Frailty in elderly people

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Lancet 2013; 381: 752–62

Published Online
February 8, 2013
http://dx.doi.org/10.1016/S0140-6736(12)62167-9

This online publication has been corrected. The corrected version first appeared at thelancet.com on October 18, 2013

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Frailty is the most problematic expression of population ageing. It is a state of vulnerability to poor resolution of homoeostasis after a stressor event and is a consequence of cumulative decline in many physiological systems during a lifetime. This cumulative decline depletes homoeostatic reserves until minor stressor events trigger disproportionate changes in health status. In landmark studies, investigators have developed valid models of frailty and these models have allowed epidemiological investigations that show the association between frailty and adverse health outcomes. We need to develop more efficient methods to detect frailty and measure its severity in routine clinical practice, especially methods that are useful for primary care. Such progress would greatly inform the appropriate selection of elderly people for invasive procedures or drug treatments and would be the basis for a shift in the care of frail elderly people towards more appropriate goal-directed care.

Introduction

Population ageing is accelerating rapidly worldwide, from 461 million people older than 65 years in 2004 to an estimated 2 billion people by 2050,[1,2] which has profound implications for the planning and delivery of health and social care. The most problematic expression of population ageing is the clinical condition of frailty. Frailty develops as a consequence of age-related decline in many physiological systems, which collectively results in vulnerability to sudden health status changes triggered by minor stressor events. Between a quarter and half of people older than 85 years are estimated to be frail, and these people have a substantially increased risk of falls, disability, long-term care, and death.[3,4] However, up to three-quarters of people older than 85 years might not be frail, which raises questions about how frailty develops, how it might be prevented, and how it can be detected reliably.

Definition and presentations

Frailty is a state of increased vulnerability to poor resolution of homoeostasis after a stressor event, which increases the risk of adverse outcomes, including falls, delirium, and disability.[3,5,6] Frailty is a long-established clinical expression that implies concern about an elderly person's vulnerability and outlook. Figure 1 shows this state of vulnerability diagrammatically; an apparently small insult (eg, a new drug, minor infection, or minor surgery) results in a striking and disproportionate change in health state—ie, from independent to dependent, mobile to immobile, postural stability to proneness to falling, or lucid to delirious. The dependency oscillations seen in frail elderly people have been referred to as unstable disability in view of the often notable changes in functional ability that are familiar to practitioners who work with such patients.[7] Panel 1 shows the common clinical presentations of frailty.

Search strategy and selection criteria

We developed a structured search strategy with the assistance of an expert librarian at the University of Leeds, UK. We searched the Cochrane Library, CINAHL, Medline, Embase, PsycINFO, and PEDro; all searches were for 2000–12. We used the search terms "frailty", "frail elderly", or "sarcopenia" with the terms "aged" or "aged, 80 and over" or "ageing/genetics" or "longevity" or "centenarian" or "oldest old" or "very old" or "very elderly". We did a further search in which the results were limited to systematic reviews of interventions for the prevention and treatment of frailty. Additional papers were identified from personal libraries and the reference lists of retrieved articles.

Pathophysiology

Frailty is a disorder of several inter-related physiological systems (figure 2). A gradual decrease in physiological reserve occurs with ageing but, in frailty, this decrease is accelerated and homoeostatic mechanisms start to fail.[8,9] Therefore, an important perspective for frailty is to consider how the complex mechanisms of ageing promote cumulative decline in several physiological systems, the subsequent depletion of homoeostatic reserve, and vulnerability to disproportionate changes in health status after minor stressor events. These complex ageing mechanisms are determined by underlying genetic and environmental factors[10] in combination with epigenetic mechanisms, which regulate the differential expression of genes in cells and could be especially important in ageing.[11,12]

Pathway

Ageing is believed to result from the lifelong accumulation of molecular and cellular damage caused by many mechanisms that are regulated by a complex maintenance and repair network.[10] The precise amount of cellular damage needed to cause impaired organ physiology is uncertain, but, importantly, many organ systems show notable redundancy, which provides the physiological reserve necessary to compensate for age-related and disease-related changes.[13] For example, the brain and skeletal muscle contain more neurons and myocytes, respectively, than are needed for survival.[13] Therefore, a key question is whether a crucial threshold of age-related cumulative decline, beyond which frailty becomes evident, exists in many physiological systems.

