

Frailty and Chronic Diseases in Older Adults

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KEYWORDS

• Chronic diseases • Frailty • Epidemiology • Efficiency

THE IMPORTANCE OF FRAILTY AND CHRONIC DISEASES

There are 2 hallmarks of aging that are primary concerns for those trying to improve health for older adults. One is an increased vulnerability to advanced and persistent loss of function that, at least initially, only becomes evident under stress: frailty. Frailty has been described as loss of ability to adapt to stress because of diminished functional reserves.^{1,2} According to this simple description, frailty may be said to provide an exaggerated example of how physiologic functions attenuate with aging. The second is the accumulation of pathologic processes that are evident and for which there is substantial agreement about definition: chronic diseases. Frailty and chronic diseases are prime modulators of a person's health trajectory in later life. An understanding of the presence or absence of frailty and chronic diseases constitutes a basic representation of physiologic reserves in old age.

This paper reviews epidemiologic associations among frailty and chronic diseases. Interrelationships among diseases and frailty are discussed, and punished inefficiency is introduced as an explanatory framework for frailty that draws on pathophysiologic relationships caused by chronic diseases and conditions. We use phenotypic definition of frailty as defined in the Cardiovascular Health Studies and in the Women's Health and Aging Studies.^{3,4} This definition was chosen because of several considerations. It was one of only 2 attempts to create a standardized and reliable definition using population-based samples of older adults. The other attempt to do this, the cumulative deficit approach by Rockwood⁵ and Rockwood and colleagues,⁶ is based on a summation of markers of impairment that is inseparable from chronic diseases. Although the cumulative deficit approach is elegant and useful for other purposes, it is not intended to guide a discussion of the mechanisms that cause frailty. We use the prior definition that was created with the purpose of creating a model to facilitate understanding of the physiologic processes that lead to the clinical presentation of

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frailty and to identify therapeutic targets. Such considerations are integral to any discussion of the interface between frailty and chronic diseases. The article by Xue elsewhere in this issue presents a more detailed overview of frailty in later life, and includes discussions of alternative concepts and operational definitions of frailty.

There are several sources of vulnerability in the poor health outcomes that, while being related to frailty, can be considered distinct from intrinsic frailty. How a person interacts with the environment and makes decisions play major roles in modulating the development and course of frailty or diseases. Physiologic frailty may be unobservable outside a specific context made up of environmental features and behavior molded by that environment, and therefore a full measure of frailty would require a matrix comprising physiologic reserves and parameters for interactions with the environment and personal choices. The discussion here focuses on physiologic contributors to changes in function at the individual level and also considers frail individuals with altered physiologic function in the context of interactions with health care systems.

INSIGHTS FROM THE EPIDEMIOLOGY OF FRAILITY AND CHRONIC DISEASES

Epidemiology of Frailty

The prevalence of frailty has been estimated to be 6.9% among older community-dwelling adults in the United States, and it increased within that group from 3.2% among 65- to 70-year-olds to 23.1% among people aged 90 years and older.³ This prevalence was also higher in women and African Americans⁷ or people of Latino origin, although using reference ranges derived from ethnic cohorts may explain some of these differences.⁸ Frailty is therefore less prevalent than most chronic diseases that are ranked highly as causes of death or morbidity. The incidence of frailty has been estimated at 71.8/1000 person years in the Cardiovascular Health Study (CHS),³ 22.5 to 38.7/1000 person years in the Precipitating Events Project,⁹ and as high as 191/1000 person years in women from among the one-third most disabled living in the community in the Women's Health and Aging Study I.¹⁰ The onset of frailty may occur most often as weakness, followed by slowness¹¹; however, among people who have developed frailty (ie, have at least 3 of the 5 criteria), slowness was found most commonly.¹² The duration of frailty is not long in comparison with most diseases. In 1.5 years, 12.9% to 23.0% of people with frailty recovered to a prefrail state, whereas 13.1% to 20.1% died.⁹ Thus, the time spent frail is also less than time spent disabled,¹³ because of higher risk of mortality.

Given the prevalence and duration, it follows that a small minority of people who have multimorbidity, several chronic diseases simultaneously, are frail. In CHS, only 9.7% of the older adults with multimorbidity were frail, whereas 67.7% of frail adults had multimorbidity among 9 diseases considered.³ The mean number of chronic diseases experienced by a frail older adult was roughly 2.1, compared with 1.4 among nonfrail older adults.⁷ These findings suggest that frailty is either (1) not caused by mechanisms that are shared with chronic diseases; (2) may be caused by mechanisms that are shared with chronic diseases once the diseases have reached a severe or advanced state; or (3) may be caused by specific interactions between disease-related physiologic impairments that occur less frequently than single diseases, but is unlikely to be caused by 1 or 2 disease pathways alone, except in the case of (2).

Frailty and Chronic Diseases

Table 1 lists the chronic diseases that have been associated with frailty in published cohort studies of older adults that used standardized disease ascertainment.^{3,14–16} Starting with the most common chronic disease among the frail, hypertension, the

Chronic Disease	Prevalence (%)				Citation(s)
	Women		Overall		
	Frail	Nonfrail	Frail	Nonfrail	
Hypertension	60.8	43.4	50.8–53.1	34.0–38.8	1b; 13a; 14b,c
Chronic kidney disease	54.3	42.5	–	–	25b
Osteoarthritis	78.2	48.1	25.9–70.8	9.7–44.8	1b; 13b; 14b
Depressive symptoms	46.3	13.3	–	–	25b
Coronary heart disease	17.2–41.5	5.8–20.8	–	–	12b; 14b
Diabetes mellitus	9.9–21.3	2.6–12.1	13.6–25.0	10.0–12.1	12a; 13; 14b
Chronic lower respiratory tract disease	9.8–15.5	2.5–4.3	12.3–14.1	7.4–5.8	1b; 12; 13; 14b
Myocardial infarction alone	–	–	8.6–13.3	4.4–7.3	1b; 13
Rheumatoid arthritis	6.4	1.6	–	–	12b
Stroke	4.4	1.1	12.3	3.8	13a; 14b
Peripheral arterial disease	–	–	3.8–14.8	1.5–5.6	1a; 13a
Congestive heart failure	3.5	0.6	12.3–13.6	2.0–3.6	12b; 14b

^a $P < .05$.

