limited data are available on the prospective change in muscle fat with aging. Data from the Health, Aging and Body Composition Study showed an increase in intermuscular fat at the mid-thigh of 3.1 cm² in older men and 1.7 cm² in older women during the 5-year follow-up [28]. This translated to an annual increase of 9.7% in men and 5.8% in women. This increase was paralleled by a decline in subcutaneous fat at the mid-thigh and shows specifically the increasing fat infiltration into muscle tissue with increasing age.

From these body composition studies it can be concluded that the amount of skeletal muscle mass declines substantially with aging. At the same time, the composition of the muscle changes and a greater fat infiltration into the muscle occurs. It is important to understand the potential impact of these changes on healthy aging.

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CHAPTER 2

Definitions of Sarcopenia

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THE ORIGINS OF THE WORD ‘SARCOPENIA’

Sarcopenia has rapidly become a common term in geriatrics and gerontology, both in academic forums and in clinical practice. This is somehow surprising, as the word sarcopenia was introduced quite recently, trying to improve understanding of a previously eluding concept. In fact, while sarcopenia seems to be common and has huge personal and societal costs, sarcopenia still has no broadly accepted definition, diagnostic criteria, ICD-9 codes, or treatment guidelines. This chapter will review the still changing concept of sarcopenia, and recent efforts that are trying to agree on a definition that may reach wide consensus and be useful both for research and clinical practice.

In 1988, a meeting was convened in Albuquerque (USA) to discuss the assessment of health and nutrition in older populations. Rosenberg, who is accredited for the first use of the word, noted that ‘no decline with age is more dramatic or potentially more functionally significant than the decline in muscle mass’ and suggested that to provide recognition by the scientific community this phenomenon needed a name. He proposed a name derived from the Greek roots sarx for flesh and penia for loss [1].

Although the word chosen only described muscle mass, from the very beginning it was acknowledged that the consequences of muscle mass loss affected ambulation, mobility, nutrient intake and status, and functional independence.

DEFINITIONS BASED ON MUSCLE MASS

Availability and standards on techniques that measure muscle mass (or lean body mass) were initially far more advanced than measures of other parameters involved in sarcopenia. It is thus not surprising that most major epidemiological studies fixed to a strict definition of sarcopenia as loss of muscle mass.
The first epidemiological studies to determine the prevalence of sarcopenia measured muscle mass (lean body mass) either using BIA or DXA. For instance, Baumgartner used a definition based on appendicular skeletal muscle mass measured by DXA, corrected for height, and defined sarcopenia as being two standard deviations below sex-specific means of healthy young persons (18-40 years) of a reference population [2].

Many studies performed in recent years use the word sarcopenia as synonymous of muscle wasting or muscle mass loss (as reviewed in Chapter 1). From them we have learned that muscle mass declines at approximately 1-2% per year after the age of 50 years. If sarcopenia is defined using only severe muscle mass (two standard deviations below healthy young) it is present in 5 to 13% of 60 to 70 year olds and 11 to 50% of those 80 and older [3]. Over a thousand publications have used this definition of sarcopenia, and the term is still used as a surrogate for muscle mass.

LIMITS OF ONLY USING MUSCLE MASS

While the definition of sarcopenia based on loss of muscle mass alone has served the scientific community fairly well, it has been less satisfying for clinicians, the pharmaceutical industry, and regulatory agencies. Unlike the measurements of bone mineral density, the measurement of muscle mass has not been widely adopted by clinicians. Regulatory agencies have failed to accept that restoration of muscle mass is, of itself, a sufficient reason to allow a drug to be approved for use. It should be noted that this is not different from the situation with osteoporosis wherein reduced bone mineral density is recognized as a legitimate indication for treatment, but for regulatory considerations, drugs have had to show a reduction in fracture incidence before approval [4].

There are many crucial aspects of sarcopenia that are missed by the simplistic use of muscle mass. Relevant patient outcomes of sarcopenia include mortality and physical disability (i.e. the inability to walk or perform activities of daily living). A number of studies have shown that reduced muscle mass is predictive of disability and mortality. However, muscle mass by itself has shown to be a weak predictor of outcomes [5–10]. It has also been shown that the link between muscle mass, muscle function (strength and power), physical performance and other downstream outcomes is not linear [10;11]. These relationships are better explored in Chapters 6 and 8.

