Chapter 1

Epidemiology of Sarcopenia and Frailty

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Abstract

Sarcopenia and frailty are common in older persons and pose particular challenges for health and social care systems especially in the context of global population ageing. Sarcopenia, the loss of skeletal muscle mass, strength and function with age is associated with adverse individual physical and metabolic changes contributing to morbidity and mortality. The health and socioeconomic implications of sarcopenia are also considerable. Sarcopenia is a core component of physical frailty that together impact negatively on an individual's capability to live independently. Frailty is a biological syndrome of low reserve and resistance to stressors resulting from cumulative declines across multiple physiological systems that collectively predispose an individual to adverse outcomes. Frailty develops along a continuum from independence through to death as physiological reserves progressively diminish an individual's capacity to recover from an acute insult or illness. Managing sarcopenia and frailty involves the multidisciplinary led completion of a comprehensive care plan that is patient centred, responsive to the needs of the patient and adaptable therefore enabling an individual to maintain their independence.

Keywords: Sarcopenia, frail, epidemiology, Comprehensive Geriatric Assessment

1. Introduction

Over the past two centuries, there has been a demographic transformation across the world and people are living longer [1]. For the first time in history, people can expect to live beyond their 60th birthday. In fact, survival to age 80 is anticipated to be the norm for all of today's young people. People aged 60 or over are set to increase from 841 million to more than 2 billion between 2013 and 2050. This equates to 21.1% of the world's population [1]. Globally, the number of people aged 80 years or over, the "oldest-old", is growing even faster. In 2000, there were 71 million people aged 80 or over worldwide. Since then, the number of oldest-old

has grown by 77% to 125 million in 2015, and it is projected to increase by 61% over the next 15 years, reaching nearly 202 million in 2030. Projections indicate that in 2050 the oldest-old will number 434 million globally, having more than tripled in number since 2015 [2]. These demographic changes are largely due to the advances in public health and modern medicine that have reduced early life mortality, reduced the rate of infectious diseases [3] and have allowed people to live with one or more long-term conditions. Whilst this is a cause for celebration, these cumulative changes pose significant challenges for delivering health and social care to older people in all nations concerned.

The situation within the UK is no different. Medical and technological advances in the treatment of illnesses and diseases have improved mortality rates in the oldest age groups. In 2013–2015, a UK male aged 85 could expect to live to age 90.8 years and a female to 91.8 years. Life expectancy at birth has increased throughout England, Scotland, Wales and Northern Ireland due to improvements in mortality in older age. Life expectancy is highest in England with Scotland having the lowest of the four UK constituent countries (Office of National Statistics 2016, *ONS.gov.uk*).

However, numerous people who are living longer in the UK do so with one or more long-term medical conditions and many are living with frailty. The clinical conditions of sarcopenia and frailty are particularly complex expressions of ageing that impact a range of health and social care settings [4, 5]. Sarcopenia is associated with adverse individual physical and metabolic changes contributing to morbidity and mortality, whilst frailty is defined as a state of increased vulnerability as a consequence of cumulative physiological decline across multiple systems predisposing to poor resolution of homeostasis after a stressor event, which increases the risk of adverse outcomes [4, 6]. In this chapter, we will review the epidemiology, pathogenesis, diagnosis of sarcopenia and frailty as well as give an overview of Comprehensive Geriatric Assessment (CGA) as a method of systematically evaluating an older person's treatment, management and long-term follow-up needs.

2. Skeletal muscle and sarcopenia

Skeletal muscle comprises approximately 40% of total body mass and therefore constitutes one of the largest organ systems of the body [7]. Skeletal muscle plays an essential role in both physical, for example, locomotion and metabolic functioning, for example, thermoregulation, metabolism of glucose and amino acids. Muscle is also a reservoir for proteins and energy that can be utilised in periods of stress or undernutrition, for example, acute deterioration in health and hospitalisation.

2.1. Diagnosing sarcopenia

Sarcopenia has previously been defined based solely on lean mass as a function of height (appendicular lean mass [ALM] is measured by dual-energy X-ray absorptiometry [DXA] divided by height squared) where sarcopenia was diagnosed −1 to −2 SD below gender-specific mean values of a younger control group [8]. However, direct proportionality between loss of muscle mass and impaired strength/function cannot be inferred as longitudinal as well as cross-sectional studies show that younger individuals can be stronger and older individuals are weaker than would be predicted by their muscle mass [9, 10]. Therefore muscle quality

or force generated per unit area is important and the definition of sarcopenia now extends to encompass loss of strength and or physical performance [6, 10]. Sarcopenia, is the progressive and generalised loss of skeletal muscle mass, strength and physical performance with age and as such it is a core component of physical frailty [6, 11, 12]. Sarcopenia is associated with a broad array of adverse physical and metabolic outcomes including falls [13], disability, hospitalisation, diabetes [14], osteoporosis [15] and also mortality [16]. The economic costs associated with 'sarcopenia' in the year 2000 were estimated to be $18.5 billion in the USA alone [17].

