



## Position Statement 22

### Frailty in Older People

#### Key Points

1. Frailty is an important concept for all those who plan and provide care for older people. It is closely linked to advanced age and disease-related processes, yet is a distinct construct. While some people remain fit and active as they grow older, others experience complex problems: chronic disease, dependency and disability. Frailty is a term to describe this latter group, capturing differences in health status among older people.
2. “Frail” older people are at greatest risk of adverse outcomes (worsening disability, institutionalisation and death) and are more likely to present with a geriatric syndrome (particularly delirium and falls).
3. There are many validated tools to measure frailty as a clinical syndrome or phenotype. The most well-known and widely used phenotypic tool is the Fried model which defines someone as frail if they meet 3 or more of 5 criteria: weight loss, exhaustion, weak grip strength, slow walking speed and low physical activity. The multidimensionality of frailty is embraced by tools such as the Edmonton Frailty Scale which derives a maximum score of 17 from assessments across 10 different domains.
4. Frailty can be conceptualised as the failure of a complex system. Deficits accumulate with the passage of time leading to a loss of redundancy. When redundancy has reached a critical threshold not in one homeostatic pathway (seen in single system medicine) but in multiple domains, the system becomes vulnerable to failure. This conceptualisation of frailty facilitates its measurement by the number rather than the nature of health problems. The more things individuals have wrong with them, the higher the likelihood they will be frail.
5. On a pathophysiological level, frailty is strongly associated with a combination (rather than by a single measure) of immunological and physiological impairments. There is also a growing body of evidence linking inflammation with frailty, an association which seems consistent across different frailty definitions. Further research is needed to establish whether inflammation is the driving force towards frailty, a compensatory response or an epiphenomenon.
6. Falling is strongly linked to frailty. When complex systems fail, they fail first with their higher order functions: processes that require a coordinated, integrated, and precise interaction between many components. Walking can be considered a higher order function. The frail older person, on the threshold of failure, can present with falls in the face of seemingly minor stressors. Comprehensive and multifaceted assessment and management programmes are needed to reduce falls in frail older people.
7. Frailty is associated with altered pharmacokinetic responses which affect the bioavailability of prescribed medications. Frail older people have multiple chronic diseases and are prescribed long lists of medications increasing their risk of adverse drug

reactions. Since frail older people have a reduced life expectancy, goals of care should be carefully considered to optimise drug prescribing.

8. Therapeutic strategies to prevent or reverse frailty remain incompletely explored. Lifestyle behaviours including smoking and the development of obesity (particularly the accumulation of abdominal fat) are associated with higher frailty levels. Complex interventions such as optimisation of nutrition, better education and exercise have the potential to delay the onset of frailty. Exercise is feasible even for very frail older adults and has beneficial effects on multiple domains, increasing muscle strength, improving balance and postponing cognitive decline.

*This Position Statement represents the views of the Australian and New Zealand Society for Geriatric Medicine. This Statement was approved by the Federal Council of ANZSGM on 16th June 2013 Authors: Dr Ruth Hubbard and Dr Kenneth Ng.*

## BACKGROUND

The care of older people is becoming a core remit of acute hospitals in Australia and New Zealand. In 2005–06, while comprising only 13.2 per cent of Australia's population, those aged 65 years or over represented 35 per cent of all hospital admissions and 47 per cent of all occupied bed days.<sup>1</sup> Older, complex patients with multidisciplinary needs are not confined to Geriatric Medicine units but are scattered throughout general medical wards.<sup>2</sup> Though many do well and are discharged home to live independently, older people remain a vulnerable group, at high risk of prolonged hospital stays, institutionalisation and death.

The term "Frail" is intended to identify those older people at greatest risk of adverse outcomes. Frailty has become the focus of considerable research interest, generating nearly 4000 publications in the last 10 years compared to 20 before 1980. Here, we briefly review different approaches to the definition of frailty and review its pathophysiology. We describe the difficulties of recognising and

measuring frailty in clinical practice. By considering the impact of frailty on falls and medication prescribing, we explore how an understanding of frailty could improve clinical care in the hospital setting.