In a 2009 cross-sectional study of 1002 women, investigators used 12 measures to assess cumulative physiological dysfunction in six different systems (haematological, inflammatory, hormonal, adiposity, neuromuscular, and micronutrient) and reported a non-linear relation between the number of abnormal systems and frailty, independent of age and comorbidity.[14] Abnormal results in three or more systems were a strong predictor of frailty. Importantly, the number of abnormal systems was more predictive of frailty than were abnormalities in any particular system. This finding supports the idea that when physiological decline reaches an aggregate crucial level, frailty becomes evident.[14]

The brain, endocrine system, immune system, and skeletal muscle are intrinsically inter-related and are the organ systems that are best studied in the development of frailty.[5] Notably, frailty has also been associated with loss of physiological reserve in the respiratory[15], cardiovascular,[16] renal,[17] and haemopoietic and clotting systems,[18,19] and nutritional status can also be a mediating factor.[3,20–22]

The frail brain

Ageing is associated with characteristic structural and physiological changes in the brain. The loss of individual neurons in most cortical regions is low,[23] but neurons with high metabolic demands, such as the hippocampal pyramidal neurons, could be affected disproportionally by changes in synaptic function, protein transport, and mitochondrial function.[23] The hippocampus has been identified as an important mediator in the pathophysiology of cognitive decline and Alzheimer's dementia[24] and is a key component of the stress response, since it senses increased glucocorticoid values and relays information to the hypothalamus via a negative-feedback loop.[25]

The ageing brain is also characterised by structural and functional changes to microglial cells, which are the resident immune cell population of the CNS and are the CNS equivalent of macrophages. They are activated by brain injury and local and systemic inflammation and become primed (hyper-responsive) to small stimuli with ageing, which can potentially cause damage and neuronal death.[26–28] Primed microglia are postulated to have an important role in the pathophysiology of delirium.[28,29] In a prospective cohort study of 273 elderly patients admitted to hospital, investigators identified that frailty is associated with both increased risk of the development of delirium (odds ratio [OR] 8·5, 95% CI 4·8–14·8) and subsequent reduced survival (median survival in frail elderly patients with delirium 88 days, 95% CI 5–171; median survival in non-frail elderly patients with delirium 359 days, 95% CI 118–600).[6] This finding suggests that the combination of delirium and frailty identifies elderly people at especially high risk of adverse outcomes.

Accumulating evidence from observational studies supports a temporal association between frailty, cognitive impairment, and dementia. In a prospective cohort study (n=750) of elderly people without cognitive impairment at baseline, the investigators reported that frailty was associated with an increased risk of the development of mild cognitive impairment during 12 years of follow-up (hazard ratio [HR] 1·63, 95% CI 1·27–2·08).[30] Increasing frailty was also associated with a faster rate of cognitive decline. An independent association between frailty and dementia has been reported in two large prospective cohort studies.[31,32]

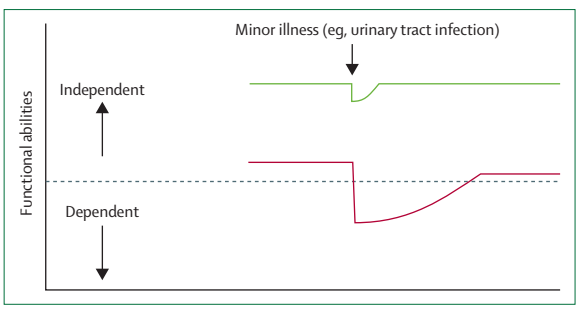

Figure 1: **Vulnerability of frail elderly people to a sudden change in health status after a minor illness**
The green line represents a fit elderly individual who, after a minor stressor event such as an infection, has a small deterioration in function and then returns to homoeostasis. The red line represents a frail elderly individual who, after a similar stressor event, undergoes a larger deterioration, which may manifest as functional dependency, and who does not return to baseline homoeostasis. The horizontal dashed line represents the cutoff between dependent and independent.

The frail endocrine system

The brain and endocrine system are linked intrinsically through the hypothalamo-pituitary axis, which controls metabolism and energy use through the signalling action

Panel 1: **Frequent clinical presentations of frailty**

Non-specific
Extreme fatigue, unexplained weight loss, and frequent infections.

Falls
Balance and gait impairment are major features of frailty, and are important risk factors for falls. A so-called hot fall is related to a minor illness that reduces postural balance below a crucial threshold necessary to maintain gait integrity. Spontaneous falls occur in more severe frailty when vital postural systems (vision, balance, and strength) are no longer consistent with safe navigation through undemanding environments. Spontaneous falls are typically repeated and are closely associated with the psychological reaction of fear of further falls that causes the patient to develop severely impaired mobility.

