Introduction to frailty in older adults

The term frail, when used to describe an older adult, has come to mean weak and failing. The term frailty is hence often used to describe an older adult who appears weak and vulnerable. Given that the care of the most vulnerable older adults is at the core of Geriatric Medicine practice, the rapid development of frailty research bodes well for improvement in the understanding of the underlying aetiologies of frailty as well as for the optimization of prevention, treatment, and management of frail older adults. Over the past decade, a major thrust of research in frailty has been to develop tools to identify frail older adults and then to use those tools to assess or to test clinical or biological hypotheses (Buta, 2016). Although frailty research has flourished, there has been to date no agreement on a gold standard definition for frailty, or a primary tool for the measurement of frailty (Rodriguez-Manas, 2013). Despite this, great progress continues to be made on the understanding of how declines in
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stress response systems and ageing-related biological changes contribute to the vulnerability associated with frailty. In addition, many clinical disciplines are now focusing research efforts on frail subsets of patients undergoing surgical or medical procedures in order to improve decision making and management processes for frail patients. As the evolution of frailty and its etiologies become clearer, preventative strategies and novel interventions are beginning to emerge that hold great promise in reducing the impacts of frailty through maintaining vigorous and resilient health in late life.

Conceptualization of frailty

Frailty has long been conceived of by clinicians, patients, and family members as a state of vulnerability that develops with ageing. Over the past two decades, two major schools of thought have emerged concerning the conceptualization of frailty. The most commonly cited conceptualization is phenotype or physical frailty (Fried, 2001; Buta, 2016), also commonly termed syndromic frailty. Physical frailty has been conceptualized as a deeply biological entity that is related to but not synonymous with ageing and disability. Molecular and cellular changes are thought to drive declines in multiple physiological systems, which in the aggregate provides a platform from which functional and cognitive decline, worsening chronic disease states, and early mortality develops. Indeed, frailty is increasingly thought of as the characteristic or hallmark geriatric syndrome, from which most other geriatric syndromes such as delirium and falls can develop (see Chapters 48–52, 54–57, and 156). This conceptualization led to the development of a hypothesized ‘cycle’ of frailty in which a spiral of decline is activated by disease states, ageing, and stressors (Fig. 57.1). The cycle posits that energy levels, sarcopenia, and nutrition are integral parts of this cycle, and that disability and comorbidities are related to but conceptually different than frailty (Fried, 2001).
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Fig. 57.1
Hypothesized cycle of frailty that differentiates between core physiological cycle and disability related outcomes.


A second major conceptualization of frailty is that frailty is caused by an accumulation of deficits, developed by Rockwood and colleagues (Rockwood, 2007). In this conceptualization, frailty is the product of unrelated aggregates of cognitive, medical, functional, and social deficits where by the more conditions that an individual has, the frailer that individual is. According to this conceptualization, the deficits are interchangeable in measurement tools, are not hypothesized to be driven by a common biological aetiology. In this concept, disability and comorbidities are considered integral components of frailty rather than related but separate entities that can be caused by frailty. Figure 57.2 further illustrates the major conceptualization differences between the two most commonly cited conceptual models.
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Fig. 57.2
Two most common conceptualizations of frailty. (a) Phenotypic frailty driven by age-related biological aetiology; (b) Deficit accumulation frailty where comorbidities drive frailty.


**Tools utilized to identify frail elders**

Although there are dozens and dozens of tools utilized to measure frailty, almost all of the tools developed try to capture one of the two major conceptualizations described above. To date, these tools have most often been developed to assess risk or to test specific hypothesis related to consequences, outcomes, and biology related to frailty in large population studies. However, more recent studies are working to identify condition specific measurements to assess vulnerability and identify frailty. The following section provides a brief survey of commonly cited measurement tools.

**Single item physical measures as physical frailty assessments:**

These tools include gait speed measured over four metres and the inability to perform a timed get up and go test. Individuals below the 25% of age-matched cohorts are considered frail. Although these tools are quick, they lack the sensitivity and specificity of other frailty assessment tools.

**Rapid screening questionnaires:**

The following tools identify frailty through questionnaires rather than physical measures, and combine concepts of frailty. Predominate among these is the Frail Scale, which uses questions about fatigue, functional abilities, comorbidities, and weight loss to assign a frailty score of between 0 and 5, with 3 or above being frail. The Study of Osteoporotic Fractures (SOF) determines frailty by questions about weight loss,
inability to rise from a chair and a question about energy level. The Canadian Study of Health and Aging Clinical Frailty Scale is a seven-point subjective scale that ranges from 1 (very fit) to 7 (severely frail). This tool provides a rapid risk assessment for older adults (Rockwood, 2005). Each of these studies can be easily deployed in a clinical setting and can provide a quick screen identify those at high risk of adverse health outcomes.

Physical frailty:

In order to operationalize the physical frailty construct, Fried et al. used measures of walking speed, weight loss, measures of grip strength, and questions regarding fatigue and physical activity in order to capture the weaker and slower subset of older adults (Fried, 2001; Bandeen-Roche, 2006). A point was assigned for each measure, if individuals fell below cut points for each of the five measurement domains, and frailty was diagnosed in those with 3 or more points. This provided a robust tool to differentiate frail from non-frail older adults and a tool to study differences between age-matched frail and non-frail populations. This tool was initially validated in two large population studies. These studies helped to identify that approximately 13% of those ambulatory older adults over age 65 were frail, and that these frail individuals were significantly more likely to become disabled or die in the subsequent three years after frailty measurement compared to non-frail older adults of the same age. This facilitated the development of studies that assessed risk, biological aetiologies, disease associations, adverse health consequences, and potential preventative and intervention strategies for frailty.

Deficit accumulation frailty:

The concept of deficit accumulation related to frailty was operationalized into an exam by identifying between 30 and 130 measures termed deficits, that range from functional measures of toileting and bathing to muscle tone and coordination to tremors and seizures to headache and malignancies to memory deficits and depression (Mitnitski et al., 2005). This tool often called the frailty index (FI) by calculating unweighted deficits that awards a 1 for each deficit. A ratio is then calculated by dividing the total number of deficits by the total number of measures where 0 is least frail and 1 is most frail. This tool can be altered to have as few as 20 deficits or comorbidities and has proven very useful in the identification of older adults at risk for adverse health outcomes. Because a wide range of biologically unrelated ‘deficits’ are included in this index, the identification of underlying biological features and the development of intervention strategies has proven more difficult using this tool.

Other measurement tools:

Over the past several years, dozens of new frailty measurement tools have emerged that are potentially useful to clinicians and researchers
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Although there are some exceptions, most have been derived directly from either the phenotype or the index conceptual frameworks. In some cases, comorbidities and deficits are combined with phenotypic measurements to assess frailty. Given that a major goal of frailty research is to disseminate it into clinical practice to improve healthcare and outcomes of vulnerable older adults, many investigators have tried to simplify and shorten the original index or physical frailty tools so that they can be more easily administered in primary care or subspecialty clinics. This includes a number of important tools for risk assessment that are targeted at hospitalized, non-ambulatory patients (Joseph, 2014a).

Cognitive decline measures are often included in frailty screening tools, although cognition is mostly considered as a separate but related condition. The Delphi report on frailty suggests that cognition is an important domain of frailty (Rodriguez-Manas, 2013). Although it is not necessarily a core component of physical frailty, it certainly often accompanies frailty. Indeed, the biology that underlies physical frailty may also drive mild cognitive impairment or worsen preexisting Alzheimer’s Disease. Further, recent studies suggest that executive function declines may precede the onset of frailty in older adults, further arguing for a close relationship between the two entities (Gross, 2016). Hence, the use of tools that include cognitive impairment measures when diagnosing frailty may be especially useful when considering risk assessment for progression of frailty.

The prevalence and consequences of frailty

Dozens if not hundreds of population studies have been performed in clinical studies of community-dwelling older adults around the world using many of the tools cited above. Although there is wide variation between studies, in general, 8–15% of ambulatory adults over age 65 are frail, and between 25–45% of them are pre-frail. A recent meta-analysis that evaluated frailty ascertained by a wide variety of tools showed that overall prevalence of frailty is 10.7% (Collard, 2012). A 2015 study analysed demographic data from the diverse US National Health and Retirement Survey (NHATS) population and showed that the prevalence of frailty increases with age (8.9% in those between 65 and 70 to 37.9% of those over 90), and that frailty is more common in women than in men (17.2% vs. 12.9%), in African Americans compared to Caucasians (22.9% vs. 13.8%), and in lower income compared to higher income groups (25.8% vs. 5.9%) (Bandeen-Roche, 2015). Longitudinal studies suggest that many ambulatory patients transition from robust to pre-frail status or from pre-frail to frail status over time (Gill, 2002). For non-ambulatory or acutely ill populations, a deficit accumulation or index type approach is often utilized to assess frailty status because most phenotypic frailty measurement tools were developed with gait speed measures. As expected, the prevalence of frailty in those who are disabled, hospitalized, or institutionalized is higher than that of
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ambulatory subjects, ranging from 27% to upwards of 80% (Joseph, 2014a).

Building on these populations studies, the relationship between frailty, chronic disease states, adverse health outcomes, and mortality has been extensively studied. Cardiovascular diseases, including hypertension, peripheral vascular disease, and congestive heart failure have been consistently associated with physical frailty (Newman, 2001; Bandeen-Roche, 2015). In addition, osteoarthritis, diabetes, COPD, stroke, and dementia are far more common in frail older adults compared to robust or non-frail older adults (Bandeen-Roche, 2015). This is likely at least in part due to the underlying and inter-related biology, described below, that drives both disease states and the syndrome of frailty in a subset of older adults.

Frailty has been used by many investigators to ascertain increased risk for future adverse health outcomes and mortality in future years. Beyond the clear relationship between chronic disease and frailty, dozens of risk assessment studies using a wide array of frailty measurement tools have clearly demonstrated a strong relationship between frailty and the development of disability, geriatric syndromes such as falls, delirium, incontinence, and mild cognitive impairment, increased risk of hospitalization, and risk of needing longer inpatient care after procedures (Joseph, 2014b; Bandeen-Roche, 2015; Makary, 2010). In fact, a number of common health conditions are far more common in frail older adults, suggesting that the biology that drives frailty may drive these commonly observed conditions (Box 57.1). Multiple studies have demonstrated that those older adults who are frail are significantly more likely to die in subsequent years compared to more robust or pre-frail individuals, with a relative risk of dying between 2 and 6 over three years for phenotypic frailty.

Box 57.1 Clinical characteristics of frailty

- Unexplained anaemia
- Functional decline
- Mild cognitive impairment
- Poor endurance
- Glucose intolerance
- Muscle weakness
- Clotting proclivity
- Social withdrawal
- Worsening disease states
The biological and physiological basis of frailty and related geriatric syndromes

Given the marked association between chronic disease, functional decline, disability, geriatric syndromes, and ultimately mortality and frailty after adjustment for age, it is increasingly evident that the prevention of frailty and the maintenance of robustness or resiliency are key to slowing the decline in health and well-being in older adults. If the aetiologies of frailty are better understood, targeted interventions to delay frailty will be more likely to be developed and tested. Over the past two decades, marked progress has been made in the identification of biological characteristics of physical or phenotypic frailty in population and observational studies. It is increasingly evident that ageing-related biological change, chronic disease states, and the dysregulation of multiple physiological and homeostatic pathways play a crucial role in the development of phenotypic frailty. In addition, environmental factors such as nutrition and education are thought to modify frailty (Bandeen-Roche, 2015). Figure 57.3 illustrates a modal pathway that represents the complex etiologies and consequences of physical frailty.

Fig. 57.3
Modal pathway of physical frailty where age-related biology, environment, and chronic disease states trigger physiological changes which in turn drive frailty and set up platform for adverse outcomes.

Ageing-related biological change

All organisms that survive into older age groups undergo molecular and cellular changes that ultimately contribute to pathophysiological change and declines in health and function (Lopez-Otin, 2013). Cellular senescence in connective tissues and the immune system transforms the function and structure of previously vibrant tissues that impacts multiple physiological systems and activates chronic low-grade inflammation (Chapters 46 and 171). Ageing stem cells and altered stem cell niches prevent rigorous replenishing of formerly vibrant tissues. Age-related accumulations in mitochondrial damage are apparent in almost all cells, which results in abnormalities in autophagy and mitophagy, declines in
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energy production, and increased levels of oxidative stress (Chapter 46). This in turn has a profound impact on energy metabolism and contributes to chronic inflammation. Age-related degeneration in peripheral, central, and autonomic nerves and supporting structures likely contribute to multiple physiological changes that are hallmarks of frailty as described below (Chapters 41 and 42). Altered protein homeostasis and accumulation of cellular debris in conjunction with altered autophagy further drives tissue changes. Finally, alterations in DNA related to methylation, direct DNA damage, and telomere shortening likely drive age-related alterations in gene expression that may contribute to physiological changes and ultimately frailty (Chapter 41).

Homeostatic system changes and frailty:

Building on prior hypothesized models for the cycle of frailty and declines in energetics, significant relationships between frailty and altered energy metabolism have been identified. For example, fasting glucose and insulin levels and levels after glucose tolerance testing are elevated in frailty compared to robust older adults (Kalyani, 2012). Lower levels of anabolic hormones including insulin like growth factor (IGF-1) and in DHEA-S in frail compared to frail suggest an impairment in endocrine pathways that protect skeletal muscle (Cappola, 2009). Other changes have also been identified including an activated innate immune system as measured by inflammatory cytokines, hypothalamic pituitary adrenal (HPA) axis as measured by salivary cortisol, and sympathetic nervous system as measured by lack of heart rate variability that provide important evidence that dysregulated stress response systems may play an etiological role in the development of frailty and its incumbent vulnerability to adverse health outcomes. Further, it is evident that these physiological systems likely activate each other (Fig. 57.4) (Walston, 2015). Extensive data suggests that these stress response systems are chronically activated at a modest level, which likely leads to chronic exposure to inflammatory and stress response mediators, which are known to patho-physiologically alter tissues and organs, and contribute to the worsening of chronic disease states (Chapters 41 and 42). Ultimately, these molecular and physiological tissue changes create a biological platform that drives frailty and related geriatric syndromes, clinically apparent changes such as anaemia of inflammation and sarcopenia, worsening of chronic disease states, and ultimately sets the stage for vulnerability to a host of adverse health outcomes and mortality as illustrated in Figure 57.3.
Fig. 57.4
Stress response systems hypothesized to be dysregulated in frailty and likely consequences of chronic activation of these systems in older adults (Walston, 2015). (SNS = sympathetic nervous system; HPA = hypothalamic pituitary adrenal.)

**Intervention and prevention strategies for frailty in older adults**

*Strategies to prevent or treat physical frailty:*

All of the validated frailty measurement tools provide an important mechanism to identify vulnerable older adults as compared to more robust and resilient individuals. Given that a major goal of Geriatric Medicine is to maintain good health and a high quality of life as long as possible, and that frailty represents a clinical state of highest vulnerability to adverse outcomes and mortality in older adults, the development of specific strategies to prevent and treat frailty are paramount. Although few studies have specifically targeted frailty rather than sarcopenia or other conditions per se, two recent studies have attempted to remediate frailty status through comprehensive interventions. One study found that cognitive and physical exercise, along with nutritional supplementation, improved short term frailty status but not eventual secondary outcomes (Ng, 2015). Another study demonstrated that intervening on components of the physical frailty such as weight loss and slow walking improved frailty score, but also did not have a differential benefit on secondary outcomes such as mortality (Cameron, 2013). Older studies in physical frail subjects demonstrated that high intensity resistance training exercise alone and in combination with nutritional interventions improved both strength measures (Fiatarone, 1994).

*Biologic strategies:*
The discovery of multiple molecular and physiological drivers of frailty has provided an important roadmap for the development of interventions that may reduce the prevalence of frailty and the host of related adverse health outcomes. Although no study targeting frailty per se has been performed that specifically targets dysregulated stress response systems, anti-inflammatory interventions such as aspirin, agents targeting the renin-angiotensin system activity such as losartan and captopril, and beta-blockers targeting overactive sympathetic nervous system tone have already been found to decrease all-cause mortality and slow the development of frailty-related conditions such as sarcopenia and mild cognitive impairment in older adults. Although not targeting frailty specifically, these findings suggest that targeting these stress response systems, perhaps independently of specific disease states, may provide a preventative or targeted treatment strategy.

A roadmap for the integration of frailty into primary and subspecialty care

Despite the surging interest in frailty research, the integration of frailty-related knowledge into routine clinical practice for older adults has not kept pace. This is in part due to lack of consensus as to best tools to measure frailty, and in part due to the lack of well vetted clinical recommendations for healthcare practitioners to follow. However, the ability of the frailty status to predict a host of adverse health outcomes, and the interest of many subspecialists to protect their more vulnerable patients from iatrogenic injury, has led to a wide variety of new studies targeting patients of subspecialists. In the following section, the potential utility of using frailty status to guide healthcare delivery in the primary care settings will be articulated, followed by a discussion of the potential utility of frailty in patient care for both risk assessment and for modification of management strategies in older adults will be in a number of subspecialties.

The management of frailty in a primary care practice:

Although two major consensus statements by international leaders in geriatric research advocate for the screening of frailty in older adults, few if any undergo a formal frailty assessment (Rodriguez-Manas, 2013). This is in part because there has been no discipline-wide consensus on the best way to define and measure frailty, and in part because there are few recommendations on how best to manage outpatients based on their frailty status. Despite this, there remains a huge need to better manage and slow the trajectory of frail older adults towards disability, worsening disease states, and other adverse health outcomes. Several groups of clinician investigators have moved forward with specific recommendations and studies that have created some forward momentum in the field. Gerontopole in Toulouse, France and affiliated investigators have moved to prevent functional decline and disability in older adults by developing and implementing a frailty phenotype screening tool that helps to identify at risk older adults, and heightens
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awareness of clinicians to focus on preventing the progression of
disability (Subra, 2012). In 2013, a group of clinician-scientists
representing six major international geriatric focused organizations
convened an international panel in order to come to agreement around
how best to proceed with the integration of frailty into primary care
practice for older adults (Morley, 2013). Building on the international
panels clinical and research expertise, the group published four major
recommendations that provide guidelines about the importance of
detecting and treating frailty in older adults (Box 57.2).

Box 57.2 Recommendations from international panel on integration of
frailty into clinical practice

1. Physical frailty is an important medical syndrome with
multiple causes and contributors that is characterized by
diminished strength, endurance, and reduced physiologic
function that increases an individual’s vulnerability to
increased dependency and/or death.
2. Simple, rapid screening tests have been developed and
validated that allow physicians to objectively recognize frail
persons.
3. For optimal management of individuals with physical frailty,
all persons older than 70 years and all individuals with
significant weight loss (≥5%) due to chronic disease should be
screened for frailty.
4. Physical frailty can potentially be prevented or treated with
specific modalities, such as exercise, protein-calorie
supplementation, vitamin D supplementation if needed, and
reduction of polypharmacy.

The British Geriatrics Society recently published a summary of guidance
that defined frailty as a condition with multiple systemic declines that
result in loss of reserve and vulnerability to loss of physical and mental
well-being after even minimal stressors (Turner, 2014). They also
recommend that older adults be screened for frailty using a simple,
validated screening tool. Frail older adults should then be guided into a
more rigorous care plan such as that afforded by a comprehensive
geriatric assessment and personalized medicine approaches (Chapter
172). This more holistic approach to patient care will help to facilitate
healthcare provider review and optimization of medical conditions,
reduction in potentially harmful medications, improved functionality and
well-being, through the development of a comprehensive and
individualized care plan that can be maintained and optimized over time.
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Using a similar more holistic and personalized approach, Ko articulated a management strategy along a spectrum of physical frailty (Fig. 57.5). This includes the early establishment of patient-centred goals, exercise interventions, comprehensive geriatric assessment, specialized housing considerations, and consideration for palliative care approaches for advanced stages of frailty (Ko, 2011).

![Fig. 57.5](image)

Possible management strategies for frail older adults along the continuum from mild to severe frailty.


The management of frailty in specialty care practices

Physical frailty assessment during preoperative surgical evaluations was demonstrated to predict adverse outcomes and especially lay term care needs for general surgery patients as well as if not better than commonly used surgical tools (Makary, 2010). This, along with observations by astute clinicians that a subset of older adults do poorly after surgical or medical procedures has led many clinician investigators to use frailty screening in an attempt to reduce procedure related adverse health outcomes. In the US, a recently convened conference on Frailty for Specialists, a number of potential uses for frailty in surgical practice were articulated (Robinson, 2015). These include the uses of frailty; 1) to assess risk and guide decision making for patients about to undergoing a procedure or treatment, 2) to identify patients who might benefit from exercise interventions and strengthening before surgery to reduce incumbent risk associated with frailty, 3) to tailor anaesthesia regimens for reduction in risk for adverse outcomes, 4) implement specific delirium reduction strategies in frail older adults, 5) trauma triage, and 6) implementation of team based care pathways and consideration of high risk of longer post-hospital recovery stays.

For medical subspecialties, it has noted that frail individuals with cancer, chronic kidney disease, diabetes, cardiovascular disease, and HIV have a much higher risk for morbidity and mortality as compared to more robust...
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individuals with these conditions. This has led to a flourishing of research into frailty as a tool for risk assessment and as a tool to guide management in each of these disciplines. A recent summary of the use of frailty tools in patients with cancer was published that highlighted the need for additional biological studies that link the two conditions and guide treatment (Huisingh-Scheetz, 2016). Given the higher risk for transplantation related failure in frail compared to non-frail individuals with CKD, frailty diagnosis has been studied as a tool to help make optimal care decisions (McAdams-Demarco, 2014). Likewise, patients undergoing cardiovascular procedures such as Trans-Aortic Valvular Replacement (TAVR) (Chapter 108) are being evaluated to determine whether or not frailty should guide management decisions for these and other cardiac procedures. Finally, in chronic conditions like diabetes and HIV, it has long been noted that those with frailty and higher inflammatory mediators tend to decline at a more rapid pace. Active research programmes aim at detecting biological differences between frail and non-frail or robust older adults with these conditions in order to develop more targeted and individualized management strategies.

Conclusions

Frailty is a geriatric syndrome of markedly increased vulnerability to adverse health outcomes. It is highly associated with and predicts the development of a host of adverse health outcomes and provides the platform for the development of other geriatric syndromes. The biology that underlies frailty is likely driven by both ageing-related molecular changes and altered physiological and stress response pathways. These include the development of senescent cells, altered mitochondria, chronic inflammation, and altered neuroendocrine communication mechanisms among others. The two major concepts that describe frailty include physical frailty, characterized by muscle weakness, slowness, and weight loss, and deficit accumulation related frailty, characterized by accumulation of diseases and comorbidities. Although no one screening exam is recognized as a gold standard, dozens of tools have been developed and validated to detect frailty. Frailty assessment tools are increasingly utilized in primary care and specialty practices as a way to identify the most at risk subset of older adults. Exercise and optimal nutrition likely improve frailty. Active research programmes are attempting to identify the optimal management approaches to prevent frailty and its adverse outcomes. Biological studies aimed at identifying common mechanisms that tie frailty, geriatric syndromes, and the accumulation of chronic disease and functional decline together are ongoing and hold promise for more individualized management strategies.

References

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