Recent diagnostic algorithms include those proposed by EWGSOP [6], The International working group (IWG) on sarcopenia [18], The Foundation for the National Health Institutes of Health (FNIH) Sarcopenia Project [11] and the Asian Working Group for Sarcopenia (AWGS) [19]; the later driven by the need to account for ethnic variations in body composition and muscle function in order to further research sarcopenia in the Asian subcontinent.

The EWGSOP definition requires the presence of slower walk speed (<0.8 m/s) [20] or weaker strength (grip <30 kg for men, <20 kg for women) [21] in combination with low muscle mass (defined as ALM/ht^2 ≤7.23 kg/m^2 for men and ≤5.67 kg/m^2 for women). The International Working Group (IWG) on sarcopenia included impaired physical performance in addition to slow walk speed before measuring muscle mass in their working definition for the diagnosis of sarcopenia. The Foundations of National Institutes of Health (FNIH) sarcopenia project based in the USA incorporated clinically relevant cut points of low muscle mass and strength (grip strength <26 kg for men and <16 kg for women and ALM adjusted for BMI <0.789 for men and <0.512 for women) [11]. Similarly, the AWGS included gait speed <0.8 mm/s, ALM/ht^2 <7.0 m^2 in men and <5.4 kg/m^2 in women and grip strength <26 kg for men and <18 kg in women [19] in their working definition of sarcopenia. From a clinical point of view, these algorithms enable case finding for sarcopenia and conceptually identify stages of sarcopenia that allow intervention. For example, the pre-sarcopenia stage is characteristic of low muscle mass without impact on muscle strength or physical performance, the sarcopenia stage is characterised by low muscle mass, low muscle strength or poorer physical performance, whilst severe sarcopenia is when all three criteria within the algorithm are met [6].

2.2. Prevalence of sarcopenia

The prevalence of sarcopenia increases with age but figures are influenced by the diagnostic algorithm used, ethnic population studied, cut-off values for lean mass and function and the health care setting, that is, community versus in hospital [22]. For example, a recent systematic review reported that the prevalence rates differed for community-dwelling older people aged ≥60 years (up to 29%), in long-term care age >70 years (up to 33%) and in an acute care hospitals, age ≥ 65 years (up to 10%) [23].

2.3. Measuring muscle mass

The commonest approach to measuring muscle mass is through bioimpedance analysis (BIA) and where available, dual-energy X-ray absorptiometry (DXA) scanning. Computerised tomography (CT) and magnetic resonance imaging (MRI) can also be used [24]. The approach that is undertaken to measure muscle mass is dependent on feasibility, access, costs and sample

size. For example, BIA utilises portable equipment and can be used across a range of health care settings and calculates fat-free mass rather than true muscle mass based on the electrical conductivity of various body tissues. Whole body DXA will enable the calculation of total and appendicular lean mass but may overestimate lean mass values in those with extracellular fluid accumulation. Computerised tomography (CT) and magnetic resonance imaging (MRI) can differentiate fat from muscle, which can be useful to make assumptions on muscle quality. However, high operational costs and radiation, in the case for CT, limits their use in the diagnosis of sarcopenia.

2.4. Measuring muscle strength

Grip strength measured using hand-held dynamometry, has gained wide acceptance as a reliable and valid measure of muscle strength across health care settings and is an integral component in the international diagnostic algorithms for sarcopenia [25–27]. Other methods to measure muscle 'strength' include ascertainment of knee extensor power, isometric knee strength and quadriceps torque but these require static and bulky equipment that are not readily portable and can be impractical in routine clinical practice as well as in epidemiological studies.

2.5. Measuring physical performance

Slower gait speed is associated with risk of future morbidity and mortality and is therefore suitable for inclusion in diagnostic algorithms for sarcopenia [28]. Other objectively measured physical performance measures such as chair rise time; time taken to complete five sit to stand actions and standing balance; and the time for sustaining balance on one leg have also been associated with higher risk of all-cause mortality in older people [16, 29]. Gait speed requires intact coordination, neural and joint control so may not be practical in context of acutely unwell hospitalised older people. Grip strength measurements in this situation may have better predictive value and be more feasible [25–27, 30].

2.6. Questionnaires to aid the diagnosis of sarcopenia

The SARC-F questionnaire was developed to predict poor muscle function [31, 32] and is based on five questions that ascertain how much difficulty an individual has performing the following parameters: ability to rise from a chair, walk assisted or unassisted, climb stairs, carry heavy loads (as a measure of strength) and ascertainment on the number of falls a person has had in the last year.

Each parameter is assigned a score: 0 (none); 1(some) or 2 (a lot); the falls parameter (none = 0, 1–3 = 1, 4 or more = 2). A total score of ≥4 (scale 0–10) suggests that the subject is symptomatic of sarcopenia. The SARC-F questionnaire has been shown to have excellent specificity but poor sensitivity for sarcopenia based on the consensus criteria from the IWG, EWGSOP and AWG. However, it has been shown to predict physical limitation over a four-year follow-up and may be useful for case identification and subsequent diagnostic evaluation for sarcopenia in community based but not hospital or care home-based settings [33].