Some reasons for this inconsistency related to muscle quality are: 1) The infiltration into muscle by fat, which is a powerful predictor of future disability and mortality [6]. The percent of body fat (obesity) to muscle mass may be a confounding factor in understanding the link between muscle mass and physical function [12]. 2) Infiltration of collagen into muscle with aging can also lead to a dichotomy in the relationship between muscle mass and strength [13]. 3) Age-associated changes in neuromuscular activation that are superimposed on changes in muscle mass may further explain the dichotomy between mass and strength/power losses [14]. Other changes in muscle that may lead to a loss of strength include deposition of abnormal proteins, contractile and structural protein misfolding, mitochondrial dysfunction, neuromuscular and plaque dysfunction.

A final problem with the definition of sarcopenia by muscle mass are the variety of measures available to measure muscle mass, even within the same technique, each based on some assumptions that may be true or not. This happens even for the gold standards based on radiology (see Chapter 14). Each measure leads to different cut-offs for muscle mass and are indirect measures [15]. As such, they can be influenced by adiposity and total
Table 2.1  Alternative names proposed for sarcopenia and related disorders

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dynapenia</td>
<td>Age related loss of strength</td>
</tr>
<tr>
<td>Kratopenia</td>
<td>Age related loss of strength</td>
</tr>
<tr>
<td>Myopenia</td>
<td>Clinically relevant muscle wasting due to any illness and at any age</td>
</tr>
<tr>
<td>Frailty</td>
<td>See Chapter 11</td>
</tr>
</tbody>
</table>

body water. Different equations and assumptions in measurements may also yield different results. For instance, some authors sum up the muscle mass of the four limbs from a DXA scan to define appendicular skeletal muscle mass (ASM), and define a skeletal muscle mass index (SMI) as ASM/height² (as kg/m²) [2]. Other describe a skeletal muscle index (SMI), where SMI = (skeletal muscle mass/body mass) × 100 [16], and use a two tier approach (class I and II sarcopenia, depending on the number of standard deviations below mean values for young adults. Other approaches have also been explored [17].

The evidence that the isolated measure of muscle mass has practical limitations has boosted a debate, and many authors have being looking for an alternative term to sarcopenia that better describes the complexity of the problem of mass and function (Table 2.1). However, if one looks at other widely used medical terms used to define common diseases (diabetes in Greek comes from ‘siphon’, dementia in Latin means ‘out of mind’), they seem to be very limited compared to the wide range of problems each disease carries. Thus, using a word that is now in common use, such as sarcopenia, and improving its definition seems to be wiser than wasting time in arguments about the best word to describe each element of a complex condition.

**RECENT CONSENSUS DEFINITIONS**

Two international consensus definitions have been published recently, supported by different scientific societies and with some common authors, which may be a step forward in our understanding of sarcopenia [18;19]. They share some common ideas, and both open the door to further refinements when evidence allows.

**European Working Group on Sarcopenia in Older People**

The first definition, published in 2010, was promoted by the European Union Geriatric Medicine Society (EUGMS) and endorsed by the European Society of Clinical Nutrition and Metabolism (ESPEN), the International Academy of Nutrition and Aging (IANA) and the International Association of Gerontology and Geriatrics – European Region (IAGG-ER) [18]. An international Working Group was convened, with the task of developing an operational definition and diagnostic criteria for sarcopenia that could be used in clinical practice as well as in research studies. The following questions were discussed:

- What is sarcopenia?
- What parameters define sarcopenia?
- What variables will measure them, and what measurement tools and cut-off points will be used?
- How does sarcopenia relate to other diseases/conditions?
EWGSOP defines sarcopenia as a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes, such as physical disability, poor quality of life, and death. The operational definition recommends using the presence of both low muscle mass + low muscle function (strength or performance) for the diagnosis of sarcopenia. Thus diagnosis requires documentation of criterion 1 plus documentation of either criterion 2 or criterion 3 (Table 2.2).