Delirium
Delirium (sometimes called acute confusion) is characterised by the rapid onset of fluctuating confusion and impaired awareness. Delirium is related to reduced integrity of brain function and is independently associated with adverse outcomes. Roughly 30% of elderly people admitted to hospital will develop delirium, and the point prevalence estimate for delirium for patients in long-term care is 15%.

Fluctuating disability
Fluctuating disability is day-to-day instability, resulting in patients with "good", independent days, and "bad" days on which (professional) care is often needed.

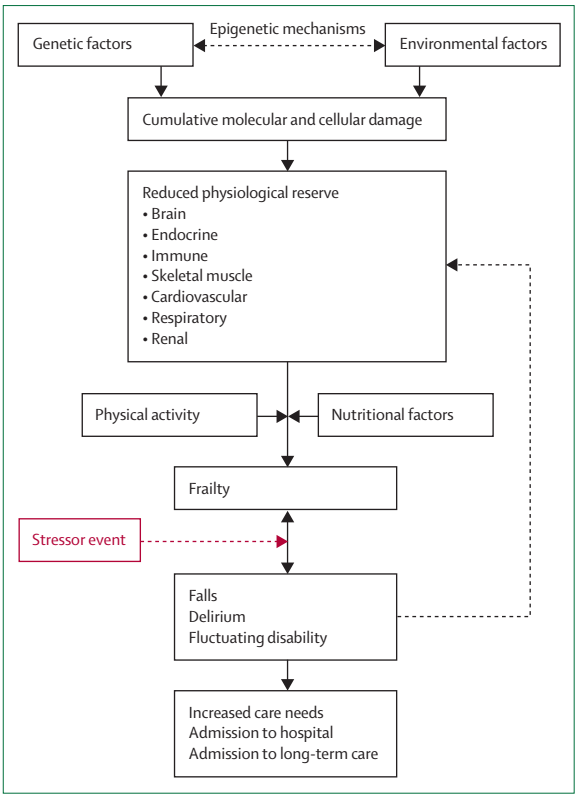

Figure 2: **Schematic representation of the pathophysiology of frailty**

of a series of homoeostatic hormones.[23] During ageing, production of three major circulating hormones decreases. First, a lessening of growth hormone synthesis by the pituitary gland causes a reduction in production of insulin-like growth factor-1 (IGF-I) by the liver and other organs. IGFs are a family of small peptides that enhance anabolic activity in many cells. Promotion of neuronal plasticity and increased skeletal muscle strength are especially important effects.[33] Second, reduced oestradiol and testosterone increase release of luteinising hormone and follicle-stimulating hormone. Third, activity of the adrenocortical cells that produce the major sex steroid precursor dehydroepiandrosterone and dehydroepiandrosterone sulphate decreases, often alongside a gradual rise in cortisol release.[34,35]

Changes to IGF signalling; sex hormone, dehydroepiandrosterone, or dehydroepiandrosterone sulphate production; and cortisol secretion are regarded as important in frailty, although the exact associations remain uncertain and need further investigation. In one cross-sectional study, investigators reported substantially lower concentrations of IGF-I in people identified as frail compared with age-matched controls.[36] However, if IGF-I has a key causal role in frailty, an association between IGF-I and mortality might be anticipated, but inconsistent associations have been reported in a series of observational studies.[37–41] Furthermore, although the muscles of frail elderly people seem to retain the capability to respond to IGF-I,[42] trials of IGF-I supplementation in elderly people have not shown a benefit.[43]

Although an association between testosterone concentration and frailty has been identified,[44] testosterone might be a sensitive marker, rather than a pathological mechanism.[45] In a cross-sectional study, investigators reported an association between dehydroepiandrosterone sulphate and frailty, but the effect of comorbid conditions could not be excluded confidently.[46] A U-shaped association between dehydroepiandrosterone sulphate and mortality has been reported in disabled elderly women.[47]

In one cross sectional study (n=214), investigators reported that frailty was independently associated with chronically raised diurnal cortisol concentrations.[48] A link between chronically high cortisol and frailty is plausible, since persistently high values of cortisol are associated with increased catabolism, leading to loss of muscle mass, anorexia, weight loss, and reduced energy expenditure, all of which are key clinical features of frailty.[49]

