Frailty 1

Frailty: implications for clinical practice and public health

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Frailty is an emerging global health burden, with major implications for clinical practice and public health. The prevalence of frailty is expected to rise alongside rapid growth in the ageing population. The course of frailty is characterised by a decline in functioning across multiple physiological systems, accompanied by an increased vulnerability to stressors. Having frailty places a person at increased risk of adverse outcomes, including falls, hospitalisation, and mortality. Studies have shown a clear pattern of increased health-care costs and use associated with frailty. All older adults are at risk of developing frailty, although risk levels are substantially higher among those with comorbidities, low socioeconomic position, poor diet, and sedentary lifestyles. Lifestyle and clinical risk factors are potentially modifiable by specific interventions and preventive actions. The concept of frailty is increasingly being used in primary, acute, and specialist care. However, despite efforts over the past three decades, agreement on a standard instrument to identify frailty has not yet been achieved. In this Series paper, we provide an overview of the global impact and burden of frailty, the usefulness of the frailty concept in clinical practice, potential targets for frailty prevention, and directions that need to be explored in the future.

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This is the first in a **Series** of two papers about frailty

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Introduction

The condition of frailty is gaining international attention as the population of older adults rises globally. Frailty is characterised by a decline in functioning across multiple physiological systems, accompanied by an increased vulnerability to stressors.[1,2] It is associated with increased mortality, hospitalisation, falls, and admission to long-term care.[1,2] There is also much individual burden for a person living with frailty, including impaired quality of life and loneliness.[3,4]

The concept of frailty is constantly evolving in the literature, and there is a progressive debate about how to define the condition.[5] This debate aside, three important factors have remained consistent over the past decades in the conceptualisation of frailty.[6] First, frailty is multidimensional, with physical and psychosocial factors playing a part in its development. Second, although its prevalence does increase with age, frailty is an extreme consequence of the normal ageing process. Third, frailty is dynamic, which means that an individual can fluctuate between states of severity of frailty.[6]

Frailty is potentially preventable, up to a probable point of no return when it becomes a pre-death phase. Therefore, strategies to prevent and slow the progression of frailty are paramount.[7] To identify which people would benefit from such strategies, an expansive body of research has been devoted to developing tools to objectively quantify frailty, with persisting disagreements about the conceptual framework to be measured. In 2001, Fried and colleagues described the clinical presentation of frailty in terms of a physical phenotype, the clinical presentation of a definable biological syndrome.[1] According to this frailty phenotype, an older adult is diagnosable with frailty if they score positive for three or more symptoms or signs out of five criteria. Also in 2001, Rockwood and Mitnitski introduced their frailty index, which is based on an accumulation of age-related deficits.[8,9] In their model, frailty is a continuous score summing signs, symptoms, disabilities, and diseases. The characteristics of these two concepts,

Search strategy and selection criteria

We searched PubMed for articles published in English up to July 4, 2019, with the search terms "frail elderly", "frailty", "sarcopenia", "frailty index", and "frailty phenotype". Additionally, we sought publications from the reference lists of identified papers and from our cumulative literature archives. Where possible, we gave priority to systematic reviews and studies published in the past 5 years.

Key messages

- The condition of frailty is associated with adverse outcomes and increased health-care costs
- Frailty occurs in adults at any age, but it is more prevalent in older adults
- The global impact of frailty is expected to increase due to population ageing, particularly in low-income and middle-income countries
- Risk factors for the onset of frailty span across a wide range of sociodemographic, clinical, lifestyle-related, and biological factors
- Considering the degree of frailty of a person in clinical practice could result in more patient-centred care and avoidance of harm in primary, secondary, and tertiary prevention of disease
- Although the concept of frailty is increasingly being used in primary, acute, and specialist care, the translation from research to clinical practice remains a challenge for the coming years; specificity and standardisation of frailty measures is essential for progress
- Longitudinal research on trends and trajectories is a high priority for the frailty research agenda, as well as randomised controlled trials focused on prevention or treatment of frailty
- Using a life-course approach might increase our understanding of how frailty and its risk factors develop in earlier life stages, and could contribute to the development of public health strategies for frailty prevention

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which currently dominate the field, are listed in panel 1. Although the concepts differ, there is some common ground, as shown by overlap in determinants and identification of frailty.[2]

There is also controversy over whether frailty should encompass functional limitations, or whether it should be viewed as a pre-disability state. In addition, increased attention has been given to frailty subtypes, such as social frailty, nutritional frailty, and cognitive frailty.[11] However, evidence for these subtypes is still limited. Another construct that has recently been proposed is the concept of intrinsic capacity, which emphasises the physical and mental capacities of an individual, instead of an approach focused on losses as captured by traditional frailty measures.[12] The concept is endorsed by WHO but has not been empirically validated.