Despite the recent progress in refining and implementing diagnostic criteria for sarcopenia over the past decade, there is no consensus on global diagnostic criteria for sarcopenia

based on cut-off values for skeletal muscle mass indices, grip strength and walking speed. In fact, the variance in the criteria indicate that ethnic, gender and cultural differences dictate population-specific criteria are required in order to account for the genome/environment interactions that contribute to sarcopenia, thus influencing the design of both observational and intervention studies [24, 34].

2.7. Pathogenesis of sarcopenia

In sarcopenic muscle, the rate of muscle injury (from normal contraction) exceeds that of repair and regeneration. There may also be decreased satellite cell (muscle stem cell), proliferative capability and renewal [35, 36] in combination with altered inter- and intracellular environments that favour catabolism. This increase in catabolism is associated with a decrease in growth factors such as circulating insulin, growth hormone and testosterone and muscle-specific IGF-1 levels [37]. Furthermore, the production of reactive oxygen species and oxidative stress can lead to mitochondrial DNA damage and a progressive decline in mitochondrial function and energy depletion [38]. At a tissue level, skeletal muscle is continuously remodelled in response to workload, tension, nutrition and anabolic stimulation. The cues associated with the age-related decline in muscle mass and strength include behavioural (i.e. decrease in physical activity/sedentary lifestyle), extrinsic (i.e. undernutrition) and intrinsic factors (i.e. hormonal changes, inflammation, oxidative stress and denervation) [39] (**Figure 1**).

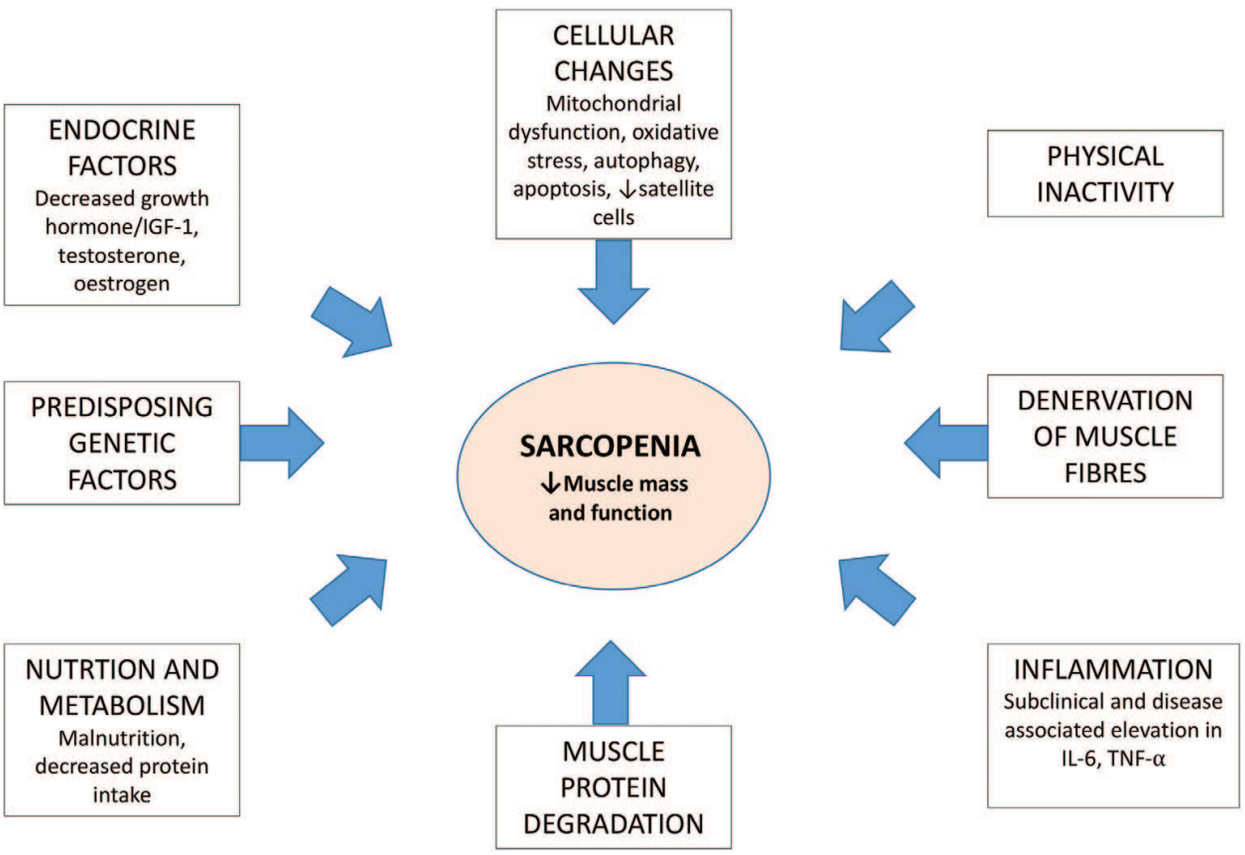

Figure 1. The main mechanisms involved in the aetiology of sarcopenia.

The complex dynamic genome/environment interplay involved in the balancing of muscle synthesis and breakdown is mediated through multiple cell signalling pathways [40] that include IGF-1/AKT/mTOR and NF-κB (nuclear factor-kB). These pathways influence the balance between synthesis and degradation. For example, the IGF-I/AKT/mTOR pathways promote protein synthesis and the maintenance of skeletal muscle mass. By contrast, the activation of NF-kB by inflammatory mediators including tumour necrosis factor (TNF) and interleukin 6 (IL-6) upregulate the E3 ubiquitin ligases MAFbx (atrogin-1) and MURF-1, which signal the muscle atrophic process. Skeletal muscle ageing is also characterised by a continuous cycle of denervation and reinnervation as a consequence of the loss of alpha-motor neurones within the central nervous system (CNS), withdrawal of nerve terminals from the neuromuscular junctions (NMJ) and axonal sprouting from neighbouring neurons collectively giving rise to larger, inefficient motor units.

Remodelling of skeletal muscle tissue through neuropathic, neurohormonal and inflammatory pathways leads to a reduction in muscle cross-sectional area, volume and a reduced rate of force generation. This is characterised by the presence of fewer type I oxidative (slow twitch) and type II glycolytic (fast twitch) myofibres as well as myofibre atrophy. The loss of type II fibres, with concomitant decrease in satellite cells [41], is associated with decreased strength and ability to generate power. Moreover, there is a concurrent increase in non-contractile material within the fascicles that affects muscle quality. Collectively, these processes lead to the reduced muscle functional performance.

2.8. A life course approach to understand the aetiology of sarcopenia

Muscle development in humans begins at 6 weeks of gestation and continues until approximately 24 weeks when the total number of fibres is set. Any subsequent increase in muscle bulk occurs by hypertrophy as evidenced by an increase in fibre cross-sectional area, and not by hyperplasia. Therefore, the number of muscle fibres formed prenatally influences the potential for postnatal hypertrophy [42]. Muscle mass increases during childhood and adolescence until adult muscle cross-sectional areas are reached shortly after puberty. Muscle mass then remains relatively constant in early adulthood until the later part of the 4th decade of life when a decline begins [43].

Skeletal muscle strength is determined, in part, by muscle mass, which is a function of myofibre size and number. On average, men have greater muscle mass and strength than women at any given point in the life course [44]. Between the ages of 20 and 80 years, total lean body mass has been reported to decline by approximately 18% in males and by 27% in females [45]. Therefore, the 'health' of skeletal muscle in an older person is a function of the peak levels attained in early life and the extrinsic and intrinsic changes operating through middle years into old age, for example, physical activity, nutrition, disease and disuse and hormonal changes. There is also robust epidemiological evidence suggesting that low birth weight, a marker of an adverse early intrauterine environment, is associated with a poorer grip strength in older adults and that the mechanism may be driven by myofibre development and number [46, 47].

3. Frailty

Frailty is a common clinical syndrome, which is often seen in older adults, especially in women compared to men and younger aged adults [48–50]. Frailty is distinct from disability and comorbidity and independently carries a high risk for poor health outcomes such as falls, hospitalisation, disability and mortality [51, 52]. Whilst, sarcopenia contributes to and is a core component of physical frailty, the syndrome of frailty is comprised of several interlinked domains that impact on an older person's independence, quality of life and medium- to long-term outcomes. Cognitive frailty refers to progressive cognitive decline in absence of a diagnosis of dementia, social frailty refers to loneliness and the lack of robust social networks as well as poor income whilst psychological frailty refers to the inherent traits in an individual that may predispose an individual to adversity, for example, bereavement, low mood, lack of motivation and labile emotions [53, 54]. Multimorbidity, defined by the UK National Institute for Health and Care Excellence (NICE, guidance 56), is the presence of two or more distinct long-term conditions, is also associated with a higher risk of developing frailty [54, 55]. This conceptual model illustrates that assessing and managing a patient who is living with frailty requires a more holistic approach to manage the cause, or combination of causes that have precipitated acute decompensation [5] (**Figure 2**).

Frailty is best understood as a multisystem disorder, with perhaps both independent and linked mechanisms operating across organ or physiological systems. Accumulating dysregulation across multiple systems can negatively affect previous normal functional homeostatic mechanisms accelerating the development and progression of frailty. This is relevant not only for improved understanding of this syndrome but also because a key implication of loss of reserve across multiple systems is that therapeutic intervention of any single system, that is, endocrine, brain, immune/inflammatory or indeed an individual domain, that is, social, physical or cognitive, is unlikely to ameliorate the abnormal health state of frailty. For those living with frailty, even a minor insult such as a minor infection or change in medication can lead to a large disproportionate change in an individual's health and social care state that inevitably results in an acute hospital admission (**Figure 2**).

Older people living with frailty do so as a consequence of accelerated loss of biological reserves across multiple systems over a lifetime and individuals experience frequent transitions between frailty states over time. Using the life course approach to conceptualise frailty is worth considering as this broadens the window of opportunity to identify markers and mechanisms contributing to frailty with a view to intervention [56] (**Figure 2**). For example, the presence of weight loss or weakness earlier in the life course, that is, slow walk speed and exhaustion may identify people at especially high risk of rapid decline [57].

3.1. Identification of frailty

Detection of frailty should be an essential part of assessment of older people and the identification of reliable tools to determine frailty within acute and community settings is currently a research and clinical priority. Recognising and identifying people who are living with frailty not only enables clinicians and health care professionals to respond quickly and

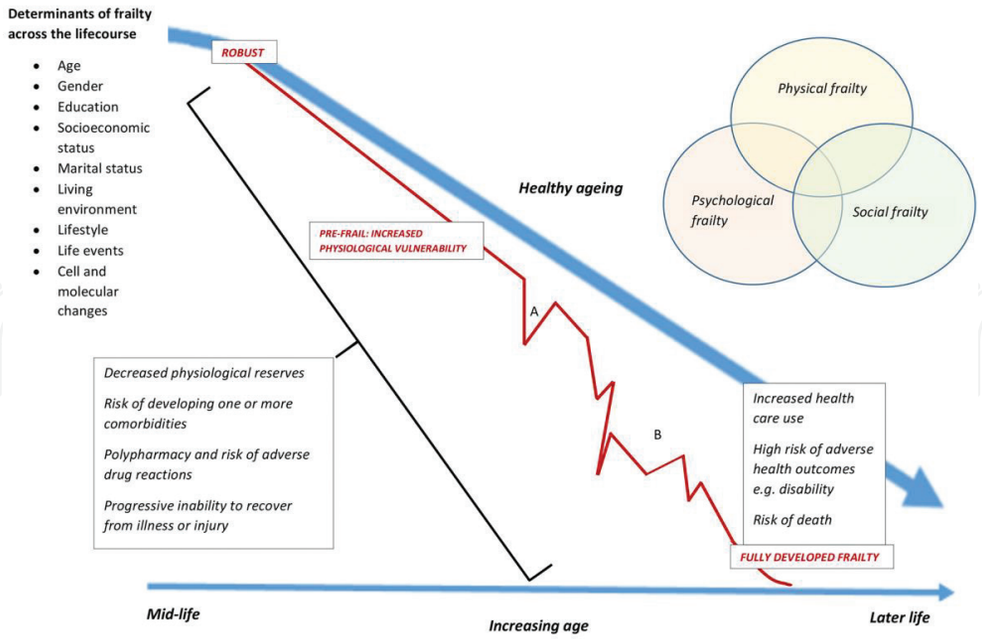

Figure 2. Healthy ageing is depicted by the blue solid line. Frailty (red line) develops as a continuum from being physiologically robust and independent to being at high risk of hospitalisation, institutionalisation and death. In more physiologically robust individuals, full recovery is likely after an insult, for example, infection (A), but later in the time course, moderate to severe frailty predisposes to recurrent hospital admissions as a consequence of a disproportionate deterioration in health and social and/or psychological health from a relatively minor insult or stress (B). The recovery from subsequent insults takes longer as physiological reserves are depleted until the individual cannot compensate adequately, and the ability to perform daily activities diminishes leading to dependency and disability.

appropriately to minimise exposures that may not be beneficial or could be harmful, that is, polypharmacy, invasive investigations, but also anticipate and prevent functional decline and potentially reverse the state of frailty with appropriate interventions.

The two established international models of frailty are the phenotype model and the cumulative deficit model. The phenotype model developed by Fried identifies frailty by the presence of at least three of five physical characteristics: weight loss, exhaustion, low energy expenditure, slow walking speed and low handgrip strength [51]. The cumulative deficit model developed by Rockwood et al. identifies frailty on the basis of the accumulation of a range of 'deficits', which can be symptoms, sensory deficits, clinical signs, diseases, disabilities and abnormal laboratory test results that then allow an index to be calculated. The frailty index is a function of the number of deficits present in an individual divided by the total number of deficits possible within the population sample [58]. The number of deficits measures accumulated vulnerability, which is related to adverse outcomes. In this regard, a frailty index will range from 0 to 1, with values over 0.67 identifying a level of frailty beyond which accumulation of further deficits is not sustainable with life [59]. Despite the difference in approaches to measuring frailty, both tools are able to predict adverse outcome, which provides support for the notion of frailty as a unified construct [60]. In clinical practice, identification of frailty using the Clinical Frailty Scale (CFS), a visual tool based on a comprehensive clinical assessment of a patient, enables assignment of a frailty category [58]. There are seven CFS categories

ranging from 1 (fit) to 7 (severe frailty) and increasing CFS frailty has been demonstrated to have predictive validity for adverse outcomes of institutionalisation and mortality. In outpatient settings, The PRISMA-7 questionnaire, can be used to identify persons who are living with frailty and disability. These questions are:

1. Are you more than 85 years? Yes = 1 point
2. Male? Yes = 1 point
3. In general, do you have any health problems that require you to limit your activities? Yes = 1 point
4. Do you need someone to help you on a regular basis? Yes = 1 point
5. In general, do you have any health problems that require you to stay at home? Yes = 1 point
6. In case of need, can you count on someone close to you? No = 1 point
7. Do you regularly use a stick, walker or wheelchair to get about? Yes = 1 point

A score of > 3 can be used to identify frailty.