The frail immune system

The ageing immune system is characterised by a reduction in stem cells, changes in T-lymphocyte production, blunting of the B-cell-controlled antibody response, and reduced phagocytic activity of neutrophils, macrophages, and natural killer cells.[50,51] This senescent immune system might function adequately in the quiescent state but fails to respond appropriately to the stress of acute inflammation.[50] Evidence suggests that inflammation has a major role in the pathophysiology of frailty through an abnormal, low-grade inflammatory response that is hyper-responsive to stimuli and that persists for a long period after removal of the initial inflammatory stimulus.[19,52–57] Several inflammatory cytokines have been independently associated with frailty, including interleukin 6, C-reactive protein, tumour necrosis factor-α (TNFα), and CXC chemokine ligand-10, a potent proinflammatory mediator.[52,54–58] However, high concentrations of C-reactive protein in very old people have also been associated with good memory function.[59] Advanced glycation end products are a group of molecules produced by the glycation of proteins, lipids, and nucleic acid that can cause widespread cellular damage by upregulation of inflammation.[60] They have been associated with ageing, chronic disease, and mortality, and could have an important role in frailty.[60]

Inflammation is associated with anorexia and catabolism of skeletal muscle and adipose tissue, which could contribute to the nutritional compromise, muscle weakness, and weight loss that characterise frailty.[41,61,62] Furthermore, frailty is associated with an impaired antibody response to influenza[63] and pneumococcal vaccine,[64] which helps to explain the observation that vaccination in elderly people is associated with only modest clinical effectiveness.[65]

Frail skeletal muscle (sarcopenia)

Sarcopenia has been defined as progressive loss of skeletal muscle mass, strength, and power, and is regarded as a key component of frailty.[66,67] Loss of muscle strength and power could be more important than changes in muscle mass.[68] Under normal circumstances, muscle homoeostasis is maintained in a delicate balance between new muscle cell formation, hypertrophy, and protein loss. This balance is coordinated by the brain, endocrine system, and immune system, and is affected by nutritional factors and amount of physical activity. The adverse neurological, endocrine, and immune components of frailty have the potential to disrupt this delicate homoeostatic balance and accelerate the development of sarcopenia. Inflammatory cytokines, including interleukin 6 and TNFα, activate muscle breakdown to generate aminoacids for energy and cleave antigenic peptides.[69] This fundamentally protective response could become abnormal in the presence of an overactive, insufficiently regulated inflammatory response that characterises frailty, leading to loss of muscle mass and strength, with an associated reduction in functional ability.

Frailty models

Reliable frailty models should be assessed by their success in predicting both natural history and response to therapeutic interventions and should be underpinned by biological principles of causality.[70] The two main emerging models of frailty are the phenotype model[3] and the cumulative deficit model, which forms the basis of the Canadian Study of Health and Aging (CSHA) frailty index.[71]

Phenotype model

In a landmark study, Fried and colleagues[3] did a secondary analysis of data obtained from a prospective cohort study (the Cardiovascular Health Study [CHS][72]) of 5210 men and women aged 65 years and older. A frailty phenotype was established with five variables: unintentional weight loss, self-reported exhaustion, low energy expenditure, slow gait speed, and weak grip strength (panel 2). The lowest quintile values were used to define absence or presence of these variables. People with Parkinson's disease, previous stroke, cognitive impairment, or depression were excluded. Those with three or more of the five factors were judged to be frail, those with one or two factors as pre-frail, and those with no factors as not frail or robust elderly people. This population was categorised as 7% frail, 47% pre-frail, and 46% not frail. Follow-up assessments were undertaken at 3 and 5 years, with the outcomes of falls, mobility and function, hospitalisation, and death. People categorised as frail were reported to have more adverse outcomes than had those categorised as not frail, with the pre-frail group having outcomes intermediate between the two. Reported mortality at 7 years was 12%, 23%, and 43% for the not frail, pre-frail, and frail groups, respectively. The 7-year adjusted hazard ratio for mortality was 1·63 (95% CI 1·27–2·08) for the frail group.[3]

Panel 2: **The five phenotype model indicators of frailty and their associated measures**

Weight loss
Self-reported weight loss of more than 4·5 kg or recorded weight loss of ≥5% per year

Self-reported exhaustion
Self-reported exhaustion on US Center for Epidemiological Studies depression scale[73] (3–4 days per week or most of the time)

Low energy expenditure
Energy expenditure <383 kcal/week (men) or <270 kcal/week (women)

Slow gait speed
Standardised cutoff times to walk 4·57 m, stratified by sex and height

Weak grip strength
Grip strength, stratified by sex and body-mass index

This work is important because it suggests that a frailty phenotype can be defined and might be a basis for detection of frailty in routine care. However, how the variables can be reliably translated into clinical practice is not clear. Additionally, the five factors were fortuitously available and selected from a prospective cohort study that was not designed to investigate frailty. Other potentially important factors such as cognitive impairment, a highly prevalent condition associated with functional decline and disability, were not included as part of the phenotype.[74] Nonetheless, despite these criticisms, the general approach of clusters of variables to define a frailty phenotype has been independently validated.[75,76]

