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The degree of frailty as a translational measure of health in aging

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Frailty is a multiply determined, age-related state of increased risk for adverse health outcomes. We review how the degree of frailty conditions the development of late-life diseases and modifies their expression. The risks for frailty range from subcellular damage to social determinants. These risks are often synergistic—circumstances that favor damage also make repair less likely. We explore how age-related damage and decline in repair result in cellular and molecular deficits that scale up to tissue, organ and system levels, where they are jointly expressed as frailty. The degree of frailty can help to explain the distinction between carrying damage and expressing its usual clinical manifestations. Studying people—and animals—who live with frailty, including them in clinical trials and measuring the impact of the degree of frailty are ways to better understand the diseases of old age and to establish best practices for the care of older adults.

I n 2014, an influential commentary decried conventional, one-disease-at-a-time approaches to age-related illnesses[1]. This geroscience view steers away from the 'whack-a-mole' approach[2] of treating specific diseases individually—a process that often yields further problems including polypharmacy[3] and hospital-induced functional decline[4,5]. Instead, the geroscience agenda envisages moving toward a systems-level approach that slows the aging process[2,6]. Progress has been made, for example, with human clinical trials of senolytic drugs that target senescent cells[7,8]. Even so, aging is multiply determined and has many manifestations[9,10] meaning that despite any one advance, gaps will remain between the diseases of aging and optimal health in old age[11].

These gaps between healthy aging and the diseases of old age reflect important conceptual and operational challenges in continuing to address age-related impairments in health. Major non-communicable age-related diseases such as cancer, coronary heart disease, dementia, diabetes mellitus and stroke share common risk factors[12,13]. Their prevention, and improving poor health in old age more generally, requires developing new systemic interventions. Some such systemic interventions already exist, such as tackling the shared and modifiable risks of physical inactivity and poor diet[12,14].

Less appreciated has been the opportunity to 'treat aging'[1], which can be operationally framed as an opportunity to 'treat frailty'[11], a proposition that can be indifferent to exactly which aging mechanism is being targeted[15]. That opportunity arises because detecting widespread effects of existing and future interventions requires integrative measures of age-related health. The degree of frailty, that is, variability in risk, is a widely used, theoretically grounded means of quantifying health in old age. Other candidate integrative measures of health include 'biological age' such as provided by 'physiological dysregulation'[16], DNA methylation clocks[17,18], telomere length and other aging biomarkers[19,20]. Frailty is a coarsely grained, system-level measure that can be used across levels from molecular and cellular measures to tissues to organs to whole organisms[21]—and can also be applied to animals[22].

Measuring frailty offers insights into clinical medicine and population health[14,23,24]. At any age, individuals with high levels of frailty are much more susceptible to adverse outcomes than those with lower frailty scores[21]. Severe frailty typically occurs more often in women[25], is observed in 12–24% of older adults and is age related[26]. Increasingly, frailty is seen as modifiable, even potentially preventable, thereby making it a target of treatment[27–31]. Trials of nutrition and physical exercise face challenges in relation to blinding, types of controls and measurement of dosing that can be more challenging than pharmaceutical studies, especially for well-tolerated compounds[27]. These challenges must be faced in sufficiently large, locally adapted, randomized controlled trials if the prospect of prevention or even mitigation is to be more than aspirational. For this, multicomponent programs will be important, including taking the social context into account[29], something not always done[31]. Even so, caution is required: one indication that the path to success may be quite long is signaled by a multicomponent trial of metformin and exercise—instead of increasing, metformin attenuated some of the benefit associated with exercise[32].

In reviewing how frailty relates to disease in old age, we explore how age-related damage and decline in repair in various guises are detectable. We examine frailty and its antecedents from cellular and molecular damage[33–36] to social determinants of health such as education, social position, race and financial stability[13,14,23]. We consider frailty as a means of understanding variability in aging, in translating interventions from preclinical to clinical studies, and as an aid to clinical decision-making. Finally, we call for the development of new intervention strategies, investigation of frailty mechanisms and use of frailty as an outcome measure in clinical trials and in improving hospital best practices.

Operationalizing frailty in humans and other animals

No one who has attended a thirtieth high school reunion doubts that people age at different rates. In 1979, variability in rates of aging was invoked to explain the apparent decline in the mortality rate at extreme old ages[37], positing that eventually only slow agers are left after the frailer rapid agers die. While late-life deceleration of mortality is still debated[38,39], the notion of frailty as variability in the risk of death in people of the same age—generalized as variability

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in the risk of an adverse outcome to people with the same degree of exposure—is an established concept. Describing people as being frail when they appear to be substantially 'older than their stated age' is now part of the clinical lexicon[40].

In 2001, several papers proposed new operational approaches to frailty[41–43]. Since then, although many frailty tools have been developed, two approaches have predominated (Table 1)[44–46]. One sees frailty as conforming to a phenotype or syndrome that underscores physical decline: low levels of grip strength, slow walking speed, loss of weight, reduction in usual activities and feeling exhausted; any three of these five features define a person as frail[41]. With the frailty syndrome, the degree of frailty can be expressed as the number of the five attributes that are present, which allows a six-point scale.

The other approach, developed by our group, sees frailty not as a specific syndrome but as a more general age-related state of poor health that is proportional to how many age-related health deficits an individual has accumulated[42]. Deficits can be drawn from a variety of attributes or functions, the relevance of which can vary depending on the context (for example, deficits related to exposure to malaria, frostbite or prolonged mechanical ventilation). The degree of frailty for any individual can be expressed as the fraction of deficits that are present in an individual to the number that were considered in a standard clinical or epidemiological study. If at least 30 age-related and adverse-outcome-associated items are considered, the degree of frailty, for the most part, does not depend strongly on which items are counted[21,47,48].

The operationalization of each approach can vary considerably (Table 1), but the results remain robust. Not all five items in the frailty phenotype are present in every database or clinic record, so that sometimes only four are used[49]. Sometimes self-reported data or different questions than those originally proposed are used[49]. The FRAIL scale, a self-report version, to which an item about the number of comorbidities has been added, is a popular variant[50]. The original frailty phenotype is sometimes referred to as 'physical frailty', to distinguish it from similarly constructed frailty syndromes for cognitive frailty[51], social frailty[52] and organ-specific frailties[53]. All of these are constructed with specific health deficits that typically increase with age and individually are associated with adverse health outcomes.

The frailty index is also subject to variable operationalization. Although a frailty index can be derived from any combination of symptoms, signs, laboratory values or other measures[42], work with a frailty index developed from laboratory data[54] or biomarkers[55] suggests quantitative differences in the distributions of the data, and slopes and intercepts in relation to age (Table 1). Other variations include the Clinical Frailty Scale, which proposes ordered combinations of high-information deficits to grade the degree of frailty[56]. The 'modified frailty index', especially in the American surgical literature, includes measures, mostly comorbidities, using a smaller number of deficits, such as a modified frailty index with 11 items (Table 1). However, such shorter versions have been criticized as being too brief to constitute a frailty index based on deficit accumulation[5,57].