A further important concept of frailty as a syndrome is that individuals may have previously unrecognised and inadequately addressed conditions that do not characteristically fall into a single organ category but can have a major impact on quality of life. Identification of these 'frailty syndromes' can help health care professionals manage and potentially delay their complications. These, often inter-related syndromes, include but are not limited to falls, delirium, weight loss and malnutrition, fluctuating disability, polypharmacy, social isolation, fragility fracture(s) and recurrent hospital admissions (**Figure 3**).

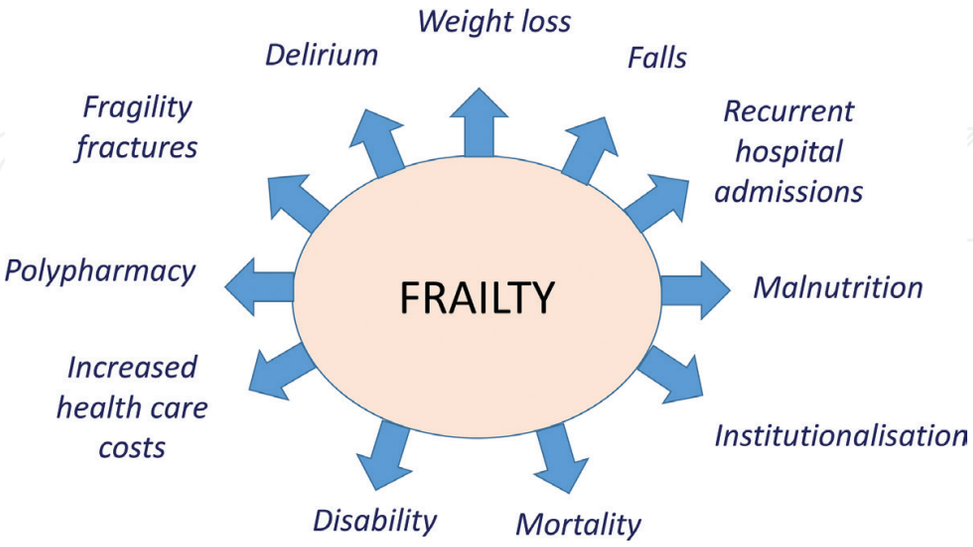

Figure 3. Consequences of living with frailty.

3.2. Prevalence of frailty

Given poor outcomes relating to morbidity, mortality and disability, it is useful to understand the prevalence of frailty to inform the provision of appropriate health and social care interventions. Prevalence figures have been well documented in many OECD (Convention of the Organisation for Economic Cooperation and Development) countries such a USA, Canada, Netherlands and the UK but data on relative incidence in developing countries is sparse [49]. Prevalence estimates based on 21 cohorts of 61,500 community-dwelling older adults across mainly developed countries estimated frailty prevalence between 4 and 59% and varied according to the operational definitions, for example, the physical phenotype versus frailty index-based models. However, there was general agreement that frailty increases with age and is higher in women than in men. In populations aged 80–84, the pooled prevalence rate was reported to be 15.7% whilst in those over 85 the prevalence increased to 26% [49]. This figure may be substantially higher in institutionalised older people. In an analysis of the Study on health, Ageing and Retirement in Europe, SHARE (n = 18,566) and Study on global AGEing and adult health, SAGE (n = 161,542), two large international data sets of adults over 50 years in which a frailty index was calculated, more women were classed as frail and frailty as a syndrome was distributed along the socioeconomic gradient amongst both higher and lower income countries such that individuals with less education and monetary income were more likely to be frail [48]. Recently, a study of 5450 older people aged 60 and over participating in the English Longitudinal Study of Ageing (ELSA) reported that the prevalence of frailty using the physical frailty phenotype rose from 6.5% in those aged 60–69 to 65% in those over the age of 90, with frail individuals reporting decreased physical function and difficulties in performing activities of daily living [50].

3.3. Interventions for individuals living with sarcopenia and frailty

A multi-dimensional approach to managing sarcopenia and indeed frailty involves promoting physical activity, optimising nutrition/prevention of malnutrition, minimising polypharmacy and attending to and individual's social and psychological aspects of health, that is, care support and home adaptations. Management goals for an older person with sarcopenia or frailty revolve around improving physical function and maintaining independence and well-being.

Exercise and nutritional interventions that impact positively on muscle mass and function play a significant role in the management of sarcopenia. For example, combination physical activity and nutritional interventions are associated with better function, strength and less inflammation in older sarcopenic people [61, 62]. In terms of physical activity, progressive resistance and aerobic exercise have been shown to be the most beneficial for the prevention and 'treatment' of sarcopenia [23, 63–65]. Whilst progressive resistance exercise improves lean mass, strength and function [66], optimising exercise capacity through aerobic activity improves metabolic control, reduces oxidative stress, insulin sensitivity and can stimulate a hypertrophic response on muscle fibres. Despite being shown to be safe and effective in older people [63, 67, 68], implementing progressive exercise in clinical practice is not always readily achievable.

Falls are serious and sometimes fatal complications of sarcopenia. In this regard, a multicomponent approach that addresses balance and gait, flexibility and endurance, lower limb strengthening exercises is required to manage fallers. Such approaches are associated with improved reaction time, gait, balance, strength coordination and physical and cognitive function [69, 70]. Group and home-based exercise programmes, which incorporate safety interventions, may reduce the rate and risk of falling [71]. Moreover, targeted home-based or group-based exercise interventions can also improve mobility and functional outcomes for older people with frailty [72, 73].

Intervening earlier in the life course before the onset of sarcopenia may have immense benefits for later skeletal muscle health. For example, increased levels of leisure time physical activity in mid-life were associated with stronger grip strength in both men and women at age 60–64. This is consistent with optimising peak strength earlier in the life course, therefore reducing the impact of sarcopenia. Therefore, regular physical activity in adolescence and adulthood may prevent steep decline in muscle strength in early old age [74].

The synthesis of muscle fibres requires adequate protein substrates. Physiological changes in the gastrointestinal system occur with age and result in older people eating less, having early satiety, losing their sense of taste and having a blunted anabolic response to ingested proteins [75]. As such, older people may require more protein to counteract the inflammatory and catabolic effects of co-existent co morbidities and their exacerbations [76]. Protein supplements vary in their composition and evidence from trials at present is inconstant to develop evidence-based recommendations for protein supplementation in sarcopenia [77]. However, observational evidence suggests essential amino acids, that is, leucine, beta-hydroxy-beta-methylbutyrate (HMB), a bioactive metabolite of leucine, stimulates muscle protein synthesis more than non-essential amino acids and may be useful for maintain lean body mass and improving muscle function [78–82]. A recent consensus statement from the multinational PROT-AGE group recommends protein intake in older people of at least 1.2–1.5 g of protein per body weight (kg) a day to maintain muscle homeostatsis [83]. Nutritional interventions in sarcopenia are covered in more detail elsewhere in this book.

3.4. Possible targets for pharmacological treatment

Observational studies indicate the potential beneficial effects of testosterone on muscle mass and function given the associated anabolic and satellite cell stimulatory activity. Randomised controlled trials of testosterone have not demonstrated benefits on muscle function because of adverse cardiovascular outcomes [34]. Studies of growth hormone (GH) supplementation have shown more harm than benefit in older patients; whilst GH therapy may increase muscle mass, it has not always increased muscle strength or functional performance. Moreover, unwanted side effects precludes GH as a treatment for sarcopenia. These include arthralgia, paraesthesia, fatigue, carpal tunnel syndrome and mortality in some observational human studies [84, 85].

There has been interest in selective androgen receptor modulators (SARMS) for sarcopenia treatment, which stems from the observed anabolic effect of testosterone. SARMS are androgen receptor ligands that display selective activation of androgen signalling in target tissues,

for example, skeletal muscle. However, none are in clinical use and trials will be needed on the safety and efficacy of SARMS in improving physical function in older people with sarcopenia [34, 86].

Myostatin, a member of the TGF-β superfamily, is a negative regulator of skeletal muscle growth and is upregulated in many muscle wasting disorders [87]. Based on these observations, myostatin and its receptor activin type IIb pose attractive targets for therapeutic intervention. Though there are currently no anti-myostatin drugs used in clinical practice, myostatin receptor antibodies are currently under review with the focus on older people with lower lean mass [34].

Angiotensin-converting enzyme inhibitor (ACEi), for example, perindopril, use was associated with improvement in 6-m walk tests in older persons with functional impairment but did not show increased benefit with additional exercise training. Whilst ACEi use may have beneficial effects on muscle function [88], a recent meta-analysis of four trials concluded that ACEi did not improve walk distance or age-related strength decline in older people therefore, further evidence from clinical trials are needed [89].

3.5. Comprehensive Geriatric Assessment (CGA)

Frailty is a dynamic process that predisposes an individual to a spiral of decline that leads to increasing frailty and risk of worsening disability, predisposition to falls, hospital as well as care home admission and death [51, 58]. Although current screening for frailty identifies individuals at risk, validated tools do not recommend intervention. It is imperative that when managing frailty, assessments should not only seek to determine and treat specific illnesses, but that they should endeavour to maintain and where possible, improve quality of life. It is clear that older person's needs are more complex and that they often have co-existent functional, psychological and social needs. This predisposes an individual to atypical clinical presentations that can often be misunderstood and which often require a different approach to care that diverts away from an organ specific diagnosis towards a holistic and integrated view of their problems.

Older people and their caregivers should purposefully be involved in making informed decisions relating to health and social care needs as well as advanced care planning. A useful method for planning the care of those living with moderate to severe frailty through a process of assessment, summation, conversation, planning, intervention, monitoring and review is Comprehensive Geriatric Assessment (CGA). CGA is a process, which is patient centred, responsive, adaptable and most effective when disseminated amongst key professionals working across the acute and community sectors. CGA is defined as a '*multidimensional interdisciplinary diagnostic process focused on determining a frail older person's medical, psychological and functional capability in order to develop a coordinated and integrated plan for treatment and long term follow up*' [90].

The purpose of CGA is to improve diagnostic accuracy, optimise treatment and outcomes and crucially, allow effective integrated case management to ensure that the care plan is enacted and remains responsive to the patient's needs over time. CGA requires the

systematic evaluation of physical, functional, medical, nutritional, cognitive and social components that influences an older person's health that can also extend to financial, spiritual, psychological and palliative needs (**Figure 4**). How CGA is delivered is variable and very much depends on the care setting, for example, home, hospital, clinic or nursing home but, to be effective, often requires coordination of several inter-professional services that can include clinicians, community nursing, therapy, social services, pharmacy, nutrition and dietetics, optometry and audiology. There are no set universal criteria to identify patients in need for a CGA however, patients who are 'too well' or are 'too sick' are less likely to derive benefit from the process. CGA becomes important for patients who are identified as living with frailty through the use of validated instruments or have one or more of the 'frailty syndromes' previously mentioned. There is evidence from multiple meta-analyses that CGA delivered to patients within the hospital setting as well as in the community is associated with better function and cognition, decrease in mortality, less likelihood of being institutionalised, less likelihood of patients experiencing deterioration in their health [90–93].

A critical component of CGA is a medication review and the STOPP/START approach to polypharmacy is a useful evidence-based tool [94]. The well-being components of the CGA may include the promotion of regular physical activity and exercise delivered through home-based plans [95] or external activity classes, social engagement through day centres and community networks, adaptations to the home environment to assist with falls prevention, caregiver support and nutritional optimisation. By undertaking a CGA with the person and those closest to them, if they wish, individuals are able to identify their own personal goals therefore reclaiming some of the lost independence they may have encountered as a result of living with frailty. Equally, the process will enable appropriate advanced care planning discussions for individuals with severe frailty in conjunction with palliative care support for those who may be entering the terminal phase of their life.

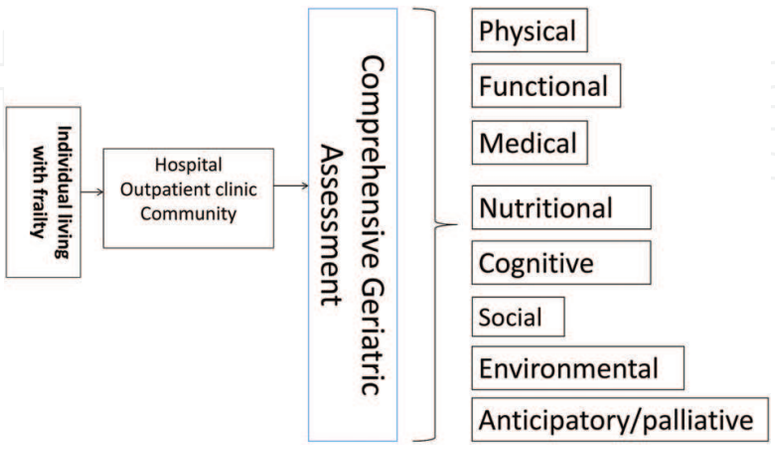

Figure 4. Core components of an inter-professional Comprehensive Geriatric Assessment. The process involves data gathering, multidisciplinary team discussions, development of the plan with the patient and their caregiver, implementation, monitoring and revision of the plan so that it remains responsive to the needs of the patient.

4. Conclusions

Sarcopenia and frailty are inter-related conditions that are common in older age and identify people who have an increased risk of a range of adverse outcomes. Sarcopenia has a complex aetiology involving neurohormonal, immunological and nutritional mechanisms. Frailty is a multisystem disorder, which commonly includes sarcopenia as a core component. Whilst there are clear physiological and pathophysiological explanations for the development and definition of frailty, there is need to understand that frailty as a term can be perceived as a state of dependency, subjugation or defeat; the appearance of being weak in later life. Not all older people are frail. These connotations and negative perceptions need to be challenged through education and training.

There is robust evidence to support the implementation of exercise and activity programmes for older people with sarcopenia and frailty, and that the adverse health trajectories of frailty may be modified through a range of interventions through the process of Comprehensive Geriatric Assessment. Better identification of sarcopenia and frailty in older age enables pro-active targeting of interventions to improve outcomes and modify future health trajectories that benefit older people as well as their caregivers.

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