This is the first of a two paper Series on frailty, based on the latest evidence. In this paper, we describe the implications of frailty for clinical practice and public health. We will focus on frailty in older adults, but frailty can occur in adults at any age—especially in those with chronic illnesses. We provide an overview of the global impact and burden of frailty, including that in low-income and middle-income countries (LMICs), the usefulness of the frailty concept in daily practice, potential targets for frailty prevention, the importance of taking a life-course perspective, and the directions that need to be explored in the future. The description of preclinical models will not be covered in the present paper. The management of frailty, including interventions, is presented in the second paper.

***Panel 1*: Two main frailty assessment instruments**

Frailty phenotype

Five criteria:

- Weakness: weak grip strength, lowest quintile stratified by sex and body-mass index
- Slow gait speed: lowest quintile of gait speed (m per s) stratified by sex and height
- Low physical activity: low energy expenditure, based on physical activity questionnaire
- Exhaustion: self-reported, based on two items from the Center for Epidemiological Studies Depression scale
- Unintentional weight loss: self-reported weight loss or measured weight loss of ≥5% in past year

Frailty states: non-frail (0 criteria present), pre-frail (1–2 criteria present), and frail (≥3 criteria present)

Validated as consistent with a medical syndrome, linked to distinct biology

Key reference: Fried et al (2001)[1]

Frailty index (deficit accumulation)

Counts health deficits (at least 30), such as:

- Signs
- Symptoms
- Diseases
- Disabilities
- Abnormal test results (eg, laboratory, imaging, electrocardiogram)

Health deficits should meet these criteria:

- Represent multiple domains of functioning or multiple organ systems
- The prevalence must increase with age
- Not be too common before the age of 65 (early saturation)
- The prevalence should not be lower than 1%

Frailty score=sum of health deficits present divided by total number of deficits measured

Continuous score between 0 and 1, higher scores indicate higher degree of frailty

Cutoffs are controversial, although ≥0·25 has been proposed to indicate frailty[10]

Key reference: Rockwood and Mitnitski (2007)[9]

Global burden and impact of frailty

Frailty prevalence

Frailty is present in millions of older adults worldwide. However, the global prevalence of frailty is not yet known, partly because frailty research has predominantly been done in high-income countries. Another reason is the use of different operational definitions of frailty across studies. One systematic review pooled findings from 61 500 older community-dwelling participants enrolled in studies from high-income countries and found a weighted average estimate of 11% for frailty. However, this review also revealed that frailty prevalence greatly varies across studies (range 4–59%) because of lack of standardisation of concepts or measures.[13] Systematic reviews have indicated that the prevalence of frailty is 53% among long-term care residents,[14] 5–29% among individuals with HIV infection,[15] and 37% in patients with end-stage renal disease.[16] Similarly, among patients with solid or haematological malignancies, a median frailty prevalence of 42% has been reported.[17]

Despite the uncertainty about frailty prevalence, some general patterns have been observed in many studies. The prevalence of frailty is higher in women than in men and rises with age (figure 1).[19,20] Furthermore, people in lower socioeconomic groups (eg, those with lower educational level or low income) and from ethnic minorities have higher frailty prevalence rates.[19,21]

Frailty and risk of adverse outcomes

Frailty is an important risk factor for mortality in older adults.[22] The association between frailty and mortality has been confirmed in many studies and across various settings and subpopulations.[17,23–26] One systematic review found that mortality risk increased in a graded manner with increasing number of phenotypic components or deficits present.[22] Frailty is also related to a broad range of other outcomes, such as disability,[27] falls,[28] fractures,[29] worsening mobility,[1] loneliness,[4] lower quality of life,[3] depression,[30] cognitive decline,[31] dementia,[32] hospitalisation,[33] and nursing home admission.[34] Further research on the effect of frailty on healthy life expectancy (without functional impairment) is needed, as it is uncertain whether increased survival among frail adults into late life in recent generations will result in expanded morbidity and disability, with resultant decreases in healthy life expectancy.[35,36]

Cost of frailty

The impact of frailty on health-care expenditure and use has been the subject of recent investigations (table). Although these studies are difficult to compare with regard to study population, sample size, and measurement instruments, they show a clear pattern of increased health-care costs and use associated with prevalent frailty or a higher degree of frailty. This pattern includes, among other factors, greater health-care use in inpatient, post-acute, and outpatient care sectors.[39,41]

Transitions, trajectories, and temporal trends

Longitudinal studies can provide information on changes in frailty with ageing, such as transitions, trajectories, and factors associated with frailty progression, but this research field is in an early stage. Ultimately, such studies may contribute to better targeted care pathways, by distinguishing different types of trajectories and risk factors for certain trajectories. Longitudinal studies evaluating transitions between frailty states on the basis of frailty phenotype (non-frail, pre-frail, frail) suggest that the condition can be a dynamic process.[48–50] Although most individuals remain in their baseline frailty state at follow-up periods ranging from 1 year to 5 years, a substantial proportion (up to 37%) experience at least one transition, which includes both worsening and improvement in frailty state.[48–50] The few reported longitudinal studies on frailty trajectories have reported that frailty levels increase with ageing.[51–53] Inequalities in frailty related to sex and socioeconomic position seem to persist during later life.[21,51,52] However, there is great heterogeneity within the older population, which is not addressed by longitudinal studies focusing on average trajectories. More advanced statistical modelling might be needed to show this heterogeneity, and to indicate the order in which frailty components emerge.[54]

To make future projections about health care, it is crucial for health policy makers to gain insight into secular trends in frailty. The few studies of birth cohort effects on frailty, mainly based on only two time-points, have shown mixed results.[35,55–57] A Swedish study showed stability in frailty levels across birth cohorts,[55] while three other studies, in the US, the UK, and Hong Kong, showed higher frailty levels in more recent generations of older adults.[35,56,57]

Frailty in LMICs

Research into frailty in LMICs continues to grow, evident in the increase in the number of studies included in recent systematic reviews.[58,59] The contextual factors for assessing frailty can be complicated in LMICs by systemic issues, including the social determinants of health (social, economic, and environmental conditions, such as poverty and health literacy, and their impacts on health in older ages), health-care accessibility, and limited numbers of trained care providers that may make assessing prevalence in LMICs more challenging than in other contexts.[58] However, a number of assessment instruments have performed well in different countries and cultural contexts.[58,60–64] One multi-country study including China, Ghana, India, Mexico, South Africa, and Russia applied both frailty phenotype and frailty index criteria, with prevalence for the former ranging from 8% to 15%, and the latter ranging from 13% to 56%.[63,64]

The growing body of research suggests that the determinants and gradients in frailty show generally similar patterns in community-dwelling older adults from both higher-income and lower-income countries. The challenge for LMICs will be for support and care systems to adapt quickly and adequately train enough care providers to address the rapidity of growth in the ageing population. Much more research is required on the interactions between older adults with frailty and social and health-care services in LMICs, and the effects on health-care systems in these countries.

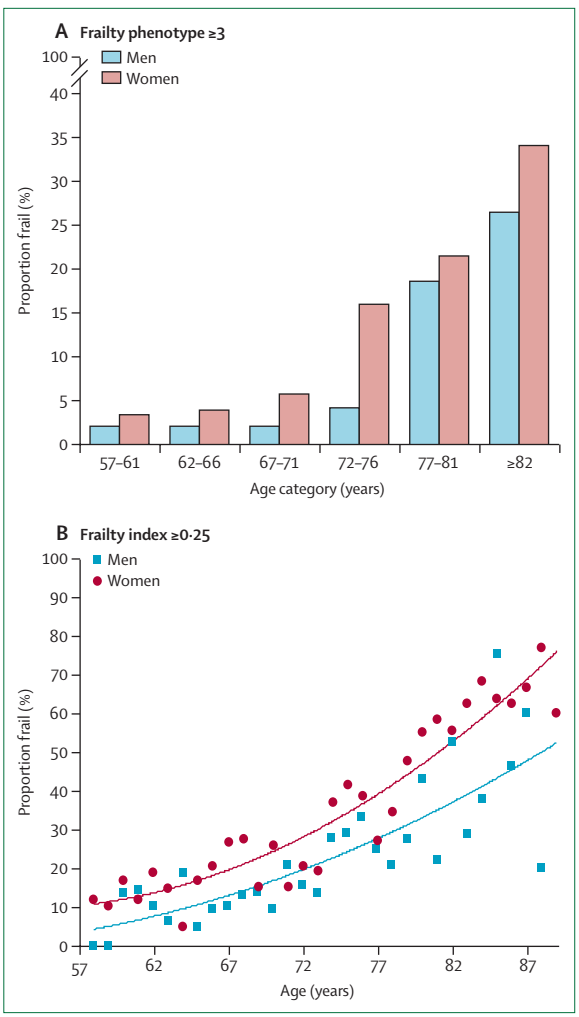

Figure 1: **Frailty prevalence for men and women by age**
Based on the frailty phenotype (A) and frailty index (B) using data from the Longitudinal Aging Study Amsterdam wave F (2005–06).[18]

	Population	Frailty instrument	Health-care data	Main findings
Gobbens et al (2012)[37]	Netherlands, community-dwelling, aged ≥75 years (n=484)	Tilburg Frailty Indicator	Self-report	A higher frailty score was associated with higher health-care use
Sirven & Rapp (2017)[38]	France, community-dwelling, aged ≥65 years (n=1284)	Frailty phenotype	Health-care insurance data	Frailty was associated with increased ambulatory health-care costs; annual incremental effect of €1270 for frail individuals
Ensrud et al (2018)[39]	USA, community-dwelling women, aged ≥65 years (n=2150)	Frailty phenotype	Medicare claims data	Frailty was associated with higher total and outpatient health-care costs and health-care use; mean annual cost US$3781 (robust) *vs* $10 755 (frail)
Segal et al (2017)[40]	USA, community-dwelling, aged >65 years (n=4454)	Claims-based frailty indicator (anchored to frailty phenotype)	Medicare claims data	Frailty was associated with incident hospitalisation and nursing home admission
Kim et al (2019)[41]	USA, community-dwelling, aged >65 years (n=7233)	Claims-based frailty index (deficit accumulation)	Medicare claims data	Higher frailty score was associated with hospitalisation and prolonged skilled nursing facility days
Peters et al (2015)[42]	Netherlands, population based, aged ≥65 years (n=713)	Groningen Frailty Indicator	Health-care insurance data	Frailty was associated with higher total health-care costs (including long-term and curative care); mean annual cost €15 611 (non-frail) *vs* €30 792 (frail)
García-Nogueras et al (2017)[43]	Spain, population based, aged ≥70 years (n=830)	Frailty phenotype	Hospital registration data	Frailty was associated with higher hospital health-care costs and hospital health-care use; mean annual cost €1217 (non-frail) *vs* €2476 (frail)
Hajek et al (2018)[44]	Germany, population based, aged ≥57 years (n=1636)	Frailty phenotype	Self-report	Frailty onset was associated with increased health-care costs; no cost estimation provided by frailty status
Comans et al (2016)[45]	Australia, post-acute care, mean age 79·5 years (SD 8·1; n=272)	Frailty index (deficit accumulation)	Government database	Higher frailty score was associated with higher total 6-month health-care costs after hospital admission; mean 6-month health-care cost AU$19 905 (low frailty) *vs* AU$28 906 (high frailty)
Robinson et al (2011)[46]	USA, hospital, patients with colorectal surgery, aged ≥65 years (n=60)	Multidimensional frailty score	Hospital registration data	Frailty was associated with increased surgical hospital costs and higher 6-month postoperative health-care costs; mean 6-month postoperative cost: US$27 731 (non-frail) *vs* $76 363 (frail)
Goldfarb et al (2017)[47]	Canada, hospital, patients with cardiac surgery, aged ≥60 years (n=235)	Frailty phenotype or Short Physical Performance Battery	Hospital registration data	Frailty was associated with increased hospitalisation costs after cardiac surgery; median hospital cost between date of surgery and date of hospital discharge: Can$23 370 (non-frail) *vs* $32 742 (frail)

This overview is based on a quasi-systematic review of recent literature (2010–19).

Table: **Associations of frailty with health-care costs and use**

Frailty in daily practice

Identification of frailty: why is it important?

Given the increasingly high prevalence of frailty and its strong association with numerous adverse health outcomes, the impact of frailty on the wellbeing of ageing individuals and the functioning of the overstretched health-care system is readily apparent. By considering a patient's degree of frailty in their day-to-day practice, clinicians can deliver more patient-centred care, which in turn might lead to better outcomes and avoidance of harm in primary, secondary, and tertiary prevention of disease (panel 2, figure 2). However, more research is needed to show whether frailty assessment and targeted treatment will contribute to benefits for the individual patient and sustainability of health-care systems.

Frailty assessment instruments

In the past decades, many frailty measurements have been developed for screening or case finding purposes, based on questionnaires, performance measures, routine data, or a combination of any of these. However, there is no global standard assessment instrument for frailty. The most widely used instruments in clinical practice are variations of the frailty phenotype or frailty indexes based on the deficit accumulation approach. These two frailty models are well validated in many populations and settings.[5] Other instruments that are being used include tools such as the Clinical Frailty Scale (CFS), gait speed measurement, the Groningen Frailty Indicator, the Edmonton Frail Scale, and the FRAIL scale.[5] A major issue is that for many frailty instruments, extensive validation studies are unavailable. Most instruments are validated for outcome prediction in population health studies, but aspects such as reliability, cross-cultural validity, and responsiveness have received much less attention. For example, the extent to which frailty instruments can be used by clinicians to monitor changes in frailty over time is largely unknown.

Making the translation from frailty research to clinical practice is one of the main challenges for the future. For health-care professionals, the clinimetric aspects of instruments are important, but they also need a frailty assessment that is simple, not time-consuming, and helpful in making decisions about interventions and care allocation. The field is currently moving towards specific instruments for specific settings and populations. Examples are the electronic Frailty Index (eFI) and the Hospital Frailty Risk Score (HFRS), which measure the number of multimorbid conditions that can be generated from electronic health record data.[65–67] A major advantage of these instruments for clinicians is that no additional data collection is needed. The national implementation of the eFI in primary care in the UK as well as the results of a recent feasibility study look promising,[68] and the eFI and the HFRS have both been validated for predicting adverse outcomes.[65,67] However, more validation and

Panel 2: Illustrative examples of frailty in primary, secondary, and tertiary prevention of disease

Primary prevention

Consider a pre-frail older person who lives a sedentary lifestyle with poor nutritional habits, and over time, develops obesity and diabetes. Identification of the individual's gradual decline in physical function and body composition (trending towards sarcopenic obesity) could have led the clinician to emphasise behavioural change, such as regular exercise, to simultaneously curb the progression of frailty and insulin resistance. Moreover, it could have led the clinician to inquire about and address the physical, cognitive, and psychosocial barriers interfering with the individual's ability to adopt healthy behavioural lifestyle changes.

Secondary prevention

The same person develops coronary artery disease, and a few years later, presents to the emergency department with unstable angina. Identification of frailty before this presentation could have led the clinician to inquire about the aforementioned barriers, as well as polypharmacy and care fragmentation with multiple providers, which might limit the patient's compliance with cardiovascular risk reduction medications and health maintenance visits. As the clinician considers whether to stratify the patient with invasive or non-invasive testing, and then, whether to treat with surgical or percutaneous revascularisation or medical therapy alone, frailty is a key consideration in predicting whether the patient will derive benefit and tolerate the iatrogenic stress inherent to the procedures.

Tertiary prevention

After undergoing revascularisation, the patient has a complicated postoperative course and a prolonged hospital stay, requiring discharge to a convalescence facility. The patient suffers from chronic heart failure with poor functional status and is frequently admitted to hospital for cardiac and non-cardiac ailments. As the clinician ponders whether to admit the patient to the intensive care unit or to consult palliative care services, frailty is a key consideration in determining if this transition of care should be recommended. In retrospect, identification of frailty beforehand could have led the clinician to enlist the help of a comprehensive geriatric assessment team and a cardiac rehabilitation programme to maximise the likelihood of functional recovery after surgery.

feasibility studies are needed to show that these instruments are actually useful in measuring a biological entity of frailty, over and above multimorbidity, and whether they support clinical decision making.

Frailty in primary and acute care

The primary care provider is naturally positioned to screen older adults early in their trajectory, to identify those who are vulnerable, and act to counter frailty and its adverse effects. Middle-aged adults with high-risk comorbidities (notably multiple sclerosis, chronic fatigue syndrome, chronic obstructive pulmonary disease, connective tissue disease, and diabetes) might warrant screening as well.[69] Evidence for interventions initiated in primary care to prevent the onset or progression of frailty is fragmented, and robust evidence from systematic reviews and meta-analyses is unavailable. Some single studies have indicated that interventions in primary care that promote physical activity and nutrition might limit the undesirable progression from pre-frailty to frailty.[70,71] Given the connection between frailty and development of various diseases,[72] limiting frailty might have ancillary benefits for primary and secondary prevention of disease. Lastly, the close longitudinal relationship forged between the primary care provider and the patient is well suited to establish priorities of care and end-of-life preferences.[73] Care needs span across physical, environmental, and psychosocial domains, with the more frail patients having more unmet needs.[74]

The emergency department is already struggling with the increasing trend of older adults presenting with frailty. The emergency department has evolved from focusing solely on acute care to mandating greater consideration of frailty.[75] The utility of identifying frailty in the emergency department is to understand the acute illness manifestations in the context of the patient's pre-existing health status, to predict adverse events during and after the index hospital visit, to implement interventions aimed at preventing these adverse events, and to guide disposition decisions. Frailty assessment instruments based on the frailty phenotype and the deficit accumulation approach have been shown to predict mortality, length of stay in the emergency department, need for hospital admission, and post-discharge functional decline.[76] Interventions addressing emergency department staffing, physical infrastructure, and delivery

Primary care	Older adult	Primary prevention
	Adoption of unhealthy lifestyle behaviours	
	Accumulation of frailty deficits and risk factors for disease	
	Diagnosis of chronic disease	Secondary prevention
Acute care	Acute decompensation of disease	
	Cycle of stabilisation and destabilisation	
Specialist care	Progression of disease to advanced stage	
	Intensive medical or surgical therapy	
	Iatrogenic complication from therapy	Tertiary prevention
	Prolonged hospitalisation	
Post-acute care	Functional decline	
	Admission to long-term care facility	
Palliative care	Readmission	
	Death	

Figure 2: Trajectory of care for the patient with frailty

***Panel 3*: Evidence base for frailty in medical and surgical specialties**

Robust evidence*
- Geriatric medicine
- Cardiology and cardiac surgery
- Oncology and oncological surgery
- General surgery
- Vascular surgery
- Transplantation
- Critical care
- Endocrinology
- Nephrology
- Family medicine
- Emergency medicine
- Physical medicine and rehabilitation

Emerging evidence†
- Infectious diseases (HIV)
- Neurology
- Respiratory medicine
- Rheumatology
- Orthopaedic surgery
- Trauma surgery
- Thoracic surgery
- Anaesthesia
- Psychiatry
- Radiation oncology
- Medical biochemistry
- General internal medicine

Limited evidence
- Allergy and immunology
- Dermatology
- Gastroenterology
- Haematology
- Medical genetics
- Pathology
- Paediatrics
- Radiology
- Nuclear medicine
- Other non-malignant surgical subspecialties

*Robust evidence supported by systematic reviews showing greater prevalence and prognostic effect of frailty in a specific population. †Emerging evidence supported by individual studies showing prognostic effect of frailty or systematic reviews showing greater prevalence of frailty.

of care have generally been shown to reduce the time spent in hospital but not the subsequent risk of functional decline or death; notwithstanding concerns about generalisability across different health-care systems.[77] Geriatric emergency department guidelines recommend multidisciplinary team-based care and education in a geriatric-friendly environment that has protocols and quality indicators for frailty screening, urinary catheters, medication management, fall and delirium prevention, and transitions of care and follow-up (the latter being crucial yet under-studied).

For **geriatric emergency department guidelines** see https://www.acep.org/geriedguidelines

Frailty in medical and surgical specialties

The specialist is increasingly challenged to treat older adults with multi-system disease and concomitant physical or cognitive impairments—a population that is heterogeneous and underrepresented in clinical trials. Assessment of frailty and its related domains is useful to help prognosticate risk in such patients, to gauge who may benefit and who may be harmed from aggressive interventions, and to postulate when interventions are likely to be futile.[78] Importantly, when frailty is advanced and advanced dementia or multiple complex comorbidities make the case irreversible, burdensome treatments should be avoided. Patient preferences should be valued above all (within reason) and efforts to optimise frailty status should be considered.

Numerous specialties have embraced the concept of frailty (panel 3) and studied its implications in relation to disease-intervention dyads, such a coronary artery disease and revascularisation,[79,80] advanced heart failure and implantable electrical or mechanical devices,[81] aortic stenosis and valve replacement,[82] cancer and chemotherapy or oncological surgery,[17] arterial disease and vascular surgery,[83] abdominal disease and general surgery,[84] chronic kidney disease and dialysis,[85] cirrhosis and liver transplantation,[86] and critical illness and intensive care unit admission.[87] In each setting, frailty has been consistently associated with short-term and mid-term mortality, complications, prolonged length of hospital stay, post-hospitalisation functional decline, and reduced quality of life.

Risk factors and prevention

Contributors to frailty

Risk factors for the onset of frailty or frailty progression span a wide range of aspects and conditions, covering sociodemographic, clinical, lifestyle-related, and biological domains (figure 3).[88] Insight into risk factors could guide public health and preventive strategies, in particular when these risk factors are potentially modifiable by specific interventions. For example, physical inactivity is recognised as one of the major contributing factors to frailty onset and progression, and physical exercise is known to preserve or improve the function of many of the physiological systems that can be altered in frailty—including muscle and heart function, cognition, endocrine system (glucose metabolism), and inflammation—and delay the onset of chronic diseases.[89] Other examples of risk factors that are potentially modifiable include the anorexia of ageing, which is generally defined as a loss of appetite or reduced food intake, deficits of various micronutrients, obesity, social factors such as loneliness, and hormonal deficits and other endocrine system alterations.

Despite much evidence on risk factors for frailty, the biological mechanisms underlying its development are still far from being understood. Biological mechanisms involved in the ageing process have been proposed to

increase susceptibility to frailty and functional limitations.[90] In-depth study of these mechanisms could characterise individual risk profiles and identify targets amenable to preventive strategies, paving the way for a better understanding of frailty and for the development of a personalised approach. However, we recognise that a precision medicine approach in the context of frailty could be problematic, because multiple pathways across multiple physiological systems are involved.

Frailty and multimorbidity

Multimorbidity is defined as the coexistence of multiple diseases and medical conditions in the same individual.[91] Multimorbidity and catabolic diseases represent a risk factor for frailty, potentially contributing to the decompensation of multiple physiological regulatory systems that underlie frailty.[92] Frailty and multimorbidity are two distinct concepts, although they may contribute to each other. A recent meta-analysis on frailty and multimorbidity examined more than 14 000 community-dwelling older adults enrolled in nine different studies.[93] The results showed that about three-quarters of people with frailty presented with multimorbidity (two or more diseases), and that frailty was present in 16% of people with multimorbidity.[93] Similarly, analyses from the UK Biobank of data from approximately half a million participants aged 37–73 years showed that frailty was associated with multimorbidity, reaching a frailty prevalence of 18% among participants with four or more diseases.[69]

Evidence concerning the treatment of chronic diseases in people with frailty is still limited, mainly because of the de facto exclusion of frail people from randomised trials and the increased risk of negative drug-related effects in such people.[94] For this reason, treatment approaches to multimorbidity and chronic diseases in those with frailty should be individualised and flexible, considering individual needs, preferences for treatments, prognosis, and health priorities rather than relying on recommendations from guidelines on single health conditions.[95]

Targets for intervention

The modifiable factors previously mentioned might be potential targets for frailty prevention and treatment. People with sarcopenia, a condition characterised by the loss of muscle mass and function, which is embedded within the concept of frailty, are a special target group for physical frailty prevention.[92] Increasing evidence on interventions targeting physical frailty and sarcopenia will probably be provided in the coming years by ongoing projects, such as the Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies (SPRINTT) trial, conducted in eleven European countries.[96] This trial tests the effect of a multicomponent intervention including personalised physical activity and nutritional programmes on mobility disability onset in people with physical frailty and sarcopenia, at an early and reversible stage of the disability process.[96]

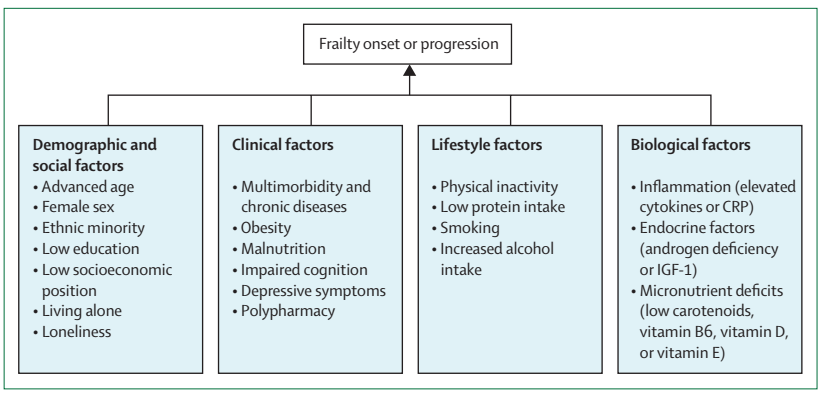

Figure 3: **Risk factors for onset or progression of frailty**
Information derived and modified from Feng and colleagues (2017).[88] CRP=C-reactive protein. IGF=insulin-like growth factor.

In the deficit accumulation model, multiple deficits may contribute to frailty onset and progression. For this approach, the implementation of a comprehensive geriatric assessment could support the identification of modifiable factors for frailty, including clinical factors as well as lifestyle and social factors, which represent possible targets for individualised interventions and care plans.

Noticeably, most of the available research in the field of frailty has focused on individual-level targets and little research has focused on system-level targets. One of the least studied, but most challenging, targets for frailty research is the re-organisation of health-care systems to focus on frailty, and the development of frailty care programmes. The few available trials focusing on care programmes for frail older adults have provided, so far, limited and conflicting data.[97,98]

Life-course approach

The life-course approach has substantially advanced insight into core ageing processes and their emergence and consequences, independent of diseases, across the life course. Life-course epidemiology is defined as "the study of long-term biological, behavioural, and psychosocial processes that link adult health and disease risk to physical or social exposures during gestation, childhood, adolescence, earlier in adult life or across generations".[99]

Recent research has examined factors from earlier life that predict ageing-related health and disease. We highlight two emerging lines of life-course evidence on frailty here. First, risk of adverse outcomes can be predicted. For example, mortality risk can be predicted by exemplar clinical diagnoses (eg, congestive heart failure, lung cancer, chronic obstructive pulmonary disease) and specific syndromes (eg, angina, frailty), and by various multimorbidity indexes that sum conditions and characteristics present to define cumulative risk, such as clinical diagnosis,[100] self-reported diseases plus physical

function,[101] biomarkers of subclinical disease,[102] biomarkers to represent allostatic load,[103] and self-reported disease, disability, function, health habits, and health status.[10] These indexes offer prognostication via quantification of clinicians' longstanding recognition that multiple health problems probably mean worse aggregate health status. However, many of these measures are not standardised, and because they are summaries of many discrete conditions they might not offer a basis for targeted clinical interventions.

Second, life-course evidence indicates that there is a clinical condition of frailty that is an outcome of biological ageing. Mutually regulating physiological systems that maintain homoeostasis, robustness, and resilience[104] show altered integrated effectiveness over the life course.[105,106] Substantial dysregulation in ageing predicts emergence of frailty.[107,108] For example, the biologically interconnected symptoms and signs that are diagnostic elements of the frailty phenotype (ie, weakness, slow gait speed, low physical activity, exhaustion, unintentional weight loss) jointly express energy dysregulation.[1,109] The escalating prevalence of frailty with old age is associated with the mounting physiological dysregulation with ageing; the association is non-linear and when frailty is present, stress responses are highly dysregulated,[107,110–112] and there is high vulnerability to adverse outcomes.[1]

Life-course evidence shows that the presence of behavioural and biomedical risk factors that emerge in midlife, such as obesity and allostatic load, are associated with frailty in later life.[113–115] Adverse childhood exposures have also been linked to frailty in later life.[116,117] However, more work needs to be done on life-course factors associated with frailty, as the evidence is fragmented, and high-quality data from longitudinal studies over a very long time period are scarce.

Future perspectives

Over the past decades, the clinical and research consensus has been that there is a subset of older adults with high vulnerability to adverse outcomes, including mortality and disability. Two major processes have emerged as drivers of these adverse outcomes: frailty and single diseases or multimorbidity. Frail older adults have a distinct underlying pathophysiology of dysregulation of multiple dynamic physiological regulatory systems, with compromised homoeostasis and resilience. When a threshold number of underlying regulatory systems is dysregulated, the clinical presentation of frailty emerges and risk of mortality and disability escalates. Dysregulation and compromised recovery becomes apparent when the frail person experiences a stressor, whether an acute illness or an iatrogenic procedure. There is mounting evidence of cellular causes underpinning altered function in multiple systems.

This evidence provides the basis for the next generation of research to ascertain clinically efficient approaches to standardised diagnosis of frailty, in the clinical setting and under conditions of acute illness. As bases for improved medical care and therapeutic treatment, we need to better understand mitochondrial and other cellular dysfunctions that compromise multisystem homoeostatic functioning in frailty; develop a test for multisystem dysregulation that has proven clinical usefulness; and define the dynamics of such dysregulation and its relation to declines in resilience and to risks.

We also need to improve clinical management of compromised homoeostatic compensations when the patient is stressed, and develop new approaches to preventing subclinical multisystem dysregulation and sarcopenia, as well as outcomes of frailty including declines in physical function and loss of independence. Effective treatments will probably need to recognise multisystem physiological dysregulation in older people with frailty as the target, more than any one system. Interestingly, physical activity provides such a model of improving function of all systems known to be dysregulated in the syndrome of frailty, including upregulating mitochondrial function.[118] Robust well powered randomised controlled trials are needed to test the efficacy of traditional and emerging therapies to treat frailty. Finally, research is needed to understand the stage of clinical frailty that is not remediable and where palliative care would be most appropriate.

How the field moves forward from these understandings is critical. Specificity and standardisation of frailty measures is essential for major progress, as is the meticulous differentiation of frailty from multimorbidity. To that end, a major challenge for the field is to move beyond the plethora of measures considered equivalent in characterising frailty in the 1980s and 1990s and carefully choose measures that match goals, to further collective understanding of diagnosis, specific causes, outcomes, and response to treatment, and to provide stratification of risk that can improve targeting of treatments or prevention.

Conclusion

Frailty is highly prevalent and is associated with adverse outcomes and increased health-care costs. The global impact of frailty is expected to increase due to population ageing. Therefore, addressing frailty is an urgent public health need. The response should be a collective effort of older adults, health-care professionals, researchers, and policy makers both in high-income countries and in LMICs, where the population is ageing more rapidly than in many high-income countries, and where circumstances are challenging because of limited resources and restrictions in health-care accessibility.

Substantial progress has been made in the past decades. Research into frailty has increased exponentially, and frailty awareness is widespread across medical disciplines. Nevertheless, the translation from research to clinical practice remains a challenge for the coming

years. The continuous debate on frailty assessment instruments does not help. Perhaps the development of a few specific instruments for specific settings, based on routinely collected data, could lead to higher acceptability and feasibility of frailty screening in clinical practice.

Longitudinal research is a high priority for the frailty research agenda, including investigations of trends and trajectories, as well as randomised controlled trials focusing on interventions for older adults with frailty. Applying the life-course approach might increase our understanding of how frailty and its risk factors develop during earlier stages in life and contribute to the development of public health strategies aimed at preventing frailty and related adverse health outcomes. This research will ultimately lead to increased wellbeing of older adults living with frailty.

Contributors

EH was part of the team that coordinated the Series, drafted key sections of the paper, did the analyses for figure 1, and the final editing before submission. JA, KE, GO, and LF drafted key sections of the paper. All authors have read and edited the paper for intellectual content and approved the final version of the paper.

Declaration of interests

We declare no competing interests.

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