^b $P < .01$.

^c Nonfrail group did not include prefrail, sometimes called intermediate group, because prevalence for that group was reported separately. In addition to sample selection, there are differences among cited studies related to disease definition and/or operationalization of frailty criteria that may explain differences. Data for men are not shown because these were not reported in the studies. Chronic lower respiratory tract disease is asthma or chronic obstructive pulmonary disease.

prevalence is shown in descending order among frail and nonfrail older adults to allow absolute and relative comparisons. This comparison is shown for women and overall, because data for men were not reported in the studies that included men. Joint examination of the studies in **Table 1** points to several findings. The prevalence of chronic diseases, even if taken one at a time, is often doubled in older women who are frail, and sometimes increased by a factor of 3 or 4 for less-common diseases for which a tripling or quadrupling is possible. However, there is no single disease-frailty association that seems to be markedly stronger than the rest, even if congestive heart failure and depression are foremost. The nonfrail group did not include the prefrail group, sometimes called intermediate group, in some studies because prevalence for that group was reported separately. In addition, besides sample selection, there were differences related to disease definition and/or operationalization of frailty criteria among cited studies that may have caused small artifacts.

Frailty and Non-Disease Conditions

Some common conditions that are causes or consequences of chronic diseases in older adults have been shown to be associated with frailty. Among these, a poor nutritional state has been strongly implicated by consistent findings that show an increased risk for malnutrition¹⁰ and evidence of low nutrient intake^{17–19} in frail older adults. Together with the low activity levels that are part of the frailty definition, these support the hypothesis that energy dysregulation may be a central issue in frailty as it is in congestive heart failure, diabetes, stroke, and chronic lung disease. These diseases were all noted to be associated with frailty in **Table 1**. What has not been

determined yet, but is currently being studied, is how frail older adults may experience a redistribution among the compartments that make up total energy expenditure: activity, resting metabolism, thermogenesis related to food intake, and other compartments. In further support of impaired energy throughput as an important pathway in frailty and chronic disease development, anemia has been shown to interact synergistically with cardiovascular disease as a risk factor for frailty with a test for interaction.¹⁴ A review of the many conditions or syndromes that are not conventional diseases but have been hypothesized to shed light on the causes of frailty is outside the scope of this discussion. Notably, inflammation,^{20,21} which can be caused by chronic diseases, overlaps with and may lead to a shared contribution to the development of frailty. In addition, frailty has been associated with blood markers of thrombogenicity.^{22,23}

Interactions Among Frailty and Chronic Diseases and Conditions and Treatments

Fig. 1 shows how chronic diseases or conditions of varying severity may act alone or in combination, have converging or diverging effects, or lead to the use of therapeutic interventions whose unintended consequences contribute to frailty. As one example, labeled A on the left side of the figure, a person has congestive heart failure, hypothyroidism, and sarcopenia. These chronic diseases and conditions may act through distinct mechanisms that converge to cause an element of frailty if each is mild. In contrast, an example person labeled B on the right side of the figure has severe depression and experiences a more developed frailty phenotype with symptoms and signs that may have a single underlying mechanism but have diverging effects. It is unlikely that any severe chronic disease will affect reserves through just 1 mechanistic pathway or have secondary effects that are restricted to 1 physiologic system. One-to-one correlations between chronic diseases or conditions and frailty are not the rule. Many diseases can converge to cause a single prominent symptom or sign, or a single disease that is severe may cause many diverging symptoms and signs.

This schematic is consistent with the hypothesis that frailty is not disease specific.⁴ In addition, the figure illustrates that, when there is access to care, diseases almost always lead to treatments, many of which can have side effects that could contribute to frailty. This possible feed-forward phenomenon among chronic diseases, frailty, and treatment is discussed later. It has been theorized that multimorbidity entails clinically overt diseases, and, distinct from multimorbidity, frailty is an aggregate of subclinical losses of reserve across multiple systems,²⁴ and may occur in parallel with multimorbidity.²⁵ These ideas may find some support from research showing that some biologic components of the metabolic syndrome (insulin resistance, inflammation), but not the whole syndrome, predict frailty.²⁶ Although clinicians caring for

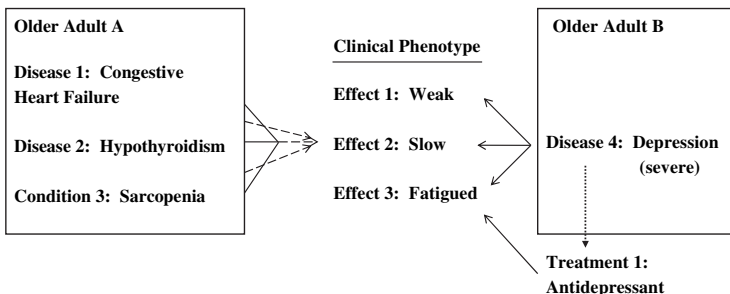


Fig. 1. Chronic diseases and conditions may act alone or in combinations, have converging or diverging effects, or lead to treatments that create frailty.

older adults know of cases in which frailty could never be ascribed to a disease diagnosis, it can be especially challenging to show empirically that frailty that is not disease related.

The possibility of interactions among diseases to cause frailty is a central issue. This possibility has been formally evaