**Title:** Musculoskeletal health, frailty and functional decline

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Abstract

Frailty in older people is associated with a vulnerability to adverse events. While ageing is associated with a loss of physiological reserves identifying those with the syndrome of frailty has the potential to assist clinicians tailor treatments to those at risk of future decline into disability with increased risk of complications, morbidity and mortality. Sarcopenia is a key component of the frailty syndrome and on its own puts older people at risk of fragility fractures however the clinical syndrome of frailty affects musculoskeletal and non-musculoskeletal systems. Hip fractures are becoming a prototype condition in the study of frailty. Following a hip fracture many of the interventions are focused on limiting mobility disability and restoring independence with activities of daily living but there are multiple factors to be addressed including osteoporosis, sarcopenia, delirium, weight loss. Established techniques of geriatric evaluation and management allow systematic assessment and intervention on multiple components by multidisciplinary teams and deliver the best outcomes. Using the concept of frailty to identify older people with musculoskeletal problems as at risk of a poor outcome assists in treatment planning and is likely to become more important as effective pharmacological treatments for sarcopenia emerge.

This review will focus on the concept of frailty and its relationship with functional decline, as well as describing its causes, prevalence, risk factors and potential clinical applications and treatment strategies.

Key words

Fragility fracture, frailty, functional decline, screening, older adult, exercise therapy, dietary therapy

Word count
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Many of the common musculoskeletal problems of old age including osteoporosis, osteoarthritis and fragility fractures are associated with mobility disability [1] and can spiral into functional decline and disability. As the population ages and patients present with more and more comorbidities it is important for clinicians to be able to identify quickly those who require resource intensive multi-component interventions delivered by teams from those who require a short physiotherapy program or a self-management program. The presence of frailty is starting to guide treatment for health conditions in older people because it has been shown that frailty can predict response to treatment and likelihood of adverse complications [2].

Frailty is a term first used in the medical literature in the 1970’s which is receiving increasing focus in research and clinical practice due to its ability to predict poor outcomes in older people of relevance to society such as falls, disability, functional decline, hospitalization, institutionalisation and mortality [3-11]. While linked to theories of aging, it has come to be thought of as a separate condition indicating abnormal aging and poor health and therefore a potential target for interventions and therapies to slow or reverse its progression [12]. In addition, it is known to occur in tandem with other clinical conditions of aging including sarcopenia, functional decline, neuroendocrine disorders, and immune dysfunction [13].

Frailty has been associated with increased risk of having a fall (OR 2.02 95% CI 1.44 to 2.83) and experiencing a greater number of fractures in community dwelling older adults (OR 3.67 95% CI 1.47 to 9.15) [14]. The costs to the US of fragility fractures seen in frail older adults such as hip fracture has been estimated as greater than $US 12 billion per year [15]. Costs of providing hospital, medical, and community services for frail older adults compared to non-frail older adults have been estimated at up to an additional £109 per week in the
United Kingdom [16]. Therefore, while debate continues regarding the identification and aetiology of frailty, the importance of developing adequate means of addressing this increasing burden on the healthcare system cannot be overestimated.

Definitions of frailty

The recent push to standardise definitions of frailty has resulted in a number of reviews of this topic published recently [3, 12, 13, 17-19]. Two models of frailty dominate the literature. Fried et al. [10] has proposed a phenotype model of frailty which evolved from factors such as chronic disease, and musculoskeletal changes, leading to reduced physical activity and energy expenditure, abnormalities in neuroendocrine regulation, and chronic under-nutrition. The consequences of the above conditions include loss of weight and muscle mass which further impact upon musculoskeletal changes producing the cyclical nature of the model. Based upon this model, Fried proposed five criteria for use in research and clinical settings including unintentional weight loss or loss of muscle mass (i.e. sarcopenia), weakness, poor endurance or exhaustion, slowness, and low activity levels. From this phenotype, a practical instrument for assessing performance in these areas based on five measures included in the Cardiovascular Health Study has been created[10]. This phenotype was validated with 5,317 participants aged 65 years and older, and was associated with an increased risk of mortality (HR = 6.47 95% CI 4.63 to 9.03, p<0.0001), first hospitalization (HR 2.25 95% CI 1.94 to 2.62 p<0.0001), first fall (HR 2.06 95% CI 1.64 to 2.59 p<0.0001), increasing ADL disability (HR 5.61 95% CI 4.50 to 7.00 p<0.0001), and worsening mobility (HR 2.68, 95% CI 2.26 to 3.18 p<0.0001) over three years of follow up[10]. Since that study, this criteria or similar has been shown to be associated with increased risk of mortality, admission to residential aged care, hospitalisation, declining ability to perform ADLs and instrumental ADLs, risk of falls and declining mobility in community-dwelling older adult populations of both men and
The other important model was developed by Rockwood et al. [23] and is often described as the accumulation model. It takes into account the interplay between “assets” or components, which help an older person to remain living in the community and “deficits” or components which are detrimental to their ability to live independently. These include biomedical factors (such as health, illness, and disability) as well as psychosocial factors (such as dependence on others and resources available). Accordingly, it is this balance between the assets and the deficits which will determine whether someone is able to remain in the community or not – if the deficits outweigh the assets for an individual, they will not be able to maintain their position in the community and require institutional input. This theory has seen the development of instruments for assessing the degree of frailty in individuals or populations, commonly referred to as frailty indexes. For a deficit to be considered to contribute to frailty it must be acquired, related to health status, and increase with age but not so rapidly that saturation is reached at a relatively young age limiting the specificity of the index [24]. Commonly, the frailty indexes list over 70 potential deficits including aspects of general health and disease status, ability in ADLs, and psychological symptoms. A 92 item version [25] validated in 1468 participants from a general population sample (Canadian Study of Health and Aging), found an association with time to death and increasing frailty index score ($r=-0.234, p<0.0001$) which was greater than that seen between time to death and increasing age ($r=-0.088, p<0.05$), highlighting the usefulness of the concept of frailty above that of age to predict adverse outcomes. Similarly, Evans et al. found an association between frailty measured by a shorter 55 item frailty index and mortality in a smaller sample ($n=752$) of older adults admitted to an acute care setting over five years (HR 1.05, 95% CI 1.04 to 1.07)[9]. Velanovich et al. [26] found a significant increase in risk of mortality with each unit increase in frailty measured using an 11 item index in a range of surgical inpatient admissions.
(p<0.0001). For orthopaedic surgical admissions, the OR of mortality for each unit increase in frailty ranged from 3.36 (95% CI 2.64 to 4.27) to 11.68 (95% CI 7.81 to 17.46), dependent on the complexity of the operation. Therefore a wide range of frailty indexes have predictive validity, providing evidence for the accumulated deficit models of frailty.

Development of frailty

There has been much debate on the factors that contribute to the pathogenesis of frailty, due in part to the variety in definitions of frailty in the literature, and current models often include psychosocial, as well as physical components [18, 19, 27, 28]. Nevertheless, physical decline and disability remains one of the key predictive features in the development of frailty and so musculoskeletal conditions are important considerations [19, 28]. An overview of some of the inter-related factors promoting development of the frailty syndrome and its consequences are illustrated in figure 1 [29].

A key cause of frailty and physical decline in older adults is sarcopenia [3, 27, 30-32]. Sarcopenia (from the Greek words sarx meaning flesh and penia or poverty) refers to the loss of muscle mass associated with aging, but recent definitions include aspects of reduction in mobility, and reduction in appendicular lean mass [30, 32, 33]. Sarcopenia has been found to be an independent predictor of physical disability and development of mobility disorders, as well as reduced bone mineral density [27, 34, 35]. Diagnosis is usually through identifying loss of lean body mass (e.g. less than the twentieth percentile for young healthy adults [34]) although it is important to note that muscle strength is not always correlated to total lean mass [27, 30]. Therefore a measurement of physical performance and muscle function is required, such as a reduced mobility or gait speed (e.g. gait speed less than 1ms⁻¹) [34]. Sarcopenia itself is a multi-system syndrome brought on by a number of inter-related factors[32], including an increasing inflammatory state, reducing protein synthesis and promoting
apoptosis, reduced growth hormone, testosterone and insulin-like growth factor-1 (IGF-1) reducing muscle growth and muscle strength, and disorders in nervous system control of muscular function. In addition, anorexia and malnutrition promotes loss of weight and muscle mass. A key factor promoting all these dysfunctions is immobility and lack of exercise, which is a driving factor behind most of these physical and immunologic changes, and promoting the cyclical decline seen in the condition, as illustrated in figure 1[32]. While traditionally associated with a low body mass, sarcopenia is increasingly being identified in obese individuals which results from the substitution of muscle mass for fat mass and related immobility and lack of use of muscular systems[27, 32]. A relationship is seen between frailty and low or very high BMI, with rates lowest in those with a BMI between 20 and 29.9[36]. In addition, a relationship is seen between high waist circumference (defined as greater than 88cm in women and greater than 102 cm in men) and increased frailty [36]. Chronic low level inflammation has also been proposed as a causative factor [37], which plays a key role in both the aging process and the development of both sarcopenia and frailty [37]. A number of the signs and symptoms of frailty (low muscle strength, exhaustion, and unintentional weight loss) are also seen with increased pro-inflammatory markers, especially IL-6 [37]. Potential pathologic causes of chronic low level inflammation proposed include persistent infection with the herpes virus cytomegalovirus (CMV) [37]. In addition, other chronic diseases such as atherosclerosis, Alzheimer’s disease, cancer, and autoimmune diseases have been shown to contribute to inflammatory status and frailty[27, 37].

*Functional decline and its role in frailty*

There is growing evidence that the development of functional limitations is such as problems with mobility are one of the first markers for frailty [13, 37]. While disability and functional limitations have been identified as a highly correlated with frailty, the concept is now
regarded as distinct to that of frailty, but sharing many common pathways for development [38]. Functional decline or disability is usually described as a loss of an individual’s ability to perform basic tasks required to maintain independence in living status (usually described as activities of daily living or ADLs) [39]. Basic ADLs include everyday tasks such as bathing, dressing, feeding, continence, toileting, and mobility [39]. Instrumental ADLs require higher level function and include tasks such as banking, shopping, and driving [39]. Measuring functional decline is of interest, similarly to the concept of frailty, for its ability to predict future mortality, morbidity, hospitalisation and institutionalisation [40-42]. Increased risk is associated with cognitive impairment, hospitalisation, poly-pharmacy, older age, history of fractures, malnutrition, low physical activity, lower strength, and depression [41-49]. Musculoskeletal conditions have long been recognised as a major cause of functional impairment and disability. The total number of disability adjusted life years associated with musculoskeletal conditions worldwide has been estimated as over 30,000,000, and they remain one of the ten leading causes of disability worldwide [50]. In recent study in France over a quarter of the population reported at least one musculoskeletal condition, with osteoarthritis and lower back pain the most commonly reported disorders [51]. Disability was common among those with rheumatic and musculoskeletal conditions, with up to 22% of those with osteoarthritis and inflammatory arthritis difficulty mobilising compared with only 5% of those without the conditions. Participants with musculoskeletal and rheumatic conditions also commonly experienced impairments in most basic functional activities, including shopping, doing housework, carrying objects, and needed more assistance from family and health professionals, and there is evidence of increasing decline over time [45, 51]. Particular risk factors for decline in arthritis suffers include pain, reduced muscle strength and joint instability, range of joint movement, comorbidities including cardiovascular conditions, diabetes and stroke, high body weight, avoidance of exercise, and
female gender, factors which are also commonly identified in the aetiology of frailty[45].

An increasingly important contributor to the burden of musculoskeletal conditions is fragility fractures. Worldwide there were over 5.2 million non-traumatic fractures in 2010 with over half of those attributable to fractures of the hip and spine [52]. A recent review has highlighted the devastating effect of hip fractures on the long-term function of older adults, with 29% of cases not regaining their pre-fracture level of function in ADL[53]. Over 40% of patients had not regained their pre-fracture level of mobility at 1 year following fracture, and over a third were unable to walk independently due to the fractures. In addition, ongoing pain is widespread in this population, with 47% reporting pain one or more years following the fracture. This widespread pain and difficulty mobilising are likely markers for overall decreasing physical exercise and function, which are independently associated frailty. As a result of this widespread functional decline, a large proportion will become increasingly dependent on community and residential care services so any identification of reversible components will impact not just on individuals but on the community as well.

*How is frailty identified or diagnosed?*

Given the rapid aging of the population, the creation of tools to identify frail older people has received increasing focus over the past decades [12]. Recent recommendations suggest that all persons over the age of 70 years old should be screened for frailty and in addition, persons of any age where significant weight loss (≥5% of total body weight) occurs unplanned and as a result of chronic disease [28]. In addition, low physical activity, and functional decline suggest problems, and older adults with musculoskeletal conditions should be screened. Screening should ideally occur early, before significant dependence in basic ADLs has developed, to develop treatment plans to prevent further or reverse decline and plan for future increased health and social support [28]. There are currently many simple rapid screening
tools available that are validated in older adult populations (see Table 1) [28]. These tools are designed to be quickly administered and based mostly on self-report of the patient, although the Cardiovascular Health Study Frailty Screening Scale [10], and Gérontopôle Frailty Screening Tool [54] require performance based measures such as gait speed and grip strength, which may pose challenges dependant on access to relevant space and equipment in a clinical setting. In addition, the Clinical Frailty Scale and Gérontopôle Frailty Screening Tool require clinical judgement in their scoring systems, requiring a degree of experience and knowledge to be used effectively [54, 55].

In addition to the four rapid screening tools highlighted above, there are over 30 different tools published for the identification of those at risk of frailty, ranging from single outcome measures, to large multi-component assessment instruments [3, 12, 13, 18, 19, 56]. A number of reviews have been published outlining the variety of instruments available and their validity [17-19]. While a large variety of tools to assess frailty in populations exist, there are two main groups [13]. One includes either single or multicomponent assessments of physical ability, the other considers a combination of physical, social, cognitive, and other factors in the identification and assessment of frailty [13, 28, 38]. A recent review focused on instruments to assess frailty for use in measuring outcomes in clinical practice and research, with a view to promoting interventions to prevent or manage frailty in practice [19]. De Vries et al. [19] identified 20 different instruments (see Table 2) and assessed their clinimetric properties by assessing content validity, internal consistency, construct validity, agreement, reliability, responsiveness, and interpretability. They subscribed to current multidimensional models of frailty, which consider impairments in multiple domains of the individual as contributing to frailty, including physical, psychological, and social domains, and assessed the instruments’ coverage of all of these areas. They found that only five instruments included items on all three of these frailty domains: the Frailty Index (FI) or
accumulated deficits model [25], Groningen Frailty Indicator (GFI) [57], Clinical Global Impression of Change in Physical Frailty (CGIC-PF) [58], Geriatric Functional Evaluation (GFE) [59], and the Geriatric Functional Evaluation Frailty Index – Comprehensive Geriatric Assessment (FI-CGA) [60]. In addition, the majority of the instruments utilized a dichotomous scoring system (i.e. frail vs not-frail), which gives minimal relevance for measuring change in populations over time [57, 58, 61-69]. Other instruments utilize either multiple levels of frailty [10, 59, 60, 70, 71] or use continuous or ordinal scoring scales [25, 72-75] which may be more relevant to clinicians wanting to determine the level of frailty in one patient compared to another, or change in the level of frailty over time.

More recently, de Vries et al. [76] have created a frailty index based on the deficit which was found to significantly correlate with measures of strength and mobility including the Timed-Up and Go test (r=0.61, p=0.00), Performance Orientated Mobility Assessment (r=-0.70 p=0.00) and the Cumulative Illness Rating Scale for Geriatrics (r=0.66 p=0.00), however the study was small in size (n=24) and further information on how the instrument performs over time and in evaluating outcomes from interventions is required.

*How prevalent is frailty?*

Studies report a range of estimates of the frailty of the population, dependent on the population studied in addition to which of the number of available instruments to identify frailty are used. Table 3 gives a range of estimates of the prevalence of frailty in general population samples. Estimates range from around 3% (using the Fried criteria in a population of community-dwelling adults included in the Whitehall II study) up to 52% (in a population of community dwelling older adults in Italy using the Marigliano-Cacciafesta Polypathological scale) [4, 5, 10, 11, 20, 21, 77-79]. Most studies indicate a level of frailty for community-dwelling older adults between 5 and 15%. Studies have also reported on the
prevalence of “pre-frailty” in the community dwelling older adult population, a state indicating risk of developing frailty in the future and the need for a targeted intervention to prevent further decline. Studies utilizing the SOF and Fried criteria have indicated a high prevalence of pre-frailty in the community-dwelling older adult population (approximately 30%) indicating the presence of risk factors which could lead to future frailty in this population, but that current physiological, social and mental resources are adequate to maintain their independence in the community [4, 5, 20, 21, 78]. Prevalence of frailty increases with age and is almost two times greater in women than in men [80]. Older community dwelling older adults the prevalence has been described as over 25% for those aged 85 years and over, compared to under 5% in those aged between 65 and 69 years [80]. In addition, frailty is increased among those with chronic conditions such as congestive heart failure, myocardial infarction, peripheral vascular diseases, diabetes, and hypertension, renal failure, cancer, and HIV [28, 37]. In addition, older adults with cognitive impairment and dementia appear especially at risk of frailty, either through the cognitive impairment influencing physical health or a shared etiological factor [37].

Studies of the prevalence of frailty specifically in populations with musculoskeletal problems are fewer in number. A study of hospitalised older adults found that up to 70% of patients admitted to a combined rheumatology and pulmonary ward were identified at risk of frailty and likely to benefit from a geriatric intervention, determined by the Groningen Frailty Indicator (GFI) [81]. Auais et al. [82] studied the change in frailty related characteristics in hip fracture patients between 2001 and 2008, and identified approximately half of exhibited significant levels of comorbidities, sarcopenia risk factors, and osteoporosis risk factors. In addition, they identified increasing frailty in the hip fracture population over time, with an increase in the prevalence of each frailty-related characteristic (such as older age, admission to long term care, number of comorbidities, osteoporosis, sarcopenia, and dementia) of
between 2 and 14% per year, including a significant increase in the risk of women (OR 1.05, 95% CI 1.04 to 1.06) and men (OR 1.04 95% CI 1.02 to 1.06) having osteoporosis risk factors, as well as having three or more relevant comorbidities (OR 1.07 95% CI 1.06 to 1.08).

Frailty rates are higher among people with osteoporosis, likely due to aspects of the shared etiological factors of the two conditions such as low physical activity, nutritional deficiency, low levels of testosterone, estrogen, sulphate of dihydroepiandrosterone (S-DHEA), and IGF-1, and increased inflammation [83]. Frisoli et al. [83] identified a link between osteoporosis, osteopenia and sarcopenia and frailty as identified using the Fried criteria and in 257 community-dwelling participants of the Women Health and Aging Study II. While the overall prevalence of frailty in the population was low (n=17, 6.8%), severe osteoporosis/osteopenia was high among those identified as frail (n=7, 42%), and lower in the pre-frail (n=33, 28%), and the robust group (n=29, 25%), although this did not reach statistical significance. In addition, lower skeletal muscle mass has been shown to be associated with lower bone mineral content, narrower bones with thinner cortices, and decreased bone strength [84]. Previous studies have also identified associations between lower bone mineral density and frailty [7, 8, 85], although other studies have indicated that the high risk of hip fracture in frail older adults may be more related their increased risk of falls rather than reduced BMD [86].

Frailty has also been indicated to be high in older adults with osteoarthritis, ranging from 26 to 70% [6, 87]. Frailty was associated with an increased risk of mortality over 12 years in older adults with osteoarthritis (HR 1.98 95% CI 1.63 to 2.95, p<0.01) as well in as those with no osteoarthritis (HR 1.32 95% CI 1.06 to 1.65, p=0.03) [6]. In addition increased risk of osteoporotic fracture has been found in women with osteoarthritis and rheumatoid arthritis,
however when asked about their self-perceived risk of fracture, women with arthritis perceived their risk as similar to women without the conditions of a similar age [88]. In addition, those women with arthritis who perceived their risk of fracture as less than those of women without arthritis of the same age, actually had a higher than average risk of fracture in the study. Therefore, while clinicians and rheumatologists are aware of the increased risks of fracture associated with arthritis, this message may not be getting through to the patients themselves which may affect their uptake of recommended preventative measures.

_Treatment strategies_

While effective pharmacological treatment strategies for sarcopenia are under investigation [30], the current effective interventions for frail older adults are nutritional therapy and resistance training [28].

Due to the role of poor appetite and resulting poor nutritional intake in the development of frailty, nutritional strategies have been highlighted as an important first step in treating frailty and pre-frailty [89]. In frail older people, intake of dietary energy and protein be can insufficient to meet requirements, and muscle stores of carbohydrate and protein, as well as adipose tissue are broken down and utilized to maintain the energy supply to essential cells of the body and maintain metabolism [90]. However, the long-term impact of using these stores is loss of body weight, adipose tissue and lean muscle mass [90]. This is directly associated with the loss of physical reserves seen in frailty, and is independently associated with increased risk of mortality, morbidity, complications, and functional decline [30, 33, 90]. In addition to promoting decline of body stores of protein, frailty has been associated with declining micronutrient levels, such as iron, B vitamins, folate [91, 92].

There are a number of potential nutritional strategies to improve nutritional intake and build up nutrient stores to improve the potential to withstand future physiological stressors [89, 93].
Consuming nutrient dense fluids and snacks between meals improves overall nutrient intake across the day, despite concern that between meal snacking will reduce intake at regular meal times [94]. Oral nutritional supplements (ONS) are commercially prepared drinks which are fortified to contain additional nutrients, especially energy and protein as well as other vitamins or minerals or bio-actives [95]. They are usually sold in tetra-packs, designed to be provided to patients with their mid-meal snacks or on their meal-trays aiming to bridge the gap between nutritional intake and estimated requirements.

There is growing evidence supporting the use of nutritional strategies in older adults with or at risk of malnutrition to improve weight status and energy and protein intake [95]. In addition there is evidence that they can reduce mortality in patients identified as malnourished (RR 0.79 95% CI 0.64 to 0.97), although the effect on patients at risk of malnutrition remains under debate [95]. Following hip fracture, meta-analysis has shown an effect on the borderline of statistical significance for reducing mortality in patients (RR 0.52 95% CI 0.25 to 1.07) [96]. However, the benefits of nutritional supplementation in some highly frail groups is still unclear, with no evidence of improvement in energy or protein intake, or lean mass in a group of nursing home residents following 10 weeks of ONS [97]. Therefore, combinations of nutrition and exercise may be required to achieve gains in this group.

But while nutritional strategies have been shown to improve oral intake, and body weight, follow on effects to functional status in frail older adults have not been clearly indicated. Daniels et al. [98] reviewed the literature for the effect of interventions to prevent disability in frail community dwelling older adults, as identified using the Ferrucci criteria [99], and found neither of the two trials including nutritional interventions showed a significant effect on disability level, despite improvements in total energy intake and weight gain. However,
the nutritional intervention in one study [100] focused on improving micronutrient intake without first determining whether individuals were deficient in these vitamins and minerals. In addition, the nutritional intervention involved fortified foods that provided a set amount of additional energy (approx. 500kJ), protein, carbohydrates, and fat (amounts not reported) which may not have been sufficient or have been provided for long enough to promote improvement in frail older adults. The other study identified [101] utilized ONS x 2 per day (providing an additional 2000-300kJ and 18 to 26g protein) for 16 weeks. The study identified significant improvements in weight status and energy and protein intake, but no significant effects on strength or functional variables overall, although there was some improvement in TUG in women in the experimental group compared to the control group (24±20s vs 21±14s, p=0.04) and in men in knee extensor strength (211±50NW vs 196±42NW, p=0.02), and the authors highlighted the importance of combining nutrition interventions with exercise interventions to achieve the most benefit on functional outcomes.

In addition to treatment effects of multi-nutrient interventions, providing supplementary vitamin D has been studied in the older adult population for its effects on muscle strength and function and reducing falls [28]. The therapeutic benefit of vitamin D is likely through its ability to improve muscle and neurological function and subsequent reduction in falls, in addition reversing aged-related hyperparathyroidism and resultant reduction in bone mineral density [32]. While studies targeting frail older adults specifically are few, effectiveness in populations of older adults likely to be frail has been illustrated. Systematic review and meta-analysis has shown the effect of supplementary vitamin D in the range of 200 to 1,000 IU on reducing falls (RR 0.86 95% CI 0.79 to 0.93) compared to calcium or placebo provision[102]. Improvements in muscle strength, and balance have been shown with daily doses of 800 to 1000 IU[103] and reductions in mortality with supplementation of vitamin D and calcium (OR 0.94 95% IC 0.88 to 0.99). However, further studies illustrating the benefit to frail older
adults specifically are needed to strengthen the basis for vitamin D supplementation in clinical practice for this group.

Exercise therapy is a key intervention in the prevention and treatment of frailty in older adults, aiming to prevent decline in muscle mass, strength, and function [27, 104]. Resistance training in particular is beneficial in combination with protein supplementation [105]. Overall, the benefits of exercise for older adults outweigh the risks for older adults of falling or suffering an injury during exercise [27, 104].

Progressive resistance strength training is considered to be the key exercise intervention in the treatment of frailty however the exercises need to be continued to maintain effects. Liu et al. [106] conducted a systematic review of the effects of progressive resistance strength training (PRT) exercises on older adults, either frail or fit and healthy. They identified 121 studies evaluating the effectiveness of PRT in predominantly community-dwelling older adults, although a few studies did focus on institutionalised older adults. PRT results in improvements in physical ability (SMD (standardised mean difference) = 0.14 95% CI 0.05 to 0.22), gait speed (MD 0.08 m/s 95% CI 0.04 to 0.12), getting out of a chair (SMD = -0.94 95% CI -1.49 and -0.68), and muscle strength (SMD = 0.84 95% CI 0.67 to 1.00). In addition there was a reduction in pain for those participants with osteoarthritis utilizing a disease specific instrument (SMD = -0.30, 95% CI -0.48 to -0.13), but no significant effect seen in other trials utilizing the bodily pain domains of the SF-36 health status measure (MD 0.34 95% CI -3.44 to 4.12). While the improvements of outcomes for older people from exercise in the short term is encouraging, information on the impact on outcomes in the long term is required as a key aspect to determine effectiveness. Kennis et al. [107] evaluated the impact of resistance and aerobic training or whole-body vibration training in older adults, and found a significant improvement in static strength, dynamic strength, speed of movement in the
intervention groups (p<0.001) compared to controls, however gains in these areas declined in a similar rate in the intervention and control groups once the intervention ceased.

Exercise improves strength and balance but has also been shown to improve quality of life and functional independence.

Chou et al. [104] undertook a systematic review and meta-analysis of the effect of exercise on physical function, ADLs, and quality of life in frail older adults. The eight studies identified utilized a wide range of exercise interventions in frail older adults including flexibility, low- or intensive- resistance training, aerobic training, coordination training, balance exercises, Tai-Chi exercises, ADL based exercise regimes, and task orientated or gait training. Exercise programs generally lasted between 60 and 90 minutes, with frequency ranging from daily to weekly for between 3 and 12 months. Their analysis identified a significant effect of exercise training on gait speed (WMD (Weighted Mean Difference) = 0.07m/s 95% CI 0.02 to 0.11, p=0.005), and on the Berg Balance Scale (WMD=1.7 95% CI 0.6 to 2.8, p=0.003) compared to controls given usual care but without exercise or with light or sham exercises. In addition, they showed a significant effect of exercise interventions in improving performance in ADLs, measured by standardised questionnaires such as the Barthel Index, the FIM, and the function subscale of the Functional Status Questionnaire (FSQ), (WMD=5.33, 95% CI 1.01 to 9.64, p=0.34).

How exercise interventions are best delivered to frail older people to maximise adherence and effects remains unclear. Chin a Paw et al. [108] conducted a systematic review of the effectiveness of exercise interventions on physical function in frail older adults, and identified 20 studies in mostly community dwelling subjects (n=11) with the remainder from residential or supported care facilities or a combination of these (n=9). Interventions evaluated included predominantly resistance training (n=9) or multi-component interventions
which included combinations of resistance training with other types such as balance, flexibility, and endurance training. The majority of the interventions took the form of facility-based group exercise programs; however this was combined with a home-exercise program in five studies. The frequency of the exercise program varied among the studies, but mostly was around three times per week, and lasted for between 10 weeks and 28 months. The studies utilized a wide range of functional performance-based measures, and benefits were seen in most studies in at least one of these measures. Three out of four studies identified a significant improvement in a performance based score, such as the modified Physical Performance Test (PPT). Over half of the studies that measured gait speed or a timed up and go (TUG) test (9 out of 17) identified significant improvements in their intervention group compared to their control groups. However six studies identified by the review did not show a positive effect of their intervention, perhaps due to intensity and duration of the interventions not being sufficient to show an improvement in older adults already identified as frail. Nash et al. [109] updated this review up to September 2010, and identified 13 additional studies. Again a variety of interventions were utilized by the studies including multi-component interventions, as well as physical activity programs such as ballroom dancing and Tai Chi, functional training in specific functional tasks, progressive resistance training for lower limb muscles, and hydrotherapy. Three studies (a functional training program, Tai-Chi, and a multi-component intervention) did not show a positive effect on any of the balance, gait, physical performance-based or ADL outcome measures utilized. The remaining studies showed significant improvements in outcomes such as arm and lower limb strength, balance, flexibility, FIM scores, performance in the chair-stand test, gait speed, PPT, and fatigue in the intervention groups compared to the control groups, however generally the results of these studies were still heterogeneous and gains were not universal across all outcomes measured. The author identified some common factors in the successful interventions reviewed
including multicomponent interventions targeting aspects of aerobic, balance, coordination, ‘speed’ and resistance exercises across the program, a focus on higher-intensity and progressive exercise programs, frequency between 1 and 2 times per week and lasting for between 30 and 45 minutes, group classes with education to reinforce the importance of the exercise and focusing on activities enjoyable to the participants, support and encouragement from staff in residential or supported care, and frequent support for home based interventions to improve adherence.

Recognising that frailty in older adults is multifactorial in cause, it is likely that patients will require treatment across a range of these modalities, and management of individual comorbidities [28, 110]. Patients are likely to need a variety of treatment tailored to the causes and effects of frailty in their individual cases [110]. Comprehensive geriatric assessment followed by an individualised multicomponent treatment has a strong evidence base and so not surprisingly is effective when applied to frail older adults. Recent frailty focused trials utilize a range of treatments, including nutritional therapy, psychiatrist or psychologist input, interventions to reduce social isolation, and exercise therapy and show effects [110, 111]. One recent trial however showed that the effects take time to accrue so interventions need to be long term. In this study the prevalence of frailty as measured by the Cardiovascular Health Study criteria was 14.7% lower in the intervention compared to the control group at 12 months. In addition, mobility measured by the Short Physical Performance Battery remained stable in the intervention group and declined in the control group (p<0.001). However, no differences were seen between the groups at three month follow up, highlighting the importance of long term treatment to allow sufficient time older adults to gain benefits.

**Practice Points**
• The prevalence of frailty in community-dwelling older adults ranges from 5 to 15% and the outcomes of this group are poor.

• Problems with mobility and falls are an early marker that a person is becoming frail and should be assessed.

• Useful treatments include nutritional interventions and progressive resistance exercise training but multidisciplinary care which can include dietitians, physiotherapists, and psychologists is associated with better outcomes.

• To identify who should receive multicomponent interventions simple screening tools for frailty are useful.

**Research Agenda**

• While screening and assessment is being promoted, the models of screening methods, target populations, frequency, and treatment require further elicitation, especially the clinical and cost effectiveness of such strategies.

• Required duration and intensity of exercise and nutritional therapy to achieve the most long term benefit is still to be determined.

• Combinations of treatment considering the multifactorial nature of frailty may be more successful in older adults, however the best way of delivering interventions to achieve adherence needs further evaluation.

**Summary**

Frailty and its associated functional decline is a growing problem across the health system, given the current aging of the population and its high correlation with older age. However, other factors such as declining levels of physical activity and chronic disease play a role in its aetiology and are likely to be influencing its increasing prevalence as well. Conversely, the
increasing prevalence of frailty is likely to impact upon the health system and the medical treatment of a range of conditions in the future, including musculoskeletal conditions, due to the influence of frailty on mortality, risk of complications and recovery and responsiveness to health interventions. There is evidence of the effectiveness of exercise and nutritional therapy on preventing treating frailty; however the long term effects of these interventions are still to be determined. Future interventions may focus on combinations of therapy and a multidisciplinary approach to the treatment of this condition.

**Conflicts of Interest:** The authors have no conflicts of interest to declare.
<table>
<thead>
<tr>
<th>Instrument/study</th>
<th>Characteristics</th>
<th>Scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple “FRAIL” Questionnaire Screening Tool[112, 113]</td>
<td>5 item self-report questionnaire focusing on: fatigue, aerobic fitness and strength, presence of comorbidities, and weight loss</td>
<td>Meeting ≥3 criteria = Frail</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Meeting 1 or 2 criteria = prefrail</td>
</tr>
<tr>
<td>Cardiovascular Health Study Frailty Screening Scale[10]</td>
<td>5 item questionnaire with mixture of self-report and performance measures focusing on: weight loss, exhaustion, low activity levels, slowness in mobility, and weakness in grip strength</td>
<td>Meeting ≥3 criteria = Frail</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Meeting 1 or 2 criteria = prefrail</td>
</tr>
<tr>
<td>Clinical Frailty Scale [55]</td>
<td>9 item descriptive scale providing criteria for classifying people based on aspects of their fitness, general health, activity level, independence, mobility, level of comorbidity, frailty</td>
<td>Clinical judgement</td>
</tr>
<tr>
<td>Gérontopôle Frailty Screening Tool[54]</td>
<td>6 item questionnaire based on clinical opinion of physician focusing on: living status, weight loss, fatigue, mobility, and memory, plus an overall assessment</td>
<td>Clinical judgement</td>
</tr>
<tr>
<td>Instrument/study</td>
<td>Characteristics</td>
<td>Scoring</td>
</tr>
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<td>--------------------------------------------------------------------------------</td>
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<tr>
<td>Evaluative frailty index for physical activity (EFIP) [76]</td>
<td>50 item Frailty Index. Self-report questionnaire</td>
<td>Total score divided by the total number of questions (50). Range 0-1 with greater score indicating greater frailty</td>
</tr>
<tr>
<td>Physical frailty phenotype (PFP), mental frailty phenotype (MFP) and social frailty phenotype (SFP) [11]</td>
<td>18 item mixture of self-report and physical performance measures and common geriatric assessment tools</td>
<td>Greater or equal than 2 criteria in the SFP and MFP and greater or equal than 4 criteria in the PFP</td>
</tr>
<tr>
<td>Tilburg Frailty Indicator (TFI) [114]</td>
<td>25 item self-report questionnaire</td>
<td>Higher score indicating greater frailty</td>
</tr>
<tr>
<td>Frailty phenotype/ [10]</td>
<td>5 item self-report questionnaire</td>
<td>Those meeting ≥3 criteria were categorised as frail, those meeting 1-2 criteria as pre-frail, those meeting none of the criteria as robust</td>
</tr>
<tr>
<td>Frailty index, accumulation of deficits [25]</td>
<td>A index of at least 40 deficits including a mix of self-report and physical assessment and examination</td>
<td>Total score divided by the total number of questions. Range 0-1 with greater score indicating greater frailty</td>
</tr>
<tr>
<td>Modified Functional Independence Measure</td>
<td>18 item self-report</td>
<td>Range from 7 to 49</td>
</tr>
<tr>
<td>Instrument</td>
<td>Description</td>
<td>Scoring</td>
</tr>
<tr>
<td>------------</td>
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<tr>
<td>Carriere Instrument [72]</td>
<td>Combination of self-report and performance tests</td>
<td>Score from 25 to 165 which is transformed on to a scale of 0 to 1. Larger scores indicate greater risk of future dependency.</td>
</tr>
<tr>
<td>‘Gealey’ Instrument[62]</td>
<td>13 item self-report questionnaire</td>
<td>Score from 0 to 24, greater score indicate greater dependency.</td>
</tr>
<tr>
<td>Groningen Frailty Indicator (GFI)[57]</td>
<td>15 item self-report questionnaire</td>
<td>Score ranging from 0 to 15, score of 4 or higher represents moderate to severe frailty.</td>
</tr>
<tr>
<td>Frail Elderly Functional Assessment Questionnaire[73]</td>
<td>19 item self–report questionnaire</td>
<td>Score ranging from 0 to 55, with higher score indicating greater frailty</td>
</tr>
<tr>
<td>‘Guilley’ Instrument[63]</td>
<td>17 item self-report questionnaire divided into five domains (sensory, mobility, physical pains, memory, energy)</td>
<td>Scoring of each item range from 0 to 3. Score of 3 or higher for one item in the domains physical pains, memory and energy, or 2 or higher for one item in the sensory and mobility domains.</td>
</tr>
<tr>
<td>‘Rothman’ Instrument[70]</td>
<td>7 item questionnaire including self-report and physical performance</td>
<td>Those meeting ≥3 criteria were categorised as frail, Gait speed</td>
</tr>
<tr>
<td>Measure</td>
<td>Description</td>
<td>Scoring</td>
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<td>------------------------------------------------------------------------</td>
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<td>-------------------------------------------------------------------------</td>
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<tr>
<td>Clinical Global Impression of Change in Physical Frailty (CGIC-PF)[58]</td>
<td>13 item instrument for use during geriatric assessment</td>
<td>Scores ranging from 1 to 7 with lower scores indicating greater decline in physical frailty</td>
</tr>
<tr>
<td>The Vulnerable Elders Survey (VES)[64]</td>
<td>13 item self-report questionnaire</td>
<td>Scores ranging from 0 to 10, higher scores indicate greater frailty</td>
</tr>
<tr>
<td>Study of Osteoporotic Fractures (SOF) instrument[71]</td>
<td>3 item questionnaire using a mixture of self-report and physical testing</td>
<td>Those meeting ≥2 criteria were categorised as frail, those meeting 1 criterion as pre-frail, those meeting none of the criteria as robust</td>
</tr>
<tr>
<td>‘Chin A Paw’ Instrument[65]</td>
<td>2 item self-report questionnaire</td>
<td>Those meeting the 2 criteria classified as frail</td>
</tr>
<tr>
<td>‘Puts’ Instrument[66]</td>
<td>9 item questionnaire combination of self-report and physical performance tests</td>
<td>Score ranging between 0 and 9, those meeting ≥3 criteria classified as frail</td>
</tr>
<tr>
<td>Ravaglia Instrument[74]</td>
<td>9 item questionnaire combination of self-report and physical performance tests</td>
<td>Score ranging from 0 to 9 with greater score indicating greater risk of mortality</td>
</tr>
<tr>
<td>Winograd Instrument[67]</td>
<td>15 item criteria covering comorbidities, physical and mental health, impairments, and social factors</td>
<td>Score for frailty</td>
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<td>-------------------------</td>
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</tr>
<tr>
<td>Grip strength[75]</td>
<td>Measurement of grip strength</td>
<td>Reduced grip strength indicating greater frailty</td>
</tr>
</tbody>
</table>

(Adapted from [19])
Table 3 Prevalence of frailty in community-dwelling older adult populations

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Range of frailty prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCPS (Marigliano-Cacciafestapolypathological scale)</td>
<td>52% [77]</td>
</tr>
</tbody>
</table>
| Frailty phenotype based on Fried et al. (2001) criteria | Frail: 2.8% [5, 78] 9.8% [20], 16.9% [21], 7.2% [10]  
Pre-frail: 31.9%[20], 48.5%[21], 37.1% [78], 38.6[5], 47% [10] |
| Study of Osteoporotic Fractures criteria (SOF) | Frail: Men: 4.1% and Women 13.0% [115], 50% [4], Pre frail: 28% [4] |
| Physical frailty phenotype (PFP), mental frailty phenotype (MFP), and social frailty phenotype (SFP) | Frailty of any phenotype = 38.8% PFP = 17.3%, MFP = 20.2%, SFP = 8.9%[11] |
Figure 1: Schematic representation of the pathophysiology of frailty. Taken from Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. The Lancet. 2013;381:752-62. Reproduced with permission.
References:


[38] Gobbens RJ, Luijkx KG, Wijnen-Sponselee MT, Schols JM. Toward a conceptual