Although this definition intends to be inclusive, it is acknowledged that sarcopenia is a geriatric syndrome, and the cause or causes that lead into it are complex and interacting. Thus, EWGSOP suggests that dividing sarcopenia into categories may be helpful in clinical practice, and proposes the use of the terms primary sarcopenia and secondary sarcopenia. Sarcopenia can be considered primary (or age-related) when no other cause is evident but aging itself, while sarcopenia can be considered secondary when one or more other causes are evident (Table 2.3). In many older people, the aetiology of sarcopenia is multifactorial so that it may not be possible to characterize each individual as having a primary or secondary condition.

Sarcopenia staging, which reflects the severity of the condition, is also considered here as a concept that can help guide clinical management of the condition. EWGSOP suggests a conceptual staging as presarcopenia, sarcopenia, and severe sarcopenia (Table 2.4). The presarcopenia stage is characterized by low muscle mass without impact on muscle strength or physical performance. This stage can only be identified by techniques that measure muscle mass accurately and in reference to standard populations. The sarcopenia stage is characterized by low muscle mass, plus low muscle strength or low physical performance. Severe sarcopenia is the stage identified when all three criteria of the definition are met.
Table 2.4 EWGSOP conceptual stages of sarcopenia

<table>
<thead>
<tr>
<th>Stage</th>
<th>Muscle mass</th>
<th>Muscle strength</th>
<th>Performance</th>
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</thead>
<tbody>
<tr>
<td>Presarcopenia</td>
<td>↓</td>
<td></td>
<td></td>
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<tr>
<td>Sarcopenia</td>
<td>↓</td>
<td>↓</td>
<td>Or ↓</td>
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<tr>
<td>Severe sarcopenia</td>
<td>↓</td>
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(low muscle mass, low muscle strength, and low physical performance). Recognizing stages of sarcopenia may help in selecting treatments and setting appropriate recovery goals, and staging may be a link with the following definition.

**Society for Sarcopenia, Cachexia and Wasting Disorders**

The Society for Sarcopenia, Cachexia and Wasting Disorders published its consensus definition in 2011 [19], after a meeting with the stated purpose to find a definition or set of definitions that are universally acceptable and can lead to easily definable endpoints for clinical trials. The definition developed would:

- be a meaningful surrogate for clinically useful endpoints (decline in activities of daily living, hospitalization, nursing home residence, injurious falls or mortality);
- allow for treatments that worked in ways different from increasing muscle mass;
- include only measurements that have been demonstrated to lead longitudinally to clinically meaningful outcomes and have definable cut points based on data;
- be independent of the molecular target(s) for drug development.

It was decided that ‘sarcopenia with limited mobility’ would be an acceptable term to define persons with a need for therapeutic interventions. This is a specific syndrome with clear loss of muscle mass and a clear target for intervention.

Sarcopenia with limited mobility is defined as a person with muscle loss whose walking speed is equal to or less than 1 m/s or who walks less than 400 m during a 6 minute walk. The person should also have a lean appendicular mass corrected for height squared of more than two standard deviations below that of healthy persons between 20 to 30 years of age of the same ethnic group. The limitation in mobility should not be clearly attributable to the direct effect of specific disease such as peripheral vascular disease, or central or peripheral nervous system disorders, dementia, or cachexia.

This definition also tried to define targets for interventions: interventions are considered clinically significant if they increase the 6 minute walk by 50 meters or they increase gait speed by 0.1 m/sec.

Although the EWGSOP looks mainly to sarcopenia as an age-related condition, this group leaves open the question of whether sarcopenia as a term should be limited to use in older persons or used as a general term for adults of any age. Thus, while emphasizing that this is a common condition in older age, the panel was not comfortable in limiting the definition to only older persons.
2: DEFINITIONS OF SARCOPENIA

COMMON ASPECTS OF RECENT DEFINITIONS

Although both definitions are clearly different, probably due to a different focus or objective of each of the panels, they both seem to reach a high level of agreement in some aspects of sarcopenia. Reviewing these aspects may lead into a better insight in the concept of sarcopenia.

Sarcopenia as a syndrome

Sarcopenia can be considered an age-related process of normative ageing, a disease or a syndrome. Both definitions consider that sarcopenia (or sarcopenia with limited mobility) is a syndrome, not a disease or normal aging. Moreover, sarcopenia can be best viewed as a geriatric syndrome [20].

