Frailty 2

Management of frailty: opportunities, challenges, and future directions

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This is the second in a Series of two papers about frailty

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Frailty is a complex age-related clinical condition characterised by a decline in physiological capacity across several organ systems, with a resultant increased susceptibility to stressors. Because of the heterogeneity of frailty in clinical presentation, it is important to have effective strategies for the delivery of care that range across the continuum of frailty severity. In clinical practice, we should do what works, starting with frailty screening, case identification, and management of frailty. This process is unarguably difficult given the absence of an adequate evidence base for individual and health-system interventions to manage frailty. We advocate change towards individually tailored interventions that preserve an individual's independence, physical function, and cognition. This change can be addressed by promoting the recognition of frailty, furthering advancements in evidence-based treatment options, and identifying cost-effective care delivery strategies.

Introduction

Frailty is without question one of the most serious global public health challenges we will face this coming century. The rapid expansion of the ageing population has brought a concomitant rise in the number of older adults with frailty,[1,2] which in turn places an increased pressure on health-care systems worldwide.[3] Unfortunately, older people with frailty have an increased likelihood of unmet care needs, falls and fractures, hospitalisations, lowered quality of life, iatrogenic complications, and early mortality.[4–9] This increased risk of adverse outcomes can occur even without the presence of comorbidities.[4] Therefore, effective strategies that target the prevention and management of frailty in an ageing population will probably reduce the condition's burden at the level of both the individual and the health system.

In reflection of increased research interest, the term frailty was introduced as a PubMed Medline Search Heading (MeSH) in January, 2018. Frailty is recognised as an age-related clinical condition[10–12] that is typically observed by a deterioration in the physiological capacity of several organ systems,[4,8,12,13] and that causes an increased susceptibility to stressors.[4,7,8,10–12] When stressor events (such as acute illness) occur, a person with frailty rapidly deteriorates in functional capacity. Thus, interventions to prevent or slow the progression of frailty before it leads to substantial functional decline are key concerns for health-care policy and provision.

In general, frailty is recognised as the physical state that exists before occurrence of disability,[7,8] although it is possible for frailty and disability to coexist.[14] Frailty is also a dynamic entity that exists on a continuum from fit to frail,[4,13,15] wherein an individual's level of frailty is able to change in either direction over time.[7] Correspondingly, frailty is potentially reversible[7,8] and

Search strategy and selection criteria

We searched PubMed and the Cochrane Central Register of Controlled Trials for relevant publications using combinations of several search terms: "frailty", "frailty/therapy*", "patient care planning/standards", "diet therapy", "physical therapy modalities", "drug therapy", "therapy", "aged", "frailty/complications", "frailty/diagnosis", "geriatric assessment", "frailty/metabolism", "frailty/rehabilitation", "micronutrients/administration and dosage" and "clinical trials". Searches were limited to work published in English. We sought additional publications from the reference lists of identified papers, and from the libraries of authors. To identify current and recently completed trials, we used the National Institute of Health's ClinicalTrials.gov database. Where possible, the research cited in this Series was from systematic reviews and clinical trials published in the previous 5 years, with the exception of key research publications. The literature search was done on Aug 27, 2018, and March 25, 2019.

Key messages

- Although presence of frailty might seem like an ideal way to identify people who need additional support services, there is a shortage of substantial research evidence to support this strategy and to identify the most effective instruments to detect frailty
- In clinical practice, the management of an older adult with frailty is complex because of the inadequate evidence base for individual and health-system interventions to manage the condition
- We need to accrue more knowledge about which intervention strategies are effective for frailty, and to determine whether they are feasible and cost-effective
- High quality clinical trials are needed that take into account the perspectives and needs of health-care providers, older people with frailty, and their carers
- In the absence of a firm evidence base for interventions, strategies to manage frailty in daily practice can be based on existing consensus guideline recommendations
- It is important that frailty does not become a new aspect of ageism that prevents access to interventions that could be appropriate

its associated functional decline is also a potentially preventable disability.[16] In many cases, frailty onset starts before age 65 years, although not all adults develop frailty, even at advanced ages.[4] Notably, the use of frailty measurements for the purposes of prognosis has recently emerged from geriatric medicine and into the medical specialties.[9,17–19] What this means is that recognition of an individual's frailty status can inform treatment decisions, goals of care, and recovery expectations.[20]

Over the past two decades, strategies to manage frailty have progressed substantially. However, to progress from traditional, episodic-based care to more proactive, person-centred care, we need to do much more. In this Series paper, we provide a critical review of the evidence base behind both individual and health-care system interventions targeting individuals with frailty. With a noticeable lack of high-quality research evidence regarding how best to identify and treat people with frailty, we provide a research-informed viewpoint of what strategies appear to work best. We acknowledge that although frailty can occur in people of all ages (particularly if comorbidities are present), the majority of intervention trials involve older populations. Hence, the focus of our review is on older adults, although findings might also be applicable to younger people with frailty. This paper is the second in this Series on frailty, with the first paper overviewing the concept of frailty, as well as its global burden, life-course perspective, and potential targets for prevention. An outline of terminology used in this Series is shown in panel 1. For this review, we consider frailty as distinct from advanced age, functional ability, and multimorbidity, even though it is related to these concepts.