The differences between frailty as a syndrome and frailty as a state of deficit accumulation, although real, are easily exaggerated. Each has been used in a variety of applications, including at the population level[58–61]. Both approaches are informative: at the group level, they consistently classify people who are at an increased risk of death and do so in ways that tend to reduce the explanatory power of age[62]. They appear to share genetic determinants[63]. Fundamentally, what the two main approaches have in common is that each sees frailty as rooted in aging. Each captures that not all people age at the same rates and that not everyone of the same age has the same risk of death. Rather than searching for a single aging biomarker, each approach uses more than one feature to define frailty. For each, once frailty is characterized, effort can be made to explore the

antecedents of differential aging. Some antecedents will be risk factors for differential aging (such as genetic influences or social vulnerability), while others will be features of aging, such as multiply determined loss of the ability to withstand stress (the idea of robustness[64]) or to remove or repair damage when it arises (the idea of resilience[64]). The loss of either robustness or resilience is seen as arising from the diminution in 'physiological reserve'. A common unifying definition of frailty includes both robustness and resilience. Frailty is an age-related, multiply determined loss of ability to respond to common stressors.

Preclinical frailty models have been developed from both the phenotypic and accumulation-of-deficits approaches;[22] so far, the best studied are murine models. Some items correspond to integrative attributes (such as gait speed, usual activities[41], health attitude, role function, instrumental activities of daily living and mobility in people[42,43,45,65]; and gait speed, grooming, body temperature, body condition score and menace reflex in mice[66–68]), although more focused attributes are also available (such as hip flexor strength, cataracts, hearing loss and specific comorbidities in people; and hearing loss, kyphosis, cataracts and tumors in mice[67]; Table 1). Frailty tools have also been developed for use in dogs[69,70] and nonhuman primates[71]. Quantifying frailty with similar approaches in both clinical and preclinical studies will facilitate translational research.

The degree of frailty contextualizes changes during aging

While frailty inspires investigators, this enthusiasm is not universal. Some are quoted as seeing in frailty "a pejorative concept that validates and reinforces the disadvantage and vulnerability of aging adults"[72]. Frail patients have multiple, interacting, medical and social problems that confound the single-problem treatments for which much of contemporary health care is organized[73]. They can be characterized by a physician as 'unsuitable' for care[74]. Nevertheless, growing evidence suggests that the degree of frailty helps us to understand not just risk, but the expression of chronic and acquired diseases in older people.

Indeed, a higher degree of frailty has been linked to a greater risk of disability in activities of daily living and falls[75,76], delirium[77–79], as well as more hospital admissions, with longer lengths of stay[75,80], and more primary care visits—all leading to greater health care costs[73,81]. Work on the degree of frailty and risk extends to a variety of clinical settings, including critical care[5], during invasive interventions[46] and in nursing homes[82].

Frailty and COVID-19. Recent experience with coronavirus disease 2019 (COVID-19) illustrates how frailty can integrate risk. Mortality in COVID-19 is related to the degree of frailty[83–87], however operationalized[88]. The mortality data from COVID-19 reflect the known dose–response relationship between the degree of frailty and the risk of death[58]. Similarly, frailty is related to the risk of COVID-19 being severe[89] and to important complications, including incomplete recovery[90] and prolonged hospital stay[85,86]. Frailty can also be more common in people with COVID-19 who develop delirium; mortality is especially high in this setting[84,91]. Indeed, new onset delirium may be a presenting symptom of COVID-19 (ref. [92]). That delirium is associated with frailty[93,94] illustrates why patients who live with frailty can be perceived as unsuitable. By not being able to describe what is wrong with them, frail patients who are delirious fail to engage providers at the typical point of encounter in health care[95]. As a result, delirium is underdiagnosed[95]. Among the patients with delirium, 37 (16%) had delirium as a primary symptom, and 84 (37%) had no typical COVID-19 symptoms or signs, such as fever or shortness of breath[96]. Despite the toll taken by COVID-19, the increased risk of adverse outcomes noted above and the potentially negative impact of frailty on the response to vaccination[97], frail older adults are underrepresented in vaccine trials[98,99].

Table 1 | Translational potential of frailty assessment tools in humans and mouse models

Frailty instrument	Selected health deficits		Strengths and weaknesses	Refs.
	Humans	**Mouse models**		
Frailty phenotype	1. Unintended weight loss	1. Weight loss, gain or not used	**Strengths:**	41,68,173– 175,187
	2. Weakness	2. Grip test/wire hang time	1. Simple five-point scoring system	
	3. Low physical activity	3. Tightrope, wheel running or open field test	2. Comparable measures in humans and animals	
	4. Slow walking speed	4. Rotorod, walking speed or treadmill running speed	**Weaknesses:**	
	5. Exhaustion/endurance	5. Hang time plus rotorod or treadmill running time, or inclined screen test	1. Focuses only on physical frailty	
		6. Tightrope test for gait and balance	2. Measures used in animal models are not standardized	
			3. No consensus on use of weight in animal models	
Frailty index, examples of clinical signs	1. Gait disorders	1. Gait disorders	**Strengths:**	42,67
	2. Vision loss	2. Vision loss	1. Frailty can be scored with a noninvasive clinical exam in humans and animals	
	3. Resting tremor	3. Tremor	2. Many similar items can be used in humans and animal models	
	4. History of malignancy	4. Tumors	3. Flexible, can use different measurements and varying numbers of items (generally >30 deficits)	
	5. Difficulties hearing	5. Hearing loss	**Weaknesses:**	
	6. Skin abnormalities	6. Skin lesions, dermatitis	1. Animal models do not consider cognitive aspects of frailty or activities of daily living	
	7. Abdominal abnormalities	7. Distended abdomen	2. Ideally at least 30 measures required	
	8. Respiratory complaints	8. Breathing disorders		
	9. Incontinence of stool	9. Diarrhea		
	10. Rectal abnormalities	10. Rectal prolapse		
	11. Difficulty with grooming	11. Coat condition		
	12. Vibration sense disorders	12. Vestibular disturbance		
	13. Feeling sad or depressed	13. Piloerection		
	14. Difficulty with memory	14. Kyphosis		
	15. History of stroke	15. Menace reflex		
Frailty index, examples of laboratory measures	1. Sodium	1. Sodium	**Strengths:**	54,183
	2. Potassium	2. Potassium	1. Frailty can be easily scored based on readily available laboratory measures	
	3. Calcium	3. Calcium	2. Many similar items can be used in humans and animal models	
	4 Glucose	4. Glucose	3. Can be created from existing datasets	
	5. Hemoglobin	5. Hemoglobin	4. Flexible, can use different measurements and varying numbers of items (generally >30 deficits)	
	6. Creatinine	6. Creatinine	**Weaknesses:**	
	7. Systolic BP	7. Systolic BP	1. Physical, psychological, and social components of frailty are not considered	
	8. Diastolic BP	8. Diastolic BP	2. Ideally at least 30 measures required	
	9. Urea	9. Blood urea nitrogen		
	10. Albumin	10. Chloride		
	11. AST	11. Anion gap		
	12. Folate	12. Carbon dioxide		
	13. Phosphatase	13. Heart rate		
	14. Protein	14. Pulse pressure		
	15. TSH	15. Ejection fraction		

Table 1 | Translational potential of frailty assessment tools in humans and mouse models (Continued)

Frailty instrument	Selected health deficits		Strengths and weaknesses	Refs.
	Humans	**Mouse models**		
Clinical frailty scale	1. Very fit	No preclinical model	**Strengths:**	56
	2. Fit		1. Simple nine-point pictorial scale that stratifies health from fit to frail	
	3. Managing well		2. Useful for frailty screening	
	4. Very mild frailty		**Weaknesses:**	
	5. Mild frailty		1. No preclinical model available	
	6. Moderate frailty			
	7. Severe frailty			
	8. Very severe frailty			
	9. Terminally ill			
Tilburg Frailty Indicator	Part A: determinants of frailty (for example, sex, age, education, income and diseases).	No preclinical model	**Strengths:**	45
	Part B: score three frailty domains (15 items):		1. Simple questionnaire with checkboxes to quantify frailty out of 15 items in three domains as in part B	
	1. Physical		**Weaknesses:**	
	2. Psychological		1. Determinants in part A are not scored	
	3. Social		2. No preclinical model available	
Groningen Frailty Indicator	Score four frailty domains (15 items):	No preclinical model	**Strengths:**	43
	1. Physical		Simple questionnaire with checkboxes to quantify frailty out of 15 items in four frailty domains	
	2. Psychological		**Weaknesses:**	
	3. Cognitive		No preclinical model available	
	4. Social			
Edmonton Frail Scale	Score nine frailty domains:	No preclinical model	**Strengths:**	65
	1. Cognition		Simple questionnaire that quantifies frailty based on nine domains; uses standardized tests including the Timed Up and Go and clock-drawing tests	
	2. General health status		**Weaknesses:**	
	3. Functional independence		No preclinical model available	
	4. Social support			
	5. Medication use			
	6. Nutrition			
	7. Mood			
	8. Continence			
	9. Self-reported performance			
FRAIL scale	Score five frailty components:	No preclinical model	**Strengths:**	50
	1. Fatigue		Simple questionnaire that quantifies frailty based on five frailty components	
	2. Resistance		**Weaknesses:**	
	3. Ambulation		No preclinical model available	
	4. Illness			
	5. Loss of weight			

This table illustrates various instruments that are used to measure frailty in human studies. The frailty phenotype and frailty index instruments, including a frailty index based solely on laboratory data, have been translated for use in animal models. AST, aspartate aminotransferase; BP, blood pressure; TSH, thyroid stimulating hormone.

Frailty and the risk of dementia in Alzheimer disease. Alzheimer disease and late-life dementia illustrate how measuring the degree of frailty can allow a deeper understanding of the relationship between aging and important diseases of old age. By 2011, it was evident that clinical trials designed to prevent the accumulation of the form of the beta-amyloid protein most associated with dementia
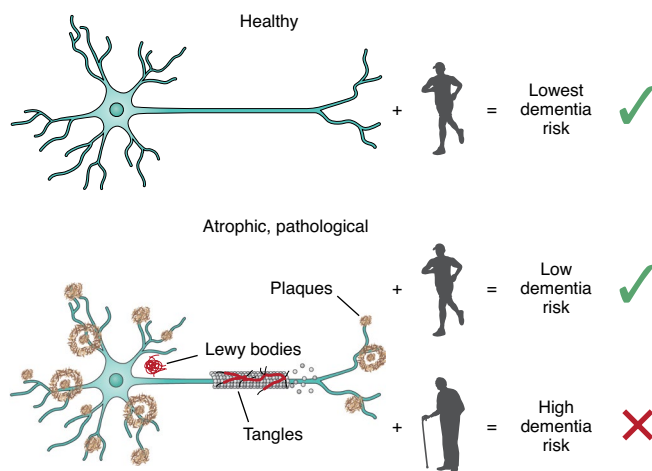
Fig. 1 | Frailty is not a disease, but it profoundly influences disease expression. The pathological changes in the brain that are thought to increase dementia risk include plaques, tangles, Lewy bodies and ischemic changes. Individuals with marked Alzheimer disease pathology may not meet criteria for dementia if they are fit, with low levels of frailty, while those with a modest neuropathological burden are at increased risk for dementia if they have a high degree of frailty. This figure was modeled on data in refs. [14,110,112,113,114,157].

pathologically were not working. A move was made to distinguish between Alzheimer disease as a biomarker-defined entity, and Alzheimer dementia as a clinical syndrome[100]. Not everyone with phenotypical Alzheimer disease demonstrated that they carried the toxic form of amyloid[101]—the resulting 'lack of target organ engagement' was understood as the reason for much of the failure rate of anti-amyloid therapy[102,103]. Drugs could result in amyloid plaques being cleared from the brain, without any detectable impact on cognition[103,104]. Indeed, pure Alzheimer disease is uncommon; instead, most older adults with dementia have multiple neuropathological markers[105–108]. Community-based neuropathological studies show that not everyone who meets clinical criteria for Alzheimer disease has dementia, and not everyone who meets dementia criteria meets the neuropathological criteria[109,110]. Instead, a host of other features, including age, atrophy and social position come into play.

Age-associated health deficits that do not include known dementia risk factors (for example, stroke, slow motor speed and functional impairment) nevertheless increase the risk of late-life cognitive impairment[111] and dementia[112]. Even people with a high burden of Alzheimer disease pathology are at less risk of meeting criteria for dementia if they have low frailty scores[110] (Fig. 1). In late-life dementia, it is now appreciated that neuropathological markers denote risk but do not permit a definitive diagnosis of cognition before death. Risks of all-cause dementia are additive when considering neuropathological markers of dementing illnesses[113] and known risk factors act even more potently in the face of frailty[114]. Risks for frailty and dementia overlap—especially in relation to social position, education and physical activity[14,115].

Frailty and clinical cardiovascular disease. Clinical studies show that the degree of frailty is related to the risk of various outcomes of cardiovascular disease, such as myocardial infarction, stroke, heart failure or atrial fibrillation [116–119]. For example, using clinical and test data, a 34-item frailty index was constructed from which were excluded deficits that were traditional risk factors for cardiovascular disease. The resulting 26-item frailty index was compared with traditional risk as assayed using the Framingham risk score[118]. Each 0.1 increment in the frailty index increased the hazard ratios

for both cardiovascular and non-cardiovascular mortality. Frailty was associated with a greater risk of both cardiovascular events and mortality, independently of traditional cardiovascular risk factors.

A meta-analysis of older adults with atrial fibrillation revealed that fewer fitter patients living with severe frailty were given oral anticoagulants for stroke prevention than were fitter people with atrial fibrillation[120]. A study using a records-based electronic frailty index[121] confirmed that the risk of atrial fibrillation, death and gastrointestinal bleeding (and among women, stroke) all increased with the degree of frailty[122]. Prescription of oral anticoagulants increased with the degree of frailty except in those with severe frailty so that fitter people had lower rates of oral anticoagulant prescription than did their frailer peers[122]. In a post hoc analysis of a clinical trial of a direct oral anticoagulant medication (edoxaban) in patients with atrial fibrillation, each 0.1 increment in the frailty index was associated with a greater risk of stroke or spontaneous embolism, and of major bleeding[123]. Patients receiving edoxaban had a similar benefit from oral anticoagulation as did those receiving the more traditional drug warfarin, but a lower risk of bleeding, save in people living with severe frailty. Thus, the degree of frailty influences responses to cardiovascular medications, including those frail older individuals who are the most likely to take these drugs.

Frailty and outcomes of hypertension. A similar body of work exists relating the degree of frailty with hypertension. Frailty indices have been calculated both retrospectively[124] and prospectively[125] in clinical trials of antihypertensive medications. Using frailty to identify and control for heterogeneous populations of older adults[125] led to recommendations for aggressive blood pressure control even in frail older adults. Even so, those same guidelines have been criticized on the grounds that they do not generalize to the general population, given how restrictive typical clinical trial enrollment criteria are, even when frailty may have been measured[126–128]. For this reason, guidelines have been proposed to move with great caution in people living with severe frailty or dementia[127,128].

The paradox of excluding those most at risk from clinical practice guidelines. In addition to brain and cardiovascular disease, and COVID-19, frailty and disease-specific risk factors overlap in disease progression in a variety of illnesses, including osteoporosis[129], HIV/AIDS[130] and systemic lupus erythematosus[131]. Despite this, excluding patients who live with higher degrees of frailty from clinical trials is a common, if derided, practice[98,99,132–134]. Nevertheless, people living with mild to moderate frailty find their way into trials and bring with them a higher risk of adverse outcomes[135]. In consequence, it has been recommended that people who live with frailty merit closer monitoring[135], and that trials in chronic diseases in which frailty is common should determine which treatments frailer patients might tolerate best[136]. Indeed, in many subgroups, including younger people, patients with higher degrees of frailty appear to be more likely to benefit from treatment.

Context matters, and especially in relation to excluding older adults who live with frailty; informative context also extends to social and economic settings[137,138], race[13,86,139] the clinical setting[5,46,82,86,140], childhood influences[141], and cohort and period effects[13,142–146].

Frailty and age-related deficit accumulation

Deficit accumulation leading to increased frailty occurs across the human life course. Early life influences are reflected in birth cohort studies[147,148] and cross-sectional population studies from ages 20 and younger[149,150]. Country-of-origin studies[151–153] also reveal important effects. Those using data on related childhood socioeconomic conditions[141,154,155] also highlight the importance of what happens in childhood. Genetic and proteomic studies have been done in special populations, such as in twin studies[156–158] including adopted twins raised apart[19], or in comparing offspring of people who come
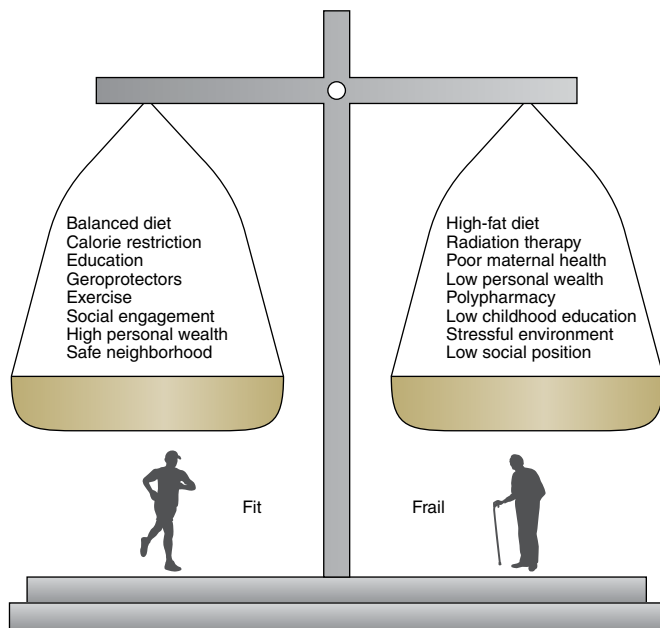
Fig. 2 | Medical interventions, lifestyle factors and social factors have a strong impact on the prevalence of frailty. The degree of fitness or frailty in an individual is profoundly affected by lifestyle factors, social factors and medical interventions. Dietary modifications (for example, calorie restriction), exercise, social engagement, education and drug therapies (for example, geroprotectors, senolytic drugs and repurposed drugs) have been shown to attenuate frailty in preclinical and/or clinical studies. Other lifestyle factors (for example, stressful environment and high-fat diet) and interventions including medical treatments (for example, radiation therapy and polypharmacy) can make frailty worse. Factors such as low social position, limited personal wealth, poor maternal health, low levels of childhood education, low per-capita gross domestic product and a host of specific disease states increase the prevalence and consequences of frailty in affected populations.

from long-lived families with those whose parents had usual survival patterns[159]. Briefly, as summarized in a detailed 2020 review[63], the heritability ranges from 25–30% (using phenotypic and deficit accumulation measures)[160] to about 45%[156].

Together, these studies suggest that genetic, environmental and social effects operate broadly and affect frailty (Fig. 2). Note that we do not have a cohort study in which individuals have been followed from birth to complete mortality, so some inferences from what data we do have are needed.

Note too that, just as with the genetics, no single influence amounts to destiny. For example, although immigrating from a lower-middle-income country to a high-income Northern European country showed a deficit never entirely caught up, people moving to Southern/Eastern Europe and people from lower- and middle-income countries were no worse off[151]. Somewhat more optimistically, and also from the Survey of Health, Ageing and Retirement in Europe, the impact of childhood socioeconomic conditions on frailty at old age could be mitigated by better conditions in adulthood: improving socioeconomic conditions can reduce health inequalities in old age[155]. Unsurprisingly, many influences will vary across the life course[148,151,155,158].

At the individual level, these influences give rise to deficit accumulation through a variety of mechanisms, including intrinsic processes that result in damage going unremoved or unrepaired[15,19,161,162]. Such damage is detectable across the levels at which maladaptive aging-related changes can be observed, for example, with decline in telomere length[163], mitochondrial DNA abundance[164] or DNA

methylation changes[18,19,162]. Deficits arising from disruptions in cellular and molecular processes then affect tissues, promote organ dysfunction and lead to clinical manifestations and frailty[21,162]. Evidence that the accumulation of subcellular deficits heralds the development of clinical frailty includes studies with a frailty index (FI-Lab) created from routine laboratory tests and blood tests[54,150,165] or from biomarkers[55]. Higher FI-Lab scores are also seen in people who live in more stressed circumstances[166].