Geriatric syndromes are common, complex, and costly states of impaired health in older individuals, that result from incompletely understood interactions of disease and age on multiple systems, producing a constellation of signs and symptoms. Sarcopenia is prevalent in older populations, has multiple contributing factors – the aging process over the life course, early life developmental influences, less-than-optimal diet, bed rest or sedentary lifestyle, chronic diseases, and certain drug treatments – and is linked with other comorbid disorders, impaired mobility, increased risk of falls and fractures, impaired ability to perform activities of daily living and increased risk of death [21–23].

Considering sarcopenia as a syndrome mandates a multidimensional approach to understand its pathophysiology, to investigate its aetiology in affected individuals, to define the molecular targets for intervention, and probably to successfully treat it.

Not only muscle mass

Although muscle mass is a constitutive part of sarcopenia, the concept of using muscle mass alone in definitions of sarcopenia has probably been stretched to its limits. Measurement of muscle mass is quite straight (although many problems persist, as described in Chapters 14 and 15), easy to understand and amenable to be used in big epidemiological studies. However, muscle mass is not enough.

One of the definitions has opted to define sarcopenia by adding reduced muscle function and/or physical performance to the loss of muscle mass. The second has opted to add poor physical performance (not due to other conditions) to the loss of muscle mass. In both cases, it seems evident that clinical consequences of muscle wasting have to be considered if sarcopenia wants to have a place in clinical practice.

Physical performance

The clinical relevance of sarcopenia depends on its being a marker of impaired outcomes, mortality being the most striking, but perhaps not the most relevant. Disability is a major concern in older people, and sarcopenia and frailty are emerging as stepping stones in the path from good health and function to disability and death. The earliest identification of the impairments that may push a subject to fall down the slope of disability would theoretically allow for an early, more effective intervention to avoid disability or reduce its speed.
The EWGSOP opted to use two dimensions that may help identify those individuals with sarcopenia that are in the highest need of intervention (muscle strength and physical performance), and to propose a wide range of methods to measure these dimensions. The SSCWD opted for a more practical approach, choosing two single measurements of physical performance (gait speed and 6 minute walk). In both cases, physical performance (not established disability [24]) emerges as a key parameter to be measured in sarcopenia.

Sarcopenia and cachexia

Sarcopenia is only one in a list of conditions associated with prominent muscle wasting, malnutrition and cachexia being perhaps the most evident. These conditions interact so deeply, that defining them as different entities is a complex task [25,26]. The main reasons to differentiate between these conditions are to encourage research into age related mechanisms and to guide targeted and appropriate therapy for each of them.

Cachexia is widely recognized in older adults as severe wasting accompanying disease states. Definitions of cachexia are also evolving in the last decade, but in most cases it includes the concept of inflammation [27–31] as a leading mechanism into muscle wasting. Thus, most cachectic individuals are also sarcopenic, but most sarcopenic individuals are not considered cachectic. Sarcopenia is one of the elements of some proposed definition for cachexia [27]. Both new definitions of sarcopenia agree with the concept that cachexia and sarcopenia are different. However, while the SSCWD definition excludes cachectic individuals from the definition of sarcopenia, the EWGSOP accepts that cachexia may be part of disease induced sarcopenia.

OPEN AREAS FOR DISCUSSION

Research and scientific discussion in sarcopenia are blooming, so many key elements of the definitions of sarcopenia are still waiting for more evidence to support before they settle down. A brief review of these open aspects may also help to gain some insight into this ongoing debate.

Case finding and populations at risk

Identifying subjects with sarcopenia, both for clinical practice, and for selection of individuals for clinical trials, seems to be an important task. Obviously, this case finding is directly linked with the definition used. However, case finding may be started in the general population, or by identifying some risk groups.

EWGSOP chooses a population approach, by suggesting screening all patients over 65 years. However, it proposes a gradual approach, starting with the measure of gait speed, and using a cutoff of less than 0.8 meters per second to identify the risk for sarcopenia [32]. Those with low gait speed will go on with further testing to determine if they reach full diagnostic criteria for sarcopenia. This approach is now being tested [33].

SSCWD uses a lower age threshold (60 years), but recommends screening for sarcopenia with limited mobility only in those who are falling, who feel that their walking speed has
decreased, who have had a recent hospitalization, who have been on a prolonged bed rest, have problems arising from a chair or need to use an assistive device for walking. This approach of looking for risk factors, clinical suspicion or functional impact to detect populations at risk has also been proposed by others [20].

Relevant outcomes

While reduced mobility and functionality are increasingly prevalent in older people, only a handful of clinical trials are under way to test potential sarcopenia treatments. The absence of standardized primary outcomes is a major challenge for the design of such studies. A very active debate is ongoing as of what outcomes should be used in sarcopenia research [34–37].

For intervention trials, EWGSOP recommends three primary outcome variables—muscle mass, muscle strength and physical performance. Other outcomes (ADL, quality of life, metabolic and biochemical markers, falls or admission to nursing home or hospital) are considered secondary by this group and of particular interest in specific research areas and intervention trials.

SSCWD opts again for a more practical approach. It states that at present there is no clear consensus pertaining to the magnitude of change in muscle mass that is predictive of clinically meaningful outcomes, and recommends that gait speeds equal or less than 1 m/s are predictive of poor outcomes, with a clinically significant improvement in gait speed of at least 0.1 m/sec as being useful. For the 6 minute walking test, which has already been utilized as a measure for drug approval by several regulatory agencies in peripheral vascular disease and pulmonary hypertension, it is recommended that, in persons who can walk at least 100m, a clinically significant change would be >50 meters.

Reference populations and cutoff values

For any given parameter included in a definition, there is a need to identify cutoff points that separate normal from abnormal values. Except in the rare occasion where disease and health are extremely separate, the choice of cutoff values is arbitrary by nature, as it depends upon the measurement technique chosen and availability of reference studies and populations. In sarcopenia research, the cutoffs determined are usually arbitrary, as the associations between variables and outcomes are usually continuous in nature. The choice of the right reference populations may also influence cutoff points [18].

Both definitions recommend the use of normative (healthy young adult) rather than other predictive reference populations, with cutoff points at two standard deviations below the mean of healthy persons between 20 to 30 years of age of the same ethnic group. However, high quality reference populations are still lacking for most groups. More research is urgently needed in order to obtain good reference values for populations around the world.

Muscle fat and sarcopenic obesity

The problem posed by the infiltration of muscle by fat and other qualitative aspects that define muscle quality is only starting to be understood [38–40]. One reason for this
inconsistency is the infiltration into muscle by fat which is a powerful predictor of future disability and mortality [6]. This seems to be an important aspect of the definition of sarcopenia. However, measurement is complex and expensive, and its relative weight compared with other parameters still waits to be known.

Some definitions of muscle mass, related to other anthropometric parameters, may miss the importance of the relative amount of muscle and fat in body composition. Sarcopenic obesity (obesity associated with low muscle mass) may be promoted by excess energy intake, physical inactivity, low-grade inflammation, insulin resistance and changes in hormonal milieu [12]. Considering both obesity and muscle mass and function may be a better predictor of outcomes than using only muscle related parameters [41]. No definition of sarcopenia has yet been able to disentangle the relation between muscle mass and body fat in a clear way (see Chapter 13).

**Sarcopenia and frailty**

Like sarcopenia and cachexia, frailty is a developing concept, and a number of different definitions for frailty have been developed (Table 2.5) [42;43]. Generally speaking, frailty is the consequence of age-related cumulative declines across multiple physiologic systems, with impaired homeostatic reserve and a reduced capacity of the organism to withstand stress, thus increasing vulnerability to adverse health outcomes including falls, hospitalization, institutionalization and mortality [44]. The conditions of frailty and sarcopenia overlap; most frail older people exhibit sarcopenia, and some older people with sarcopenia are also frail. The general concept of frailty, however, goes beyond physical factors to encompass psychological and social dimensions as well, including cognitive status, social support and other environmental factors. These complex relations are further explored in Chapter 11.

**SUMMARY**

Sarcopenia was originally defined as age-related muscle mass. More recent definitions have extended this to include muscle strength, function and limited mobility. These definitions seem more likely to be predictors of poor outcome and to be useful for clinical trials of drugs used to treat sarcopenia (muscle loss). The evolving process of refining the definition of sarcopenia in accordance with the clinical needs and improved understanding of the complex etiology of this condition will continue [45].