The natural history of frailty

There is much heterogeneity in the course of physical frailty in the absence of treatment, with different initial manifestations often leading to different trajectories of frailty progression.[12] Nevertheless, epidemiological studies have reported commonalities with regards to the first components of frailty to develop. For instance, on the basis of two large-scale cohort studies (the Longitudinal Aging Study Amsterdam with 15-year follow-up, and the InCHIANTI study with 9-year follow-up), the first physical component of frailty that manifests tends to be exhaustion, followed by slowness of gait, lowered physical activity, and weakness.[27] This result does differ from earlier research from the Women's Health and Ageing Study II, which suggested that weakness develops first;[28] although this difference could be because of differing definitions of exhaustion.[27] What is consistent across the literature is that weight loss tends to develop later than the other physical components of frailty.[27,28]

Moreover, the functional decline associated with frailty is gradual, incessant, and begins several years before death.[29] Compared with other conditions, frailty has the slowest rate of functional decline observable in the last year before death,[29] and the most functional dependence in activities of daily living at 1 year before death.[30] Once frailty is established and progresses in its natural course, other geriatric syndromes are more likely to emerge, including falls, incontinence, rapid functional decline, pressure ulcers, mild cognitive impairment, and delirium.[12]

Identification of frailty

Frailty instruments are prognostic across a broad range of medical interventions, including chemotherapy doses,[31] cardiology procedures,[17,20] and abdominal surgery.[18] In long-term care facilities, these instruments can be used to grade severity of frailty, thereby identifying individuals who might benefit most from a palliative approach and advanced care planning.[32] Relatedly, in the acute care setting, frailty instruments can be used to

Panel 1: Key terminology

Frailty
An age-related clinical condition, typically with deterioration in the physiological capacity of several organ systems, that is characterised by an increased susceptibility to sudden, disproportionate functional decline following stressor events.

Frailty instrument
A score or set of criteria used to identify frailty. The two most common frailty instruments used in research and clinical practice are the physical frailty phenotype[8] and the Frailty Index (FI) of accumulative deficits.[21,22]

Frailty phenotype
The phenotype model of frailty developed by Fried and colleagues considers frailty as a biological syndrome,[8] and classifies an individual as frail when three or more of the following five physical components are present: shrinking (unintentional weight loss of 4·5 kg or more in the last year), weakness (low grip strength), exhaustion (self-reported), slowness (slow walking speed), and low physical activity.[8] A classification of pre-frailty is given when only one or two of these physical components are present; robust is the classification given to an individual who has no frailty components present.[8]

FI of accumulative deficits
Rockwood and Mitnitski's FI represents an alternative viewpoint on frailty that incorporates the condition's multidimensional nature; it is based on the degree of accumulation of 30 or more health deficits, which increase in prevalence (but do not saturate) with age.[21,22] Health deficits included are comorbidities, psychological factors, symptoms, and disabilities.[21,22] The FI provides a score on a continuum from 0 (no deficits) to a theoretical maximum of 1 (all items exhibit deficits).[21,22]

Multimorbidity
The concurrent existence of more than one medical condition in the same individual.[23]

Disability
Defined by WHO's World Report on Disability as "impairments, activity limitations and participation restrictions" affecting any of six domains: cognition, mobility, self-care, getting along (interacting with other people), life activities, and societal participation.[24]

Comprehensive geriatric assessment (CGA)
A CGA is specialist, multidisciplinary, co-ordinated care that addresses the physical, mental, medical, and social needs of an older person with frailty.[25] CGA was originally developed to address disability, well before the emergence of the concept of frailty.[26]

	Components	Frailty classification	Setting		
			Primary care	Hospital	Long-term care facility
Frailty phenotype[8]	Five items: weight loss, low physical activity, exhaustion, slowness, weakness	Frailty: ≥3 items; pre-frailty: 1–2 items; robust: 0 items	Yes	Yes	Yes
Frailty Index[21,22]	30 or more accumulated health deficits: scores range from 0 (no deficits) to 1 (all deficits)	Continuous score; suggested cutoff score for frailty >0·25[34]	Yes	Yes	Yes
Electronic Frailty Index[35]	As for the Frailty Index, with variables derived from routine electronic health records in primary care; also considered to be a case-finding instrument	Severe frailty: score >0·36; frailty: score >0·24–0·36; mild frailty: score >0·12–0·24; fit: score ≤0·12	Yes	No	No
Clinical Frailty Scale[36]	Visual and written chart for frailty with nine graded pictures: 1=very fit; 9=terminally ill	Frailty: score ≥5	Yes	Yes	Yes
FRAIL scale[11]	Five items: fatigue, resistance, ambulation, illness, loss of weight	Frailty: ≥3 items; pre-frailty: 1–2 items; robust: 0 items	Yes	Yes	Yes
Study of Osteoporotic Fractures frailty criteria[37]	Three items: weight loss, exhaustion, unable to rise from a chair five times	Frailty: ≥2 items; pre-frailty: 1 items; robust: 0 items	Yes	Yes	No
PRISMA-7[38]	Seven self-reported items: age (>85 years), male, social support, and ADLs	Frailty: score ≥3	Yes	No	No
Tilburg Frailty Indicator[39]	15 self-reported items in three domains: physical, psychological, and social	Frailty: score ≥5	Yes	No	No
Geriatric 8 frailty questionnaire for oncology (G8)[40]	Eight items: function (ADL and IADL), mobility, nutrition, comorbidity, cognition, depression, social support	Frailty: score ≤14	No	Yes	No
Groningen Frailty Indicator[41]	15 self-reported items in four domains: physical, cognitive, social, psychological	Frailty: score ≥4	Yes	No	No
Short Physical Performance Battery[42]	Three measured items: gait speed, standing balance, and repeated chair stands; each item scored from 0–4, maximum score of 12	Frailty: score ≤9	Yes	No	No
Edmonton Frailty Scale[43]	Nine items: cognition, health (2 ×), hospitalisation, social support, nutrition, mood, function, continence	Frailty: score ≥7	No	Yes	No
Multidimensional Prognostic Index[44]	Eight items: comorbidity, nutrition, cognition, polypharmacy, pressure sore risk, living status, ADL, IADL	Frailty: score >0·66; pre-frailty: score 0·34–0·66; robust: score <0·34	Yes	Yes	No
Kihon Checklist[45]	25 dichotomous items in seven categories: physical strength, nutrition, eating, socialisation, memory, mood, and lifestyle; scoring as per the Frailty Index	Continuous score; suggested frailty cutoff score >0·25	Yes	Yes	No
Frailty Risk Score[46]	Formula: age (per 10 years) × 4 + male sex × 10 + no partner × 5 + body mass index <18·5 kg/m² × 12 + cardiovascular disease × 4 + diabetes × 4 + number of drugs ≥2 × 5, EMS<20 × 5 + ADL motor deficit × 4 + ADL process deficit × 7. Also considered to be a case finding instrument.	Very good: score <45; good: score 45–50; moderate: score 51–55; poor: score 56–61; very poor: score >61	No	Yes	No
Hospital Frailty Risk Score[47]	109 summed items from ICD-10 frailty-relevant codes from administrative hospital data. Also considered to be a case finding instrument.	Low risk: score <5; intermediate risk: score 5–15; high risk: score >15	No	Yes	No

EMS=Elderly Mobility Scale. ADL=activities of daily living. IADL=instrumental activities of daily living. ICD-10=International Statistical Classification of Diseases and Related Health Problems, 10th revision. Derived and modified from Dent and colleagues, 2016.[33]

Table 1: **Commonly used frailty instruments**

assign triage categories to patients for the purposes of referral to appropriate management plans.[33]

Many frailty instruments are in common use (table 1), with much variation in both their biological basis and their included components. This variation has sparked intense research and debate as to which frailty identification instrument is best for clinical practice. By and large, when selecting an ideal frailty instrument, a clinician needs to consider the instrument's validity across the setting of interest, as well as its ultimate purpose (for example, risk assessment in clinical practice).[48,49]

Because of the substantial challenge that frailty places on health-care systems, effective and pragmatic screening or case finding is often recommended as a first step in the process of frailty management.

In England, the National Institute for Health and Care Excellence (NICE) has advised that frailty should be identified in all encounters with older people with multimorbidity.[50] Additionally, England's National Health Service general practice contract for 2017/2018[51] includes frailty identification as a requirement. Organisations focused on frailty, such as the Canadian Frailty Network[52] and the Asia-Pacific Clinical Practice Guidelines for the Management of Frailty,[49] have also recommended that all older people should be screened for frailty during health-care encounters.

However, there is no robust evidence yet to support routine frailty identification as a means to improve clinical care and cost-effectiveness in older populations.[53] Results of frailty screening and case finding may in fact have no influence on physician decision making regarding patient management, at least based on studies in the acute care setting.[33,54] Following from this, many frailty instruments often have low completion rates in clinical practice,[33] rely heavily on proxy input,[55] and can

lack reliability in specific settings,[55] and it is often not clear which frailty instrument should be applied in which setting.[13,20] To compound these issues, various frailty instruments do not identify the same individuals or predict the same adverse outcomes.[4,56,57] Thus, although frailty identification may seem like an ideal strategy to identify someone who is in need of additional support services, there is currently a lack of substantial research-evidence to support the effectiveness of this strategy and to identify the most effective frailty instruments.

Evidence from clinical trials targeting the individual

Table 2 outlines several individual strategies used for the management of people living with frailty, all of which have been shown to be superior to usual care in recent systematic and structured reviews. We excluded systematic reviews that did not use a validated frailty instrument to identify frailty. Also excluded were reviews that combined results of studies on both treatment and prevention, noting that older adults with frailty might respond differently to interventions than those without.

On the whole, the evidence suggests that although several interventions have yielded positive outcomes compared with usual care, the certainty of evidence was either low or very low for all outcomes analysed, indicating that further investigation is required to ascertain effectiveness of interventions. Table 2 covers three settings: all community-dwelling people (screening and case identification in primary care); community-dwelling older people living with frailty (home and community interventions); and older people with frailty in the hospital setting. The first of these settings is discussed earlier in this paper and in the first paper in our Series; the other two settings are discussed below. No systematic reviews identified positive interventions

	Evidence	Outcomes analysed	Certainty of evidence
All community-dwelling older adults (primary care)			
Identify frailty or pre-frailty through screening and case identification in primary care	Four systematic reviews[58–61]	Accurate identification of frailty or pre-frailty	Low
Community-dwelling older adults living with frailty (interventions targeting the management of frailty in home or community settings)			
Prescribe physical activity programmes (resistance-based training, aerobic training, or balance or coordination training)	Three systematic reviews[62–64] (excluded: reviews on frailty prevention or with merged frailty and pre-frailty groups[65–67])	Physical performance (SPPB); gait speed; muscle strength; mobility	Very low for all four outcomes
Prescribe multicomponent physical activity programmes	Three systematic reviews[62–64] (excluded: reviews on frailty prevention or with merged frailty and pre-frailty groups [65–67])	Disability; falls; balance; muscle strength	Very low for all four outcomes
Provide community-based group physical activity classes	Systematic review of six trials of mild frailty or pre-frailty,[68] and one systematic overview with one relevant trial[69]	Physical function; muscle strength; balance	Very low for all three outcomes
Protein or protein-energy, micronutrient supplementation	Systematic review of three nutritional trials,[66]* and one systematic overview with one relevant trial[69]	Frailty; physical performance; strength (leg or grip); gait speed; physical activity	Low for all five outcomes
Provide individually tailored management of clinical conditions	Systematic review of three trials of frailty[66]*	Frailty; ADL	Low for both outcomes
Provide advice on health behaviour improvement	Systematic review of six education trials[70]	Physical function	Low
Ensure practical social support	Systematic review of 13 trials on enabling health-behaviour change[70]	Physical function	Very low
Modify home environment for health behaviour change	Systematic review of five trials[70]	Physical function; health behaviour	Very low for both outcomes
Older adults with frailty in hospital (hospital care)			
Ensure targeted care delivery through CGA intervention (CGA done in emergency department, short stay unit, or clinical decision unit)	Systematic mapping review of eight studies covering CGA intervention for older people with frailty[33]*	Physical function; readmission; emergency department readmission	Very low for all outcomes
Review medications using implicit criteria	One systematic mapping review[33]*	Prevention of emergency department readmission	Very low
Ensure patient is placed on a frailty-specific care pathway	One systematic mapping review[33]*	Prevention of emergency department readmission	Low

All intervention strategies listed in this table have been reviewed for effectiveness in recent systematic and structured reviews; intervention strategies without systematic review appraisal were not included. Reviews were only listed if their included studies defined frailty using objective measurement, regardless of whether they had the word frail in their title. All strategies and outcomes listed have been found to be superior to usual care; strategies and outcomes not showing consistent or substantial evidence of benefits compared with usual care have not been included. Certainty of evidence was defined according to GRADE criteria[71] as applied by the authors: high (further research is very unlikely to change our confidence in the estimate of effect and there are no suspected biases); moderate (further research will likely change our confidence in the estimate of effect and may change the estimate); low (further research is very likely to have an important impact on confidence in the estimate of effect, and is likely to change the estimate); very low (any estimate of effect is uncertain). The search for relevant reviews was based on a quasi-systematic review, and thus the list of interventions might not be exhaustive. CGA=Comprehensive Geriatric Assessment. ADL=activities of daily living. IADL=instrumental activities of daily living. SPPB=Short Physical Performance Battery test. *Although these systematic reviews combined results from older adults in general and those with frailty, this table shows trial results for those with frailty only.

Table 2: **Single strategies superior to usual care for management of frailty, by target population**

for older people with frailty residing in long-term care facilities.[69]

Interventions in home and community settings

Compared with usual care, single-mode physical activity programmes (resistance-based training, aerobic training, or balance and coordination training) were reported to improve gait speed, muscle strength, mobility, and physical performance in older people with frailty (table 2). Similarly, multicomponent physical activity programmes and group exercise classes both improved participant muscle strength and balance. However, the evidence base to support these findings was of low to very low certainty, indicating that future research is needed to truly gauge effectiveness in this context.

The optimal programme mix for physical activity is not yet known, with studies showing much variation in the frequency, intensity, type, and duration of exercise.[62–64] In terms of outcomes, there is insufficient evidence to gauge whether physical activity programmes can improve frailty or functional ability, predominantly reflecting the paucity of trials that include these two important outcome measures. Furthermore, physical activity trials do not seem to re-test for frailty post-intervention.[72] When older adults with pre-frailty are considered, community-based group physical activity classes seem to improve physical function, although again, the evidence base is thin.[68]

A recent meta-analysis suggested that nutritional supplementation for frailty improves physical performance and muscle strength, yet is ineffective for improving body-mass index or body weight;[66] the evidence base here was reported as of moderate-level certainty. However, this certainty of evidence could be inflated, given that the evidence consisted of only three small-scale clinical trials, which had inherent randomisation issues, high attrition rates, and a lack of blinding of study personnel.[66]

There was insufficient evidence to gauge the effect of hormone therapy, cognitive training, or telehealth monitoring on either outcome improvement or frailty reduction.[66,68] Similarly, there is no evidence from randomised controlled trials on reduction of unnecessary medications in individuals with frailty.[68] There is a paucity of published evidence on pharmacological intervention for the management of frailty.[49,73,74]

Hospital care

Hospital care for older people with frailty is an expensive and lengthy process, often encompassing multiple hospital admissions and intervention strategies.[33] Single strategies that are useful for the management of frailty in the hospital setting are outlined in table 2.

In the acute care setting, medication review and use of a frailty-specific care pathway might prevent emergency department readmission;[33] however, the evidence here is only of low or very low certainty (table 2). Targeted care delivery through implementation of Comprehensive Geriatric Assessment (CGA) appears to improve physical function, but not reduce emergency department readmission,[33] with a low or very low certainty of supporting evidence. Insufficient evidence exists to estimate the influence that CGA has on other outcomes specific to older adults with frailty in the acute care setting. However, when older adults as a whole group are considered, use of CGA on admission might reduce the likelihood of readmission[75] and post-hospital mortality rates.[25] Indeed, CGA has been found to work well in populations of older adults (including those with frailty) when applied in specialist geriatric medicine wards,[25] although more evidence specific to frailty is needed in the acute care setting.

In the surgical setting, clinical trials are emerging with mixed results regarding clinical outcomes.[76–78] In the medical specialties of orthogeriatrics and cardiology, to our knowledge, no clinical trials (excluding screening interventions) have explicitly focused on interventions to improve outcomes for patients with frailty. In oncology, there has been a call-out for trials in older adults with frailty,[79] reflecting the shortage of trials for this population group.

Panel 2: An example of a potential care plan for an older person living with frailty

A comprehensive strategy to guide the treatment of an older person living with frailty encompasses several strands, each with a distinct rationale, applied in accordance with the situation and priorities of individual people:

- Reversing (or slowing progression of) the features that characterise physical frailty: weakness, slowness of gait, unintentional weight loss, fatigue, and low physical activity levels.[8] The clinical rationale is that these factors directly result in lost capacity, such as impaired activities of daily living and instrumental activities of daily living (eg, weakness), are predictive of future losses (low physical activity), or reduce the resilience of the individual faced with a new external stressor.
- Identifying and optimising the management of comorbidities and their associated medications. The rationale here is that common conditions associated with frailty, such as renal impairment or cardiovascular disease, could drive progression of frailty through biological (eg, inflammation) and behavioural mechanisms (sedentariness) and independently contribute to functional limitations and poor quality of life.
- Identifying and addressing other losses of intrinsic capacity (such as vision and hearing impairment, or low mood and affective problems) that contribute to the severity of frailty. The rationale is that functional ability is the product of the accumulated impact of these common losses in the context of the individual's interaction with their total environment.
- Assessing an individual's priorities and psychosocial resources, which can affect social functioning and quality of life.
- Crucially, appreciating the attributable contributions of frailty and individual conditions to the outcomes of interest to the older person, assessing the potential for modifying these factors, and estimating the likely benefits, risks, and burdens of pharmacological and non-pharmacological treatments. Informed consent requires these estimations to be made explicit.
- Promoting the achievement of generic older adult physical activity recommendations coupled with targeted additions such as reducing sedentary behaviour[85] and improving strength and balance to prevent falls seems a reasonable approach, at least in people with pre-frailty.

Additional considerations concerning clinical trials

Overall, the variable methodological quality of studies across care settings and specialties provides a sparse evidence base for the clinical management of frailty. Cost effectiveness is rarely studied, and intervention outcomes are rarely person-centred. Such knowledge is vital to add evidence-based clinical value to treating older people with frailty.

Several fundamental barriers need to be overcome to improve the robustness of clinical trials on the management of frailty. First, older people with frailty are often excluded from clinical trials, despite being the population group that often uses the treatments being studied. Second, when trials are undertaken, recruiting and retaining participants is complex. For example, the National Institute of Health's clinicaltrials.gov database shows that trials on frailty are still in recruitment or stalled mode for substantial lengths of time. Finally, negative trial findings are often not disseminated in a timely manner. Addressing these issues will undoubtedly progress the research field forwards.

Potential goals and strategies of care

The management of frailty is not limited to physical and psychosocial domains.[73] The objectives of clinical care for people with frailty are to maintain functional independence and quality of life, while avoiding unnecessary admissions to hospital or long-term care facilities.[73,74] Major evidence gaps in treatment strategies can be filled with existing consensus guideline recommendations. For example, NICE guidelines for multimorbidity encompass recommendations for the clinical management of people with frailty,[50] and WHO's "Integrated Care for Older People (ICOPE)" guidelines document provides strategies to maintain and improve a person's *Intrinsic Capacity* (physical and functional capacity), which is applicable to individuals with frailty.[80] Likewise, consensus-based guidelines from the British Geriatric Society/Age UK/Royal College of General Practitioners,[73] the British Columbia (Canada) guidelines for the early identification and management of frailty,[74] and the Asia-Pacific guidelines for the management of frailty[35] all provide strategies to manage frailty. Importantly, all recent consensus-based guidelines have included physical activity and adequate protein intake as first-line therapies for the management of frailty.[49,50,73,74,80]

In cases where frailty has manifested from an underlying medical condition or treatment for that condition, pharmacological treatment for these conditions is paramount.[81] Regarding deprescription, consensus-based guidelines for frailty[35,73,74] recommend that inappropriate medications be deprescribed using standard approaches[35,73,74] such as the Screening Tool of Older Person's Prescriptions criteria,[82] or Beer's criteria.[83] However, the benefit-to-risk ratio of deprescription is not clear, and the quality of studies on the topic is low.[84]

Panel 2 outlines an example of potential goals and strategies of care for an older person with frailty. Collating these care strands into an integrated and person-centred clinical management plan to be agreed with the patient themselves is a skilled task that can necessitate an interdisciplinary approach over several encounters. When addressing frailty, an individual's preferences, priorities, and psychosocial resources should be incorporated into their care management plan; these factors have an influence on an individual's quality of life.[80] Allied health professionals can deliver interventions currently offered for the clinical management of frailty.

Interventions focusing on health-system targets

To manage the complexity of frailty and its array of associated factors, it seems logical to offer multicomponent intervention packages at the public health and system levels (table 2). Theoretically, these packages will achieve their desired outcomes if their component strategies are implemented effectively. However, in practice, success rates of such packages have been underwhelming,[86–88] which could perhaps reflect good

	Intervention	Result
Kusatsu, Japan	A focused effort over 10 years to screen for frailty in primary care, with those identified as pre-frail or frail referred to a group community programme involving physical activity, nutrition, and social participation[91]	Substantial functional improvements in the population[91]
Hong Kong	The Hong Kong Jockey Club CADENZA project implemented a community frailty prevention project that has had a strong response rate;[92] the project has been running for over 9 years and involves the integration of health and social care, provision of caregiver support, and community group classes involving physical activity[92]	Not yet evaluated in the academic literature
Canada	The Seniors' Community Hub[93] builds capacity in primary care to address the health and social needs of older adults with frailty, including encompassing the needs of the older person with frailty in terms of their intrinsic capacity and frailty levels	Improvements in quality of life and functional maintenance or improvements in people with frailty[93]
UK	The NHS General Practice contract for 2017–18 requires practices to identify adults aged 65 years and older with severe or moderate frailty according to an eFI based on routine primary care coding; this identification is paired with a clinical review incorporating medication and falls reviews, and activation of a care summary record[51]	Effects on clinical outcomes have yet to be evaluated, and might help to clarify whether the eFI is generalisable to primary care in terms of acceptability, feasibility, interpretation, and implementation[60]
Singapore	The Ministry of Health has implemented a Silver Generation Ambassadors programme, which integrates health and social services to support seniors, specifically targeting older adults with frailty[94]	Not yet evaluated in the academic literature

NHS=National Health Service. eFI=Electronic Frailty Index.

Table 3: **Selected examples of frailty-specific interventions that focus on health-system targets, by location**

usual care (including primary care services) in countries where interventions have been delivered.[89,90]

Another factor might be that many intervention packages aim to achieve multiple outcomes, which although seemingly pragmatic, can lead to undesirable consequences. For instance, resources might be spread thin, outcome prioritisation can become difficult, and the intervention package can become too complex to roll out as originally planned. In turn, complex intervention packages run the risk of only being partially implemented because of time constraints and other difficulties faced by both health professionals and older people with frailty.[90]

Nonetheless, there are several examples of successful community-based long-term frailty intervention packages, as outlined in table 3. These interventions have been designed to promote equity and a continuum of care, and are promising examples of strategies that could work. Notably, most intervention trials for frailty have focused on individual-level interventions; very few intervention trials exist on health-system based improvements.

At the system level, successful management of frailty requires a simple, clearly defined, low-cost strategy that can be easily adopted by health-care policy makers. Unfortunately, the few studies that have investigated cost-effectiveness have not shown promising results.[86,88] Recently, two systematic reviews highlighted that interventions based on the identification of frailty could lead to recognition of unmet need and increased engagement with health-care professionals and home care services.[33,53]

Panel 3: **Proposed strategies to address evidence–practice gaps for the clinical care of frailty**

Expand knowledge of pathophysiology and natural course of frailty
- More physiological-based studies that identify precise biomarkers of frailty
- Studies which better articulate links between biological changes and changes in organs and tissues that drive frailty and vulnerability
- Cross-cultural, large-scale, longitudinal cohort studies

Enhance clinical care of older adults with frailty
- More efficient care delivery strategies which focus on both the equity and continuum of care
- Evidence-based clinical practice guidelines for specific settings (primary care, acute care, rehabilitation, oncology, cardiology, surgery), which in turn need a stronger evidence base for their formation
- Improvements in health-care accessibility (including affordability, acceptability, availability) to decrease gaps between who needs treatment and who receives treatment
- More evidence of how to manage frailty and people with frailty, including around the organisation of services, cost-effectiveness and the effectiveness of specialty care
- Knowledge translation studies (including process evaluation methodology) investigating barriers and enablers to intervention success in everyday practice

Improve methodological quality of clinical trials
- Person-centric metrics (patient reported outcome measurements; patient reported experience measurements)
- Standard sets of outcomes across studies (eg, from the International Consortium for Health Outcomes Measurement)[104]
- Cost-effectiveness evaluations
- Efforts to reduce bias

Broaden scope of interventions to health-care system targets and strategies
- Study designs that promote the implementation of community-based frailty intervention packages (eg, an interrupted time series design, or a trial within cohort design)

Assess effectiveness of routine screening for older adults with frailty
- Evaluation of whether frailty screening adds value to the clinical care of an older adult with frailty
- Identification of when and where screening is best applied

Identify the best instrument to detect frailty across settings
- Need for an international consensus definition for frailty, rigorous validation studies, and cross-cultural studies
- Recognition that pursuit of this goal should not detract from other research priorities, such as identifying strategies for best clinical care

Expand knowledge of how to prevent frailty in community-dwelling older adults (and middle-aged adults)
- Targeting of risk factors of frailty to determine which strategy is most effective
- Research into effectiveness of system-level interventions, particularly in low-to-middle–income countries

Expand scope of intervention research
- More rigorous research into dietary patterns such as the Mediterranean diet
- High quality research into the role of oral health and sedentary behaviours in management of frailty

Reform health care, including improvement of health-care service coordination
- Education and training programmes for health-care professionals designed to improve the knowledge and recognition of frailty
- Health-care policies which promote quality of care for older people with frailty
- Clinical indicators for frailty
- Health-care policy that targets the recognition and management of frailty in everyday practice

For instance, earlier home discharge from hospital might mean that more home services are needed.[95] In addition, many system-level interventions for frailty focus on reducing hospital readmissions, and consequently, individuals may be displaced to health-care settings considered more appropriate for their care needs.[33] This displacement seems to be towards primary care, and its extent, cost, and clinical implications are not yet known.[33] It is therefore reasonable to propose that general practitioners should be provided with support when designing and implementing system-based intervention packages for frailty.

In principle, much of the management of people with frailty can make use of clinical care initiatives already in existence for older adults with non-communicable diseases or complex care needs. For instance, comprehensive care packages and the use of multidisciplinary care teams are applicable to older adults with frailty and make use of existing resources and infrastructure. Nonetheless, limited research exists on the feasibility and cost-effectiveness of this strategy, and many low-to-middle income countries might not have such care pathways. In the future, intervention packages that facilitate independence, such as re-enablement and restorative care, could become crucial.[96] Moreover, since the implementation of frailty intervention packages faces many challenges and uncertainties, alternative strategies that remove community barriers to care services are needed, including a greater knowledge and understanding of accessibility issues that older adults with frailty face when accessing health and social care services.

Implementing frailty identification in clinical practice

Health practitioners need to be aware of the great responsibility faced by caregivers of older adults with frailty.[97] Recent work has also highlighted the importance of identifying the social support networks, resilience, and coping skills of older adults with frailty;[98–100] these health assets can be used to ameliorate the challenges that frailty presents. The implementation of frailty identification in clinical practice should also take into consideration the potential burden of labelling an older adult as frail.[101] In the absence of evidence-based interventions for frailty, screening might inadvertently contribute to biasing clinicians and negatively influencing patients' behaviour.[102] Furthermore, older adults themselves consider frailty to be an irreversible condition,[103] and in turn, might not wish to be acknowledged as frail. Indeed, it is important that frailty does not become an aspect of ageism that prevents access to potentially appropriate interventions.[15]

Future directions

Closing gaps between evidence and practice

Possible strategies to close gaps between evidence and practice in the field of frailty are outlined in panel 3.

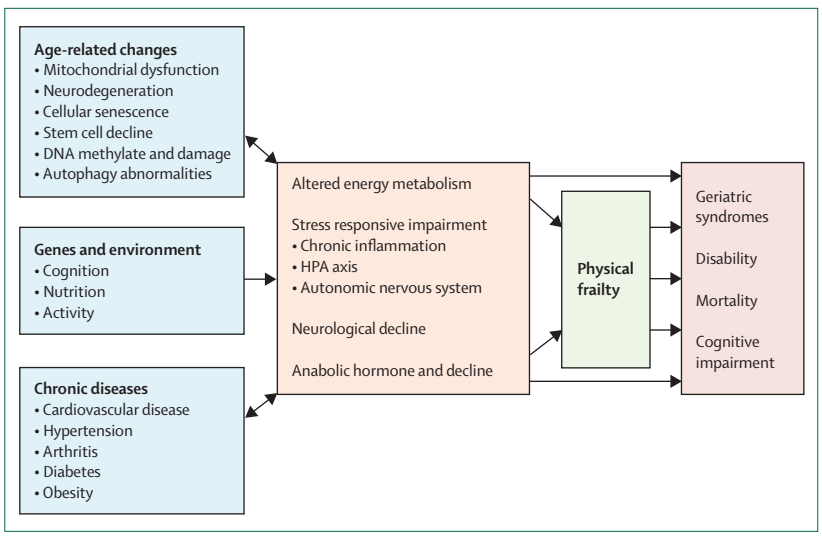

Figure: **Model pathway for physical frailty**
Reproduced from Michel et al[107] by permission of Oxford University Press. HPA=hypothalamic-pituitary-adrenal.

Examples of the most urgently required strategies are: high quality clinical trials with a broadened focus on health system targets and strategies; robust evidence on how to best manage frailty (including cost-effectiveness and the effectiveness of specialty care); and efficient care delivery strategies. We also need to derive precise biomarkers of frailty that will facilitate the development of more precise treatment strategies.

Personalised medicine

In older adults with frailty, personalised (person-centred) medicine provides a strategy to target the treatable causes of frailty, support early identification, and promote informed decision-making.[105] This personalised strategy can address individual variations in lifestyle and genetic factors, which might improve patient care.[105,106] The figure illustrates a conceptual framework by which basic cellular ageing processes, in combination with environmental, genetic, and chronic disease states, act together to drive the development of the physical frailty phenotype. In future, an understanding of ageing-related biological changes in older adults, such as mitochondrial changes, stem cell decline, and senescent cell emergence, will be a crucial next step for the management of frailty.[108]

However, there are many challenges to developing effective personalised medicine for someone with frailty. Foremost, frailty is unarguably complex. To successfully prevent or treat frailty, we must appreciate its complex underlying biological processes, many of which are not yet clearly known. If it takes many decades to develop personalised medicine approaches to target single-gene diseases,[106] it will inevitably take much longer to develop a successful, personalised strategy to target the multiple organ systems that associate with frailty. Furthermore, there is much heterogeneity in prognosis and response to treatment in those with frailty, which in turn reduces

accuracy in predicting which individuals will or will not experience adverse outcomes. For personalised medicine to be effective, predictive accuracy is paramount.[106]

Conclusion

In response to population ageing, recent years have seen a rapid expansion in the recognition and knowledge of the phenomenon of frailty. At this point in time, many interventions for the clinical management of frailty are available, including physical activity, protein-calorie supplementation, and de-prescription of unnecessary medications. However, the effectiveness of these interventions is not supported by a firm evidence base. We need to accrue more evidence-based knowledge regarding which intervention strategies are effective for frailty, and ascertain whether they are feasible, cost-effective, and in line with the preferences of older people with frailty. In addition, because individuals with frailty are able to dynamically transition between states, it is important to have strategies for the delivery of care that range across the continuum of frailty. The clinical care of older people with frailty should also focus on maintaining functional independence and other person-centred outcomes. The opportunities, challenges, and future directions we have discussed give hope that the next generation of frailty management will improve the health outcomes of older people living with the condition, as well as promote equity and quality of care. Given the rapid expansion in the ageing population, frailty is indeed the new frontier of medicine.

Contributors

ED was part of the team that coordinated the Series, and she performed the final editing of the manuscript before submission. All coauthors drafted key sections of the manuscript. All authors have 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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