Deficits accumulate at a constant rate, doubling roughly every 12–15 years[167,168]. The resulting pattern of accumulation shows acceleration in the number of deficits in later life, suggesting that deficits do not accumulate independently: people who enter old age with fewer deficits will accumulate fewer, and those who enter with many deficits will accumulate more, as longitudinal studies show[169]. In consequence, even small differences in early life can have increasingly larger impacts across the life course, even into late old age. Further, within-person acceleration in the frailty index score can appear as a preterminal event[170]. Factors that affect deficit accumulation include sex/gender, education, maternal health, social position, race, financial stability, childhood frailty states, early signs of chronic inflammation and a host of specific disease states, together with the complex relationships between factors[13,86,137–139,148,170,171]. Different studies report differing mean frailty scores. Secular effects on the lethality of frailty appear to be important. Most studies[13,143,144] but not all[146] report decreasing lethality in relation to frailty. In general, even with secular improvements in the mean degree of frailty[13], disadvantaged groups do less well than advantaged ones. Disadvantage is related to race, as well as to social disparities[13,41,139,151–153,166]. Some of the greater lethality of frailty in disadvantaged groups can be linked to a higher pathogen burden (for example, cytomegalovirus, human immunodeficiency virus and human papilloma virus) through a variety of mechanisms that consist of either greater exposure or less ability to mitigate the burden[172].

Frailty from molecular to organismal scales

Heterogeneity in effects of aging is detectable in cellular and molecular processes. The degree of frailty affects the risk of adverse outcomes and treatment responses in a variety of cardiovascular diseases. Consistent with the geroscience hypothesis, frailty may set the stage for such diseases before they present themselves clinically. For these inquiries, animal models are well suited (see below), given that frailty increases with age and is associated with adverse events including increased mortality in mice, rats and dogs[66,67,69,70,173–177].

In the cardiovascular system, links between chronological age, frailty and maladaptive changes in heart function have been investigated in mice of different ages. On average, the ability of the heart to contract deteriorates with age[35,36]. Unsurprisingly, there is also considerable interindividual variability—not all older mice exhibit age-associated deterioration in function[35,36]. When measures of cardiac contraction are plotted as function of an animal's frailty index score rather than age, a linear relationship is revealed where the frailest mice exhibit the most profound dysfunction[35,36]. This may underlie why frail older individuals develop exercise intolerance and heart failure, as seen clinically[178]. Similarly, the speed with which electrical impulses are conducted across the atria declines with age, an effect clearly evident in mice with high levels of frailty[33,34]. Slowed atrial conduction then provides a substrate for the development of arrhythmias, like atrial fibrillation, that are common in frail people[179]. We summarize the heterogeneity of age-associated changes in function and how these changes are graded by frailty scores in Fig. 3.

The effects of frailty are seen across physiological scales. Poor overall health, quantified with a frailty index, predicts functional decline at the organ level in experimental models. These models provide the opportunity to explore how deficits might arise at the
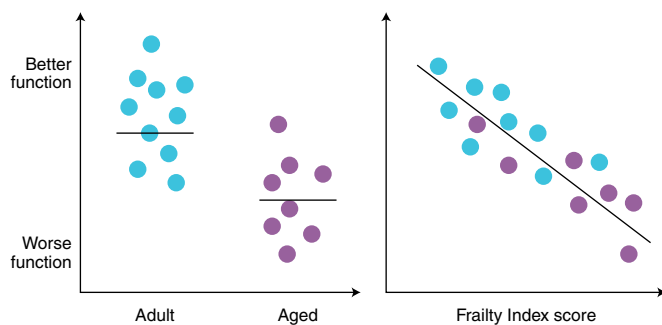
Fig. 3 | Age-dependent deterioration is heterogeneous and is graded by frailty index scores. Schematic illustrating the marked heterogeneity in the effects of age on structural and functional parameters (left). This illustrates that age-associated, detrimental changes in function reflect average responses, but many older individuals have function equal to or better than younger adults. When these parameters are plotted as a function of frailty index scores rather than chronological age, responses are closely graded by frailty (right). This figure was modeled on data from our previously published work[33–36].

cellular and subcellular levels, then scale up to adversely affect function at the organ and system levels. This idea has been tested most fully in the heart. The heart contracts less forcefully in frail mice because there is less calcium influx to trigger contraction in individual heart cells; this is attributable to fewer calcium channel proteins in the heart cell membrane[35]. There are also posttranslational modifications in the contractile proteins themselves that are graded by the level of frailty in older mice[36]. Slower electrical impulses in the atria arise from connective tissue deposition, known as fibrosis, and this in turn arises from increased collagen secondary to changes in enzymes involved in extracellular matrix remodeling[33,34]. These cellular and subcellular modifications are also graded by the degree of frailty. Clinical studies where the degree of frailty is quantified as the frailty phenotype have similarly shown that advanced glycation end products (AGEs) that arise in chronic kidney disease bind to receptors in skeletal muscle[180]. This leads to capillary rarefaction that may contribute to sarcopenia and physical frailty[180]. The idea of scaling by the degree of frailty, where deficits arise at the microscopic level and then scale up to the macroscopic level to affect function at the organ and organism levels, is illustrated in Fig. 4.

Translational potential of frailty

Animal models of frailty. The ability to quantify the degree of frailty in humans and other animals can facilitate translational geroscience research. Although frailty assessment tools are used to investigate the association between frailty and age in different species, few studies have explored animal frailty across the life course. Estimates now suggest that frailty index scores increase in a similar fashion from early to late life in mice and in humans, and there is a strong link between frailty and mortality at all ages[67,174].

Although women generally live longer than men, they are frailer at most ages, a phenomenon called the 'sex–frailty paradox'[25]. Studies in older mice and dogs also report that females have higher frailty scores than males[69,181–183]. While clinical studies suggest that behavioral and social factors are also involved in this sex–frailty paradox[25], work in preclinical models could help identify biological mechanisms.

Quantifying the degree of frailty can be used to explore fundamental mechanisms involved in its development. For example, neutrophil dysfunction increases with age but is highest in frail older people[184]. There is also emerging evidence that older mice with high levels of inflammation are frailer than mice of the same age with low inflammation[183,185]. Future work should investigate inflammation

and other hallmarks of aging[9,10] to address fundamental questions about how frailty accumulates.

Preclinical models of frailty offer advantages. When compared with their equivalent human scales, both the frailty phenotype and frailty index tools exhibit similarities in the items of which they are composed (Table 1). These measures are responsive to frailty interventions and are relatively easy to administer. Further, these tests are noninvasive so they can be used in longitudinal studies to track the impact of interventions over time for a given individual. Nevertheless, existing preclinical models have limitations. For example, lifestyle, environmental and social factors that profoundly influence the degree of frailty in humans have yet to be investigated in preclinical models. In addition, deficits in domains such as cognition and activities of daily living have not yet been included in preclinical tools (Table 1). Future studies should further refine these instruments to better model the breadth of human frailty during aging.

Testing frailty interventions in preclinical models. Frailty assessment in preclinical models provides a translational platform to test new frailty interventions (Table 2). This can include interventions that attenuate frailty as well as those that exacerbate it. It is well established that voluntary aerobic exercise and high-intensity interval training reduce frailty in animal models (for example, in refs. [186–189]). Known longevity interventions, including calorie restriction, antioxidants (for example, resveratrol) and mechanistic target of rapamycin (mTOR) inhibitors (for example, rapamycin) also reduce frailty in naturally aging mice[181,190], as well as in genetically manipulated mice[191,192] and nonhuman primates[71]. In contrast to these findings, a ketogenic diet that mimics calorie restriction has little effect on the level of frailty in aging mice[193]. Other dietary interventions like protein restriction[194] or intermittent fasting[195] also reduce frailty or components of frailty, but only in male mice. This indicates that the effects of frailty interventions can be sex specific, which is important as many intervention studies have used only one sex—generally male (Table 2).

Other approaches to mitigate the degree of frailty have been investigated. Hematopoietic stem cell transplantation using new transplantation technology can both increase life span and reduce the degree of frailty[196]. Drugs that inhibit the renin–angiotensin system (for example, the angiotensin-converting enzyme inhibitor, enalapril) reduce FI scores in aging mice[182]. Enalapril also reduces biological age and increases life expectancy, as shown by two new 'clocks' estimated from FI scores using machine-learning techniques[197]. Known longevity interventions (for example, methionine-restricted diet) also reduce frailty, lower biological age and increase life expectancy[197]. Dietary supplements like alpha-ketoglutarate or allicin (a compound derived from garlic that inhibits inflammation) attenuate frailty in aging mice[198,199]. This suggests that currently approved drugs and supplements may be repurposed to treat frailty in people. There is still much work to be done here as most drugs identified as geroprotectors for use in clinical studies[27] have not yet been investigated for effects on frailty. Preclinical models of frailty can also be easily used to investigate whether combination therapies (for example, drug treatment plus an exercise regimen) may better attenuate or even reverse frailty accumulation in aging.

While some interventions can attenuate frailty in preclinical models, others can make frailty worse. For example, genetic disruption of mTORC2 in the brain impairs glucose homeostasis and increases frailty[200]. In addition, when aging mice were treated with five commonly used medications to model polypharmacy, their frailty scores increased[201]. Interestingly, de-prescribing reversed this effect on frailty, which suggests that de-prescribing may be a viable strategy to combat frailty in older adults[201]. Other work has shown that sublethal whole-body irradiation causes premature frailty, which has implications for the long-term health of patients
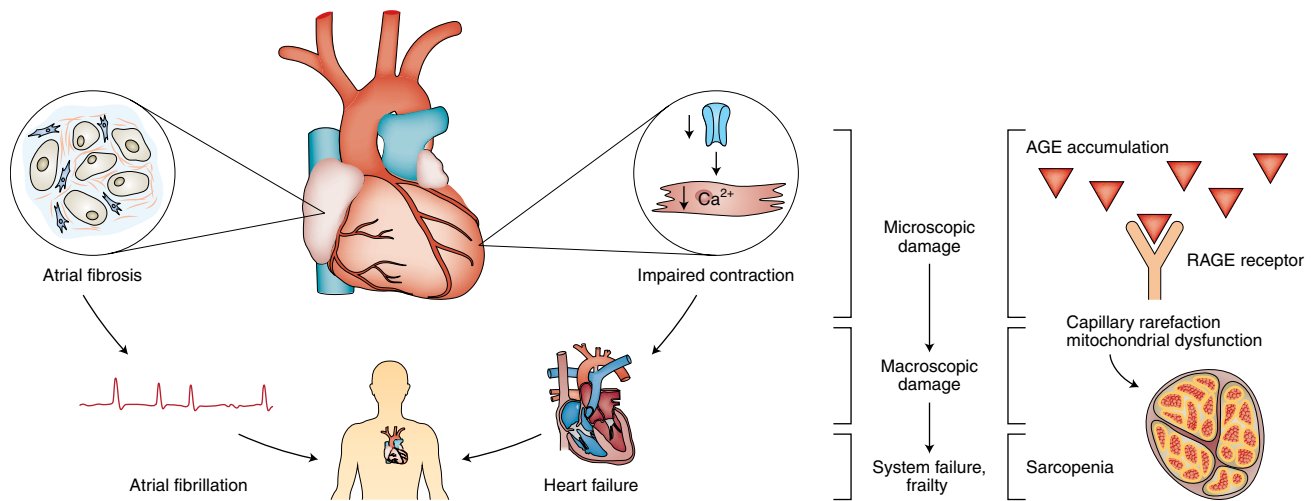
Fig. 4 | Age-associated deficits arise at the molecular/cellular level in frail individuals, scaling up to affect function at the organ and system levels. Left, accumulation of subcellular damage such as collagen deposition in the atria and reduced calcium channel expression in the ventricles results in atrial fibrosis and impaired cardiac contraction, respectively. These changes may promote chronic diseases like atrial fibrillation and congestive heart failure, which can ultimately lead to system failure and frailty. Preclinical studies show that age-related changes in the heart are closely graded by the degree of frailty, so that for both young adult mice (7–12 months, depending on the study) and aged mice (>22 months), those with high frailty scores have the most subcellular damage. Right, the accumulation of AGEs in aging can reduce blood supply in skeletal muscle, leading to sarcopenia and impaired physical performance. Clinical studies indicate that individuals with high levels of frailty exhibit more AGE accumulation and functional impairment than those with lower frailty scores. This figure was modeled on data in refs. [33–35,180].

with cancer[202]. Mice fed a high-fat diet showed an increase in body weight in both sexes, but frailty increased only in male animals[181]. This sex difference could reflect male–female differences in the ability to resist a stressor, although additional work to generalize this result is needed.

Computational models can facilitate translational research. Aging individuals are complex, interconnected systems. This interconnectedness implies that predicting the specific effects of multiple interventions (for example, deleterious polypharmacy, but also useful interventions) in the face of multiple ailments (multimorbidity) for a particular aging individual will be impossible without embracing the system complexity. Computational models that embrace the complexity of aging (Box 1) will help us to translate results from animal and cellular models to human medicine, and to improve the life course of individual adults at any given point in their life by appropriately choosing from a suite of treatment options. Dynamical models that include interactions between cellular, laboratory and clinical scales of function over individual lifetimes will help us to understand the benefits of specific therapies. Personalized medicine for aging individuals—one that respects individual priorities and capacity for important lifestyle change—will also be facilitated by a deeper understanding of the complexity of aging. Optimized treatment choices and timing to best extend or improve the health span of individuals may then be possible.

Conclusion

As we age, each of us moves closer to death—although not everyone of the same chronological age has the same risk of death. Heterogeneity in rates of aging motivated the idea of frailty. The complexity that underlies heterogeneity in aging reflects its multiply determined nature. This complexity is belied by striking regularities: everyone accumulates health-related deficits with age; women live longer on average than men do, although often in worse health; poor people tend not to live as long as those who are very well off; and everyone dies. Understanding frailty is motivated by two goals: to finely grade risk, and to understand the basis of

differential risk, both with a view to modifying or managing it. How should we proceed?

Frailty helps us manage risk. As a clinical construct, frailty identifies people whose age-related health status puts them at greater risk than their aging peers. That risk can be graded by the degree to which someone is frail. The degree of frailty can be practically operationalized both for only a few key variables (as in the frailty phenotype or the Clinical Frailty Scale) and with many variables (as in the frailty index). Greater frailty correlates with worse outcomes[58,84,87,118,203,204]. The degree of frailty can thereby inform clinical decision-making, where prognosis is the key. This is especially true regarding informed consent about procedural risk or tolerability of chemotherapeutic regimens. Better informed consent follows from better risk gradation for specific interventions. For example, if an intervention transiently increased the degree of frailty by about 0.3, then the chance of dying can be better quantified with respect to the baseline frailty because mortality is high when a frailty index score approaches 0.7 (ref. [205]).

Knowing that increased frailty increases risk does not mean that the increased risk is irreversible. The elements that are giving rise to frailty for that individual can be treated or managed. Especially for elective interventions, undertaking pre-procedural management and prehabilitation may offer risk mitigation[206,207]. Monitoring outcomes by the degree of pre-intervention frailty and the risk of the procedure could also incentivize innovations in care. Some of that innovation might simply be knowing which days after an intervention are the riskiest, with attention being paid to the types of adverse events that arise in relation to the degree of frailty. As attention is increasingly paid to frailty treatment[208], there will then be a need to understand what represents a clinically meaningful treatment effect[209–211].

This approach to quantified risk can be extended to hospital care. Any number of routine hospital practices are often accepted even though they exacerbate risk—for example, being malnourished, lonely, in pain, unnecessarily immobilized, deprived of sleep, over-sedated, otherwise over-medicated, not having personal agency or being exposed to intermittent fear-inducing events.

Table 2 | Frailty interventions in preclinical studies

Model	Age	Sex	Key findings	Effect on frailty	Refs
C57BL/6 mice	6 and 28+ mos.	M	An aerobic exercise program (voluntary wheel running) improves physical performance and reverses frailty, assessed with the frailty phenotype tool, in aging mice.	↓	186
C57Bl/6J mice	3 to 28+ mos.	M	Lifelong aerobic exercise (voluntary wheel running) reduces frailty assessed with the frailty phenotype. Sedentary animals become frail as they age.	↓	187
C57BL/6 and short-lived DBA/2J mice	18 to 24 mos.	M/F	Known longevity interventions (for example, CR and resveratrol treatment) reduce FI scores in C57BL/6J mice. Short-lived male mice (for example, DBA/2J) are frailer than controls (effect not seen in females).	↓	190
NIH Swiss mice	2 to 24 mos.	M/F	Rapamycin (an mTOR inhibitor) increases longevity in female mice but not in male mice. Rapamycin has no effect on frailty in either sex, except that it reduces frailty in male mice fed a high-fat diet.	↔↓	181
NIH Swiss mice	2 to 24 mos.	M/F	A high-fat diet reduces life span and increases frailty in male mice but has no effect in female mice.	↑	181
C57BL/6 mice	2–4 mos. to 30 mos.	M	A ketogenic diet, which mimics aspects of CR, reduces midlife mortality but not life span, improves memory, with only a modest effect of FI scores in aging mice.	↔	193
Nonhuman primates (rhesus monkeys)	10–28 years	M/F	CR reduces frailty (assessed via frailty phenotype) and increases healthy life span in nonhuman primates. CR reduced frailty and mortality in both sexes. No obvious sex differences.	↓	71
C57BL/6J	24 to 28 mos.	M	High-intensity interval training reduces frailty, assessed with the phenotype approach in aging mice, in aged male mice.	↓	188
C57BL/6J	24 to 26 mos.	F	High-intensity interval training reduces FI scores in aging female mice, even when started late in life.	↓	189
C57BL/6 mice; NF-κB KO mice	4 to 24+ mos.	M	Rapamycin (an mTOR inhibitor) treatment extends health span and reduces FI scores in mice with enhanced NF-κB signaling and accelerated aging (the $Nf\kappa b1^{-/-}$ mouse model).	↓	191
Hypothalamic mTORC2 KO	4–6 mos. to 22+ mos.	M/F	mTORC2 signaling in brain regulates metabolism in aging. Genetic ablation of mTORC2 in hypothalamic neurons impairs glucose homeostasis, reduces life span and increases frailty in both sexes.	↑	200
AQ-RKO mice	2–3 mos. to 40+ mos.	M/F	Adipose-specific deletion of mTORC *Rictor* (AQ-RKO) disrupts adipose mTORC2 and blunts metabolic adaptations to CR. Despite this, CR reduces FI scores and increases life span in AQ-RKO mice in both sexes, as it does in wild-type mice.	↓	192,145
C57BL/6 mice	9–13 mos. and 16–25 mos.	M/F	Enalapril (an angiotensin-converting enzyme inhibitor) treatment reduces FI scores in both sexes, via reducing pro-inflammatory cytokines in females and increasing anti-inflammatory cytokines in males. FI scores are higher in females than males.	↓	182
C57BL/6 mice	5–12 mos. and 22 mos.	M	Treatment of 5- to 6-month-old male mice with three sessions of sublethal irradiation increases FI scores at 12 mos. to levels like those seen in much older (22 mos.) nonirradiated mice.	↑	202
C57BL/6 mice	18 to 33+ mos.	M/F	Dietary supplementation with alpha-ketoglutarate (major metabolite in tricarboxylic acid cycle) extends life span in middle-aged female mice and reduces FI scores across the life course in both sexes. No apparent sex differences in frailty.	↓	199
C57BL/6J mice	19 to 27+ mos.	F	Replacement of aged hematopoietic stem cells with donor cells from young mice increases life span and reduces frailty in aging mice.	↓	196
Fischer 344 rats	6 to 21 mos.	M	Allicin, a component of garlic that attenuates inflammation, attenuates osteoporosis by reducing bone turnover and reduces FI scores in aging rats.	↓	198
C57BL/6J mice	12 to 24+ mos.	M	Mice treated with a chronic polypharmacy regimen with a high drug burden index have high FI scores and poor physical function. These adverse effects are attenuated by de-prescribing.	↑	201
C57BL/6 mice	21 to 39+ mos.	M	With machine-learning approaches, longitudinal FI scores can be used to develop the FRIGHT clock (predictor of biological age) and the AFRAID clock (predictor of life expectancy). Both clocks respond to interventions that attenuate frailty (for example, enalapril and a methionine-restricted diet).	↓	197
C57BL/6 mice	16 to 36+ mos.	M/F	A protein-restricted diet low in BCAAs reduces FI scores and increases life span in male but not female wild-type mice. A low-BCAA diet also increases survival in two short-lived progeroid mouse models.	↓	194
C57BL/6 mice	20 to 39+ mos.	M/F	Intermittent fasting in late life reduces frailty components in males not females. Effects of dietary restriction depend on increased renal H_2S production; H_2S levels were increased by intermittent fasting and correlated with lower frailty in males only.	↓	195

AQ-RKO, adipose-specific *Rictor* KO mice; BCAAs, branched-chain amino acids; CR, calorie restriction; F, female; FI, frailty index; H_2S, hydrogen sulfide; KO, knockout; M, male; mTORC2, mTOR complex 2; NIH, National Institutes of Health; NF-κB, nuclear factor kappa B.

Box 1 | Mathematical modeling can embrace the complexity of aging

- **Embracing complexity**. Health is multidimensional and individually heterogeneous, with strong coupling between health characteristics. Complex computational models will help us to embrace the complexity of aging.

  - **Reconciling multiple health measures**. Multiple biological ages are correlated with frailty, but do not coincide[19]. Multidimensional models can help us to both reconcile and improve disparate measures.
  - **Exploring the processes behind changing individual health**. The dynamical processes of damage and recovery underlie the net changes to individual health that are captured by frailty. Recovery or repair can be described by 'resilience', while resistance to damage can be described by 'robustness'[64]. Measurements of health, frailty, resilience and robustness are interdependent, and can be included in complex models of aging[15].
  - **Moving between individual and population health**. Complex models of aging are typically models of individuals, but can also be used to study populations of individuals. They are natural tools to see how population data constrains the process of individual health trajectories, and conversely how personal health interventions may affect population health.

- **Embracing the complexity of health interventions for individuals**. The complexity of polypharmacy and multimorbidity highlights the difficulty of treating aging health as a collection of independent ailments. Personal health priorities and personal capacity to undertake, for example, dietary restriction and exercise, make treatment even more complex. Complex models of aging could help individuals to navigate this landscape, to help people see how accessible interventions may impact their future prognosis.

- **Understanding aging phenomenology**. Mathematical models can provide simulated aging individuals and populations. Joint models of health and mortality can capture heterogeneity within populations and interactions between aspects of health and with mortality. Joint network models have highlighted complex interactions during aging[15,223].
- **Analysis of aging data**. Mathematical models can help us to develop new approaches to data analysis. Interactions between different measures can be described by correlation networks[224] and can be included in complex network models of aging. Different frailty maxima observed with systematic approaches to data dichotomization[225] can be recapitulated in network models[48]. Machine-learning techniques provide appealing approaches to incorporate large amounts of aging data[226].

Multicomponent interventions that target such features[31], such as the Hospital Elder Life Program, are effective in improving outcomes[212], including delirium, for example, by applying cognitive screening, physical and social measures for delirium prevention, and reducing medications likely to increase delirium risk[213]. Indeed, understanding the relationship between frailty and delirium, and frailty and dementia, offers a pragmatic means to reduce dementia incidence[214,215]. A nuanced understanding is needed to strike a judicious balance between therapeutic adventurism and nihilism.

Frailty provides context for age-related changes. Measuring the degree of frailty helps us understanding the extent to which mechanisms of aging operate. We can understand how mechanisms change with age. We can also understand how some changes have more widespread effects than others[216]. This synergizes with the geroscience agenda of treating aging mechanisms that have wide-ranging effects, following the example of exercise or diet.

The geroscience theory of fundamental aging processes posits that only a few key processes underpin how age-associated diseases arise: chronic 'sterile' immune activation; macromolecular dysfunction (from DNA damage to protein misfolding and mitochondrial dysfunction); stem, progenitor and immune dysfunction; and cellular senescence[10]. The theory posits that treating any one mechanism should affect the rest as well[216]. However, to avoid diluting the impact of separate interventions, some way must be found to integrate different treatment effects. The wide range of potential individual effects from treating fundamental aging processes obliges multicomponent measures so that the benefits, not just the problems, of old age can come as a package[1]. Frailty provides such a broad multicomponent measure.

Of course, many other quantifiable approaches to summarizing the effects of aging exist. They will offer complementary information to understanding the degree of frailty or the overall biological age, based on tailored features that explicitly relate to putative aging mechanisms. Moving forward, cohort studies can provide that level of detail for new aging treatments and relate them to

clinically detectable grades of frailty[63,217–219]. A focus on multimorbidity to study the treatment of what are termed 'aging-related rather than disease-specific outcomes' is already under way[220], as is a testing program of established interventions from the US National Institute of Aging in a genetically heterogenous mouse model[220–222].

The complexity of aging can be addressed in large-scale animal studies of naturally aging animals. Mouse models currently predominate, given their suitability for genetic manipulation. Diversification into studies of other animals, especially rats, non-human primates and companion animals, would help to translate interventions and clarify our understanding of how human aging is both similar to and distinct from animal models of aging research.

Quantitative models of aging can also advance our understanding. Frailty invites consideration of how measurable aspects of health interact. Approaches and techniques borrowed from other disciplines, such as complex networks, information theory, queuing theory and machine learning, can be used to understand how the degree of frailty is related to change in frailty states or mortality. While a specific health deficit can be understood as a cumulative imbalance between damage and repair, measuring these processes directly over individual life courses is not simple. Quantitative models will let us separately consider sources of damage, including the social environment, from factors that facilitate resisting damage such as vaccination, from factors that facilitate repair such as health care.

The impact of aging on health. Policymakers and the scientific community have been exhorted to prepare for an aging population. Often, attention is drawn to some disease becoming more common as the population ages, so that progress relies on studying how that illness arises, and how to treat it. Seldom do we consider how diseases become more likely to manifest as an individual ages, beyond a cumulative exposure to risk. Even so, we must conceptualize, measure and mitigate the impact that aging has on health. The geroscience agenda has advanced the conceptualization and is aimed at developing treatments. Frailty provides a way of measuring the impact of aging on health. It embraces the complexity of aging in

ways that can make its heterogeneity comprehensible. The measure of successful interventions to mitigate the impact of aging on health will be to reduce frailty at the individual and population levels.

Here we have shown that quantifying the degree of frailty addresses two issues raised as fundamental—one in geriatric medicine, and the other in geroscience. The geroscience agenda rests on the assertion that with aging comes myriad changes that impact on any one disease of aging. In basic science investigations of the heart, we see that many of the changes attributed to aging not only arise in old age, but also can be seen in middle age, where they influence disease expression, a feature seen in humans too. Understanding the degree of frailty can add value in considering the heterogeneity of changes in cardiovascular, cognitive and sensory function, even in the presence of other measures of biological age. The degree of frailty also appears to be responsive to a variety of interventions, including in preclinical models. In geriatric medicine, the complexity of aging is reflected in measures that can usefully summarize information to quantify the degree of frailty. That information in turn can be used to target interventions and, using the information gathered in understanding baseline frailty, to develop individualized care plans that embrace the complexity of frailty.

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Author contributions

S.E.H. and K.R. conceived the review and wrote the first version of the manuscript. A.D.R. provided constructive input and wrote additional sections in subsequent revisions of the manuscript. All authors approved the final version of the article and figures.

Competing interests

K.R. has asserted copyright of the Clinical Frailty Scale through Dalhousie University's Industry, Liaison and Innovation Office. Use is free for education, research and not-for-profit health care. Users agree not to change or commercialize the scale. In addition to academic and hospital appointments, K.R. is cofounder of Ardea Outcomes, which (as DGI Clinical) in the last 3 years has contracts with pharma and device manufacturers (Biogen, Hollister, Novartis, Nutricia, Roche and Takeda) on individualized outcome measurement. In 2019, K.R. was paid an honorarium for an interview with Biogen. In 2020, he attended an advisory board meeting with Nutricia on dementia, and chaired a scientific workshop and technical review panel on frailty for the Singapore National Research Foundation. Otherwise, any personal fees were for invited guest lectures, rounds and academic symposia, received directly from event organizers, for presentations on frailty. K.R. is associate director of the Canadian Consortium on Neurodegeneration in Aging, which is funded by the Canadian Institutes for Health Research, the Alzheimer Society of Canada and several other charities. S.E.H. has a paid consulting role with Ardea Outcomes. A.D.R. has no competing interests to declare.

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