Cumulative deficit model

The frailty index was developed as part of the CSHA study,[71] which was a 5-year prospective cohort study (n=10 263) designed to investigate the epidemiology and burdens of dementia in elderly people in Canada (mean age 82 years). 92 baseline variables of symptoms (eg, low mood), signs (eg, tremor), and abnormal laboratory values, disease states, and disabilities (collectively referred to as deficits), were used to define frailty.[77] The frailty index was a simple calculation of the presence or absence of each variable as a proportion of the total (eg, 20 deficits present, of a possible 92 gives a frailty index of 20/92=0·22). Thus, frailty is defined as the cumulative effect of individual deficits—"the more individuals have wrong with them, the more likely they are to be frail".[78]

The statistical distribution of the frailty index (a γ-distribution) was consistent with a probability model that typically describes systems with in-built redundancy. This is an attractive mathematical model for frailty because it implies that the frailty index has properties that fully support the idea of reduced homoeostatic reserve. Thus, although every individual deficit carries no obvious or imminent threat of mortality (eg, hearing impairment), the deficits contribute cumulatively to an increased risk of

death. This idea is consistent with the increased vulnerability and threat of impending homoeostatic failure that is essential to the notion of frailty. Importantly, the cumulative deficit model expresses the theory of a gradation of frailty with progressive accumulation of deficits, each of which has an equal weight in mathematical modelling of the frailty index. This model is clinically attractive because it allows frailty to be regarded as gradable, rather than present or absent. Moreover, the number of equally weighted deficits, as a measure of accumulated vulnerability, rather than particular clusters of deficits, is related to adverse outcomes.[79] Importantly, a value of 0·67 seems to identify an amount of frailty beyond which further deficit accumulation is not sustainable and death is likely.[80] This value might represent the warning sign of being close to the so-called tipping point that characterises a complex system on the brink of collapse.[81]

Subsequent work has shown that the rather daunting initial list of 92 variables can be reduced to the more manageable number of about 30, without loss of predictive validity.[4] The criteria for variable inclusion into the frailty index are: biologically sensible, accumulation with age, and saturation not too early.[82] These factors make the index very adaptable as a conceptual approach.

Several studies that used data from the CSHA showed that the frailty index was strongly related to the risk of death and institutionalisation.[4,79] The 10-year adjusted hazard ratio for mortality was 1·57 (95% CI 1·41–1·74) for the frail group,[4] which was a statistically similar estimate to the phenotype model.[3] Mortality has previously been demonstrated to be exponentially related to the value of the index.[83]

Comparison of phenotype and cumulative deficit models

The phenotype and cumulative deficit models show overlap in their identification of frailty[84] and have notable statistical convergence.[85] This overlap is especially important because the demonstration of convergent predictive validity for adverse health outcomes between two conceptually different models of frailty could help to advance the debate about whether frailty is best defined as a syndrome or a state by providing support for recognition of the condition as a unified construct.

The continuous frailty index showed greater discriminatory ability for people with moderate and severe frailty than that shown by the categorical phenotype model—a finding that has been validated independently.[86] Use of continuous models could help more accurate identification of frail elderly people for interventions to improve outcomes, and a 2011 study re-scaled the phenotype model to make it more continuous, to provide improved discriminatory capacity.[87]

Epidemiology

Evidence for the importance of frailty as a leading cause of death in elderly people comes from a 10-year prospective cohort study of community-dwelling elderly people (n=754).[88] Cause of death was based on clinical home-based assessments done at 18-month intervals and on death certificates. The most common disorder leading to death was frailty (27·9%); the others were organ failure (21·4%), cancer (19·3%), dementia (13·8%), and other causes (14·9%).

Prevalence

Investigators assessed the prevalence of frailty in a recent systematic review.[89] 21 community-based cohort studies of 61 500 elderly people were identified. The operational definitions for frailty and the inclusion or exclusion criteria varied between the studies, which largely explained the substantial variation in reported frailty prevalence rates of 4·0–59·1%. When the reported rates were restricted to the studies that used the phenotype model, the weighted average prevalence rate was 9·9% (95% CI 9·6–10·2) for frailty and 44·2% (44·2–44·7) for pre-frailty. In 11 studies, frailty was statistically more prevalent in women (9·6%, 9·2–10·0) than in men (5·2%; 4·9–5·5). Frailty increased steadily with age: 65–69 years 4%; 70–74 years 7%; 75–79 years 9% 80–84 years 16%; older than 85 years 26%. Rates seem to be higher in studies that used the graded frailty index, which would categorise as frail some people whose increased risk is captured in the pre-frail category of the phenotype model.[4]

Most frailty models were developed in white populations, and the prevalence of frailty might be higher in people living in southern Europe[90] and in elderly Hispanic and African–American people;[3,91] therefore, different cutoffs for frailty might be necessary in different populations.