## DEFINITION OF FRAILITY

Although precise and standardised definitions are always desirable in medical sciences, in the case of frailty this has been a challenge. Early definitions of frailty painted bleak pictures of irreversible age-related decline. A leading article in the BMJ in 1968 described "confused, restless, incontinent old patients" and 20 years later, frailty was still considered to equate to "elderly people with multiple problems".<sup>3,4</sup>

The conceptualisation of frailty is now more refined. The term "frail" is intended to identify vulnerable older people at high risk of adverse outcomes including falls, worsening disability, institutionalisation and death. The prevalence of frailty increases with chronological age and there is likely to be an age point, say 95 years, at which all individuals are vulnerable to adverse outcomes.<sup>5</sup> Similarly, co-morbidities can incur vulnerability and some chronic diseases are associated with very high frailty levels.<sup>6</sup> Yet, frailty is not synonymous with either age or disease. Chronological age alone is not a sensitive predictor of inpatient mortality, for example,<sup>7</sup> and there is considerable variation in how older people tolerate disease, even when disease severity is taken into account.<sup>8</sup>

Gavrilov and Gavrilova's reliability theory provides a conceptual framework of ageing that may help us understand why and how frailty occurs.<sup>9</sup> They propose that ageing is due to the progressive accumulation of random damage to a complex system composed of redundant parts; defects accumulate with the passage of time (age) resulting in an increased risk of death (ageing). As defects accumulate, the organism loses its redundancy until eventually it becomes comparable to a system with elements connected in series. Such a system has no resilience and is vulnerable to external or internal stressors. This reduced adaptability

and ability to maintain equilibrium results in organ systems that are at, or near the threshold of failure, and therefore an individual who is at increased risk of adverse outcomes. This individual is frail.

## MEASUREMENT OF FRAILTY IN CLINICAL PRACTICE

A variety of tools identify frailty as a clinical syndrome or phenotype (a set of signs and symptoms that tend to occur together, thus characterizing a specific medical condition). These tend to be summative impairment lists and algorithms derived from clinical judgment. Combinations used to define frailty include physical inactivity and weight loss; gait speed, peak expiration, hand grip, sitting position, visual impairment; inability to rise from a chair 5 times without using arms plus reduced energy level and fatigue, resistance, ambulation, illness, loss of weight (the FRAIL scale).<sup>10,11, 12,13</sup> Of note, the FRAIL scale has recently been validated as predictive of mortality and disability in community-dwelling older Australian men and women.<sup>14,15</sup> Slow gait speed in itself is strongly linked to functional decline and disability and has been used in isolation as a frailty measure.<sup>16</sup> The most well-known and widely used phenotype was defined by Fried et al. in 2001 and identifies frailty as the presence of  $\geq 3$  of 5 criteria: unintentional weight loss of  $\geq 10$ lbs in the preceding year, self-reported exhaustion, weak grip strength, slow walking speed, low physical activity.<sup>17</sup> This phenotype has been validated as a predictor of adverse outcomes in large epidemiological studies and was recently used to define frailty as the most common condition leading to death in community-dwelling older people.<sup>18,19</sup> Fried's model has many strengths: it is clinically coherent, reproducible and identifies frailty as a wasting disorder with sarcopenia as a key pathophysiological feature.<sup>20</sup> However, many very "vulnerable" older people on inpatient wards are unable to attempt performance based tests and cannot be stratified by phenotypic measures.<sup>21</sup> The omission of disorders of cognition and mood from these models is also controversial: frailty in the clinical setting consists of more than

weakness, slowness and wasting.<sup>22</sup>

An alternative to phenotypic approaches is the measurement of frailty based on the clinician's subjective opinion.<sup>23, 24, 25</sup> While such measures have strong face validity, their reliance on judgement (which may vary between clinicians and between health systems) and dependence on geriatric expertise (e.g. accurate assessment of functional status) does limit their generalisability.

The multidimensionality of frailty has been embraced by scoring systems that include assessments across different domains. The Edmonton Frailty Scale (EFS), for example, was designed for geriatricians in both inpatient and outpatient settings and derives a maximum score of 17 from 10 sampled domains; cognition, balance and mobility, mood, functional independence, medication use, social support, nutrition, health attitudes, continence and quality of life.<sup>26</sup> In older adults, high pre-operative scores on the EFS have been shown to be associated with increased complications and a lower chance of being discharged home after surgery.<sup>27</sup> A Reported Edmonton Frailty Scale (REFS) has recently been developed, using the same domains as the EFS but substituting the observed 'get up and go' with a report of physical function before the current illness.<sup>28</sup> In a sample of 111 acute care older inpatients in Sydney, a REFS score correlated moderately well ( $R= 0.61$ ) with a Geriatrician's Clinical Impression of Frailty and was associated with factors known to be linked with frailty: increasing age, polypharmacy, comorbidities, disability, cognitive impairment and malnutrition.<sup>24,28</sup> However, the relationship of the REFS score to adverse outcomes has not yet been investigated.

The conceptualisation of ageing as the accumulation of deficits facilitates the measurement of frailty as a multidimensional risk state which can be quantified by the number rather than by the nature of health problems.<sup>29</sup> The Frailty Index (FI) model employs a well-defined methodology to create an index as a proportion of deficits.<sup>30</sup> In large,

community based studies, they have been well validated as a means of health status quantification, correlating highly with institutionalisation, worsening disability and death.<sup>31</sup> Since Frailty Indices can be constructed from different numbers and types of deficits, a measure of frailty status can be derived from information routinely collected in the assessment of an older person.<sup>32</sup> Studies are investigating the predictive validity of a Frailty Index derived from Comprehensive Geriatric Assessment. The interRAI instruments in particular have the potential to address these research questions since they collect data across multiple domains. This data could be coded as deficits to derive Frailty index scores. Integration of frailty quantification into an existing assessment system, which serves other clinical and administrative purposes, could optimise utility and minimise costs, without losing fidelity.

## **FRAILITY PATHOPHYSIOLOGY**

While the exact pathophysiology of frailty has not yet been established, there is a growing body of evidence linking frailty with inflammation.<sup>33</sup> This association seems consistent across different frailty definitions.<sup>34</sup> In community-dwelling older women, frailty has been shown to be associated with an elevated total white cell count.<sup>35</sup> In particular high neutrophil and monocyte counts.<sup>36</sup> Alterations in T-cell subsets have also been implicated, with significantly higher CD8+CD28- lymphocyte counts among women who were frail compared with pre-frail and non-frail women.<sup>37</sup> Impaired innate immunity, measured by a low production of pro- and anti-inflammatory cytokines after stimulation with bacterial lipopolysaccharide, was predictive for frailty in the Leiden 85-plus cohort.<sup>38</sup> In this study, the role of the anti-inflammatory cytokine interleukin 10 (IL-10) was explored: a significant genetic association with the IL-10 promoter gene was found, indicating that people genetically predisposed to produce lower IL-10 levels were at a higher risk of frailty development. A pivotal role for IL-10 had previously been suggested by studies of mice genetically altered not to express IL-10. With increasing age, these mice developed

biological and physical manifestations of frailty, including elevated IL-6 levels and muscle weakness.<sup>39</sup>

However, further studies are needed to establish the exact nature of this relationship. Inflammation may be primarily causal (in which case, anti-inflammatory strategies would be desirable), a compensatory response to viral antigens or subclinical disease (for which anti-inflammatory strategies would be undesirable) or an epi-phenomenon, merely a marker of another key pathophysiological process such as excessive oxidative stress (where anti-inflammatory strategies would be irrelevant.)

Furthermore, it has recently been recognised that frailty is most strongly associated with a combination of immunological and physiological impairments rather than a single biomarker.<sup>40</sup> This supports the conceptualisation of ageing as the progressive accumulation of damage to a complex system resulting in aggregate loss of system redundancy. A critical mass of abnormalities across different systems seems to be a more important determinant of frailty than any individual pathway.

## **FRAILITY AND FALLS**

Frail older people are more likely to present with any geriatric syndrome and there is now increasing evidence linking frailty specifically to falls.<sup>41, 42</sup> Understanding frailty as the failure of a complex system provides a framework for exploring why and how the frail older person is at risk of falls.

A key characteristic of a complex system (whether biological, mechanical, political etc.) is its inherent ability to withstand stresses because of the presence of multiple defences.<sup>43</sup> As a result of these defences, failure of a complex system is rarely the result of a single cause but is the cumulative effect of many small insults, each of which may appear to be harmless on its own. When system failure does occur, each small stressor that contributes to the breakdown is necessary but not sufficient to cause the failure on its own. The first processes to be compromised in the

event of failure are typically higher-order functions, because they require a coordinated, integrated, and precise interaction between many components of the complex system. In humans, such higher order functions include bipedal ambulation. Normal ambulation requires the coordination of many different muscles acting on multiple joints and is accomplished by the integration of activity in spinal neuronal circuitries with sensory feedback signals and with descending commands from the motor cortex.<sup>44</sup> Consequently, it should not be surprising that frail individuals (who are comparable to a system in which redundancy has been lost) become unable to integrate multiple inputs in the face of seemingly minor stressors and present with falls.

In frail older people, falling should be recognised as a macrostate indicator of complex system failure rather than a specific disorder of particular organs (such as the brain or heart). This is congruent with existing clinical guidelines that falls require multifaceted assessment and holistic management.<sup>45</sup> Yet valuable time and resources are still often spent identifying the cause of a non-syncopal fall in a frail elderly patient, leading clinicians to embark on a journey of endless investigations for incidental findings. If falling in the frail is truly a manifestation of complex system failure then searching for the cause of the incident is futile since this single cause does not exist. After all, failure of a complex system is the cumulative effect of multiple faults and it is only the intricate linking of these detrimental processes that leads to the overt collapse of the system.

## **PRESCRIBING IN FRAIL OLDER PEOPLE**

The implementation of guidelines for the management of chronic disease has resulted in an increase in the cost and number of prescribed medications. However, older people (particularly those who are frail) are often excluded from drug trials.<sup>46</sup> Treatment decisions are therefore often based on evidence extrapolated from more robust patient groups with fewer physiological deficits.

Frailty is associated with altered pharmacokinetic responses which affect the bioavailability of prescribed medications. Increases in body fat and reductions in lean body mass affect the distribution of drugs; low albumin levels reduce drug binding and the activity of enzymes of drug metabolism becomes impaired.<sup>47,48</sup> Older people also have pharmacodynamic changes, such as increased sensitivity to benzodiazepines and warfarin which increase their risk of Adverse Drug Reactions.<sup>49,50</sup> Indeed, the risk of Adverse Drug Reactions (ADRs) seems to increase with increasing patient frailty: the prevalence of potentially inappropriate medications (those in which the likelihood of an ADR outweigh therapeutic benefit) has been reported as up to 20% of older people living in the community, one third of patients in hospital and as many as 50% of older people living in residential aged care facilities.<sup>51, 52, 53</sup>

While frailty is not synonymous with either co-morbidity or disability, many frail older people have multiple chronic diseases and functional impairment and are prescribed long lists of medications. Polypharmacy has negative consequences above and beyond the risks of individual drugs. Increasing numbers of medications are associated with a higher likelihood of non-compliance and a significantly greater risk of ADRs.<sup>54, 55</sup> Older people taking 5 or more medications are at significantly higher risk of delirium and falls, independent of medication indications.<sup>56,57</sup>

When prescribing medications for frail older people, goals of care should be carefully considered.<sup>58</sup> The improvement in quality of life through symptom control remains an important (intended) outcome of therapeutic intervention. However, the risks of secondary prevention may outweigh benefits in those with limited life expectancy. For example, in one study the median life expectancy for frail older adults with delirium was 88 days (95% CI: 5-171); the loss of physiological reserves and homeostatic instability of these patients renders them vulnerable to ADRs and they may not survive to reap any benefit from treatment with medications such as statins, ACE inhibitors or bisphosphonates.<sup>59,60,61,62</sup>

## PREVENTION OF FRAILITY

While there are no proven strategies to reverse frailty, epidemiological data exploring factors associated with frailty development provide information on potential interventional strategies.

Frailty is associated with co-morbidities, particularly cerebrovascular, chronic kidney and cardiovascular disease.<sup>63</sup> and primary prevention of these conditions could reduce the prevalence of frailty in old age. The role of alcohol is unclear. While alcohol use (versus abstinence) is linked with a lower incidence of frailty<sup>64</sup>, earlier studies found a positive association between excessive alcohol consumption and frailty status<sup>65</sup>. Smoking, on the other hand, has been strongly linked to frailty and smoking cessation could have benefits above single disease prevention. Cigarette smoke is a powerful inflammatory stimulus causing the influx and activation of inflammatory cells and may therefore have a direct causal role in frailty development.<sup>66,67</sup> The association between frailty and inflammation is well established and has been previously discussed.<sup>33</sup> Yet in observational and epidemiological studies to date, anti-inflammatory therapy or nutrients with anti-inflammatory properties do not seem effective to prevent or delay the incidence of frailty. For example, in the Women's Health Initiative Observational Study (n = 25,378), current statin use had no association with incident frailty over 3 years.<sup>68</sup>

Obesity, particularly the accumulation of abdominal fat, is also associated with higher frailty levels.<sup>69</sup> Even among underweight older people, those with a higher waist circumference are more likely to be frail.<sup>69</sup> Abdominal obesity among older people with low BMIs may therefore be an additional target for intervention. Physical activity decreases abdominal fat, and endurance exercise training stimulates mitochondrial biosynthesis.<sup>70, 71</sup> Reduced abdominal adiposity and increased oxidative activity may underlie physical activity's benefit to function independent of its effects on weight reduction.<sup>72</sup>

Exercise, like optimal nutrition and better education, are of particular interest as therapeutic strategies for frailty since they are complex interventions which may modify the accumulation of deficits across many systems.<sup>73</sup> While the evidence regarding the impact of such interventions in hospitalised patients with established frailty is less clear cut, exercise does seem to be a safe intervention for all older people, resulting in functional improvement even for those at the frailer end of the health status spectrum.<sup>74, 75</sup> Whether frail older inpatients would benefit from longer periods of rehabilitation in units designed to offer tailored exercise programmes and nutritional support should be the focus of further enquiries.

## CONCLUSIONS

Frailty identifies a vulnerable group of, usually but not invariably, increasingly aged people at highest risk of adverse clinical outcomes. Frailty status can be measured by a number of phenotypic tools or by the accumulation of deficits but their feasibility and utility in the clinical setting have yet to be fully investigated. As with the development of most screening tools and their transition into everyday clinical practice, there is the potential for an undercurrent of scepticism from clinicians about the necessity for such a tool, seeing it as an unnecessary addition to expertise and common sense. However, in a healthcare system increasingly dependent on evidence-based medical management and standardised protocols and guidelines, a dependable screening system that provides accurate prognostic information can only improve our overall management of the older patient. The development of a consistent and practical system would facilitate communication with patients and their relatives, and could help to reduce the subjectivity often associated with the designation of the label 'frail' to older individuals. A system with robust predictive abilities for adverse outcomes would lend much needed evidence-based support to the frequent use of frailty in making treatment decisions. It may also allow the dissemination of important skills to many other health

professionals who do not have a background in gerontology or geriatric medicine but are likely to have increasing levels of contact with older people as the population ages.

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