Outcomes

The table shows the associations between frailty and adverse outcomes reported in four large prospective cohort studies,[3,92–94] with the worst outcomes in the most frail people. Frailty is a dynamic process[95] but transition to a level of worse frailty is more common than is improvement in frailty, and the development of frailty often leads to a spiral of decline of increasing frailty and higher risk of worsening disability, falls, admission to hospital, and death.[3] Risk of admission to long-term care is also higher in those with mild frailty (adjusted risk ratio 2·54, 95% CI 1·67–3·86) and moderate or severe frailty (risk ratio 2·60, 1·36–4·96)[96] than in non-frail individuals.

The CHS study population[3] was used to investigate the overlap between frailty, comorbidity, and disability.[97] Frailty and comorbidity (defined as two or more of the following nine diseases: myocardial infarction, angina, congestive heart failure, claudication, arthritis, cancer, diabetes, hypertension, and chronic obstructive pulmonary disease) was present in 46·2% of the population; frailty, and disability (defined as the presence of restriction in at least one activity of daily living) was

present in 5·7%; and the combination of frailty, disability, and comorbidity in 21·5% of the study group. Importantly, frailty was present without comorbidity or disability in 26·6% of the study group, which provides support for frailty as an independent factor that is distinct from comorbidity and disability. However, more recent work[98] suggests that the overlap is more frequent and increases with greater frailty. The contribution of subclinical disease might be especially important, and physiological measurements to identify elderly people at risk of frailty could help to guide the development of early preventive interventions.[87]

Instrumentation

The demonstration of large between-group differences for people who are frail compared with those who are not frail[4] is important because it leads clinicians away from judgments based on chronological age towards the idea of frailty. Researchers and clinicians, therefore, need simple, valid, accurate, and reliable methods to detect frailty. Monitoring outcomes of interventions in frail people also needs methods that are sensitive to change.[99]

Standardised questionnaires to identify frailty

In a systematic review with broad study selection criteria, investigators identified 20 candidate methods for the identification of frailty.[100] However, most studies included described either primary research to investigate models of frailty or focused on functional restriction, which, although an important manifestation of frailty, is insufficient for reliable identification of the disorder. The frail elderly functional questionnaire (19 items)[101] was identified as a potential outcome measure for frailty intervention studies because it is suitable for use by telephone or proxy, is valid and reliable,[101] and is sensitive to change.[102]

The Groningen frailty indicator[103] and the Tilburg frailty indicator[104] are straightforward[105] questionnaire-based approaches to detect people with frailty. Aspects of validity have been investigated but, importantly, studies of diagnostic accuracy against well-defined community populations of elderly people are not yet available. Moreover, both these questionnaires need new information to be gathered. The option to use existing patient data from primary care records to construct a frailty index consistent with the cumulative deficit model needs to be investigated.

Assessments to identify frailty

The timed-up-and-go test, which is a straightforward standardised measure of mobility that needs a stop watch,[106] and hand grip strength test that needs a hand-held dynamometer,[107] have been investigated as potential single assessments to detect frailty. Pulmonary function is associated with frailty[15] and could be useful as a simple detection test. However, the diagnostic accuracy of these assessments has not been confirmed. A systematic review identified nine prospective studies (n=34485) investigating slow gait speed.[108] Slow gait speed successfully characterised the subgroup of elderly people who had adverse outcomes, and had similar accuracy to complex multivariate models that included itemisation of chronic diseases.

The Edmonton Frail Scale is a multidimensional assessment instrument that includes the timed-up-and-go test and a test for cognitive impairment.[109] The test is quick (it takes less than 5 min) and is valid, reliable, and feasible for routine use by non-geriatricians, but its diagnostic accuracy has not been investigated.

Various International Resident Assessment Instrument (interRAI) devices are widely used internationally to standardise the assessment of elderly people. Nine items

	Year	Country	Participants (n)	Length of follow-up (years)	Falls (HR*/OR† [95% CI])		Worsening disability (HR*/OR† [95% CI])		Hospitalisation (HR*/OR† [95% CI])		Care home admission (HR*/OR† [95% CI])		Mortality (HR*/OR† [95% CI])	
					Intermediate frailty	Severe frailty	Intermediate frailty	Severe frailty	Intermediate frailty	Severe frailty	Intermediate frailty	Severe frailty	Intermediate frailty	Severe frailty
Cardiovascular Health Study (CHS)[3]	2001	USA	5317	7	1·12* (1·00–1·26)	1·23* (0·99–1·54)	1·55* (1·38–1·75)	1·79* (1·47–2·17)	1·11* (1·03–1·19)	1·27*, (1·11–1·46)	NA	NA	1·32* (1·13–1·55)	1·63* (1·27–2·08)
Canadian Study of Health and Aging (CSHA)[92]	2004	Canada	9008	5	NA	NA	NA	NA	NA	NA	2·54 † (1·67–3·86)	2·60† (1·36–4·96)	2·54† (1·92–3·37)	3·69† (2·26–6·02)
Women's Health and Aging Study (WHAS)[93]	2006	USA	1438	3	0·92* (0·63–1·64)	1·18* (0·63–2·19)	NA	NA	0·99* (0·67–1·47)	0·67* (0·33–1·35)	5·16* (0·81–32·79)	23·98* (4·45–129·2)	3·50* (1·91–6·39)	6·03* (3·00–12·08)
Study of Osteoporotic Fractures (SOF)[94]	2008	USA	6701	4·5	1·23† (1·02–1·48)	2·44† (1·95–3·04)	1·89†, (1·66–2·14)	2·79† (2·31–3·37)	NA	NA	NA	NA	1·54† (1·40–1·69)	2·75* (2·46–3·07)

HR=hazard ratio. NA=not available. OR=odds ratio. *Hazard ratio. †Odds ratio. The comparator for hazard ratios and odds ratios is people who are not frail.

Table: **Covariate-adjusted associations between frailty and adverse outcomes (falls, disability, hospitalisation, care home admission, and mortality) from four large prospective cohort studies**

that are embedded in many of the instruments can be extracted and form the changes in health, end-stage disease and signs and symptoms scale. Although not explicitly a frailty measure,[110] this scale has proved a strong predictor of mortality,[111] and further validation studies are in progress.

Comprehensive geriatric assessment has become the internationally established method to assess elderly people in clinical practice. It is a process of specialist elderly care delivered by a multidisciplinary team to establish an elderly person's medical, psychological and functional capability, so that a plan for treatment and follow-up can be developed.[112] In hospitals, the process of comprehensive geriatric assessment is usually led by a geriatrician alongside specialist elderly care nurses, physiotherapists, occupational therapists, and social workers. In the community, the process can be led by either a community-based geriatrician or a primary care physician with specialist expertise in the medical assessment of elderly people alongside a similar multidisciplinary team. The process, provided it is closely linked to interventions, is associated with superior outcomes[113] and has been used successfully outside elderly care medicine.[114,115] Two studies embedded in the CSHA study[71] programme were used to investigate the predictive validity of comprehensive geriatric assessment as undertaken by more than 70 clinicians.[71,116] In both studies, the clinically obtained comprehensive geriatric assessment results were strongly associated with the research standard CSHA frailty index and were predictive of death and need for institutional care. These studies are the first objective confirmation that comprehensive geriatric assessment is sensitive to the reliable detection of degrees of frailty. This assessment is the gold standard to detect frailty and should be used more widely. The practical limitation of the assessment is the time and expertise needed.

Interventions

Reduction of the prevalence or severity of frailty is likely to have large benefits for individuals, their families, and society. Several approaches have been investigated in clinical trials. Frail elderly people receiving inpatient comprehensive geriatric assessment on specialist elderly care wards are more likely to return home, are less likely to have cognitive or functional decline, and have lower in-hospital mortality rates than do those who are admitted to a general medical ward setting.[113] Complex interventions based on comprehensive geriatric assessment delivered to elderly people in the community can increase the likelihood of continuing to live at home, mainly through a reduced need for care-home admission and fewer falls,[117,118] but the most frail patients seem to receive the least benefit.[117]

Exercise has physiological effects on the brain, endocrine system, immune system, and skeletal muscle.[42,119–122] Three systematic reviews of home-based and group-based exercise interventions for frail elderly people showed that exercise can improve outcomes of mobility and functional ability.[123–125] A meta-analysis identified that the effect sizes are likely to be small to moderate (pooled standardised mean difference for mobility 0·18, 95% CI 0·05–0·30; for functional ability 0·27, 0·08–0·46).[123] The most effective intensity (duration and frequency) of exercise intervention is uncertain, but adherence was characteristically high across a range of interventions.

In most trials, investigators did not use a validated measure or established model to record frailty at baseline or follow-up but, when results were stratified by frailty, the most frail patients seemed to gain the least benefit.[126] However, this finding contradicts the results from a Cochrane review[127] that incorporated 49 randomised controlled trials of exercise interventions for long-term care residents (a group of elderly people who are likely to be very frail) and concluded that interventions, particularly those with strength and balance training, can successfully increase muscle strength and functional abilities. Therefore, even small gains in strength of long-term care residents might translate into important functional gains.

Nutritional interventions might be able to address the impaired nutrition and weight loss of frailty. However, evidence is scarce. One randomised controlled trial that investigated the effects of exercise and nutritional supplementation in 100 frail elderly people in long-term care reported that such supplementation had no effect on muscle strength, gait speed, stair climbing, or physical activity.[128] In a Cochrane review of nutritional interventions for prevention and treatment of pressure ulcers in elderly patients in hospital (a group who are likely to be frail), investigators reported that firm conclusions could not be made because of the absence of trials of high methodological quality.[129]

Few pharmacological agents have been investigated in frailty. Angiotensin-converting enzyme inhibitors have proved to improve the structure and biochemical function of skeletal muscle[130] and evidence suggests that these inhibitors could halt or slow the decrease in muscle strength in old age[131] and improve exercise capacity and quality of life.[132] Testosterone improves muscle strength but also increases adverse cardiovascular and respiratory outcomes.[133] IGFs have direct effects on skeletal muscle[5] but IGF-I does not seem to improve muscle strength or bone density in healthy elderly women.[134] Low concentrations of vitamin D have been associated with frailty[135] and this vitamin has improved neuromuscular function.[136] Although vitamin D prescription for elderly people who are deficient in the vitamin might reduce the number of falls,[137] and the combination of calcium and vitamin D supplements for elderly people in long-term care can reduce fractures,[138] the general use of vitamin D as treatment for frailty is still controversial.[43] The use of pharmacological agents for the prevention and treatment of frailty is an important topic for future research.

Conclusions

Modern health-care systems are mostly organised around single-system illnesses.[139] However, many elderly people have multiorgan problems. Frailty is a practical, unifying notion in the care of elderly patients that directs attention away from organ-specific diagnoses towards a more holistic viewpoint of the patient and their predicament. It is a state of vulnerability to poor resolution of homoeostasis after a stressor event and is strongly associated with adverse outcomes. Distinction of frail elderly people from those who are not frail should therefore be an essential part of assessment in any health-care encounter that might result in an invasive procedure or potentially harmful medication. It allows practitioners to weigh up benefits and risks, and for patients to make properly informed choices. Failure to detect frailty potentially exposes patients to interventions from which they might not benefit and indeed could be harmed. Conversely, exclusion of physiologically well (non-frail) elderly people merely on the basis of age is unacceptable.

The most evidence-based process to detect and grade frailty for severity is comprehensive geriatric assessment. However, this assessment is a resource-intensive process and we urgently need to find equally reliable but more efficient and responsive methods for routine care. The necessary requirements of future frailty instruments, including the important issue of clinical sensibility, have been defined.[140] This aim might be achieved by development and further validation of currently available frailty-specific multidimensional questionnaires, but the usefulness of existing clinical datasets, especially in primary care, is attractive. This approach would be underpinned by the cumulative deficit frailty model and implies that frailty could be both positively identified and graded for severity. Such a simple method would help essential research to gain a deeper insight into the complex mechanisms of frailty and aid the development and evaluation of interventions to improve outcomes. It would also have considerable clinical merit because it would be the basis for a shift in the care of frail elderly people towards a more appropriate goal-directed care in which individually framed clinical outcomes that span organ systems are negotiated with patients.[141]

Contributors

AC and JY initiated and coordinated the Seminar. All authors contributed to the writing of the paper.

Conflicts of interest

KR has applied to various Canadian government schemes to commercialise a new version of the Frailty Index based on a comprehensive geriatric assessment and a new screening method, adapted from the Clinical Frailty Scale of the Canadian Study of Health and Aging. To do this, with colleagues he has formed a company called Videx Canada. He has not asserted copyright on any frailty measure discussed here. The other authors declare that they have no conflicts of interest.

Acknowledgments

We thank Deirdre Andre, research support librarian at the University of Leeds (Leeds, UK) for her assistance in the creation and running of the search strategy for this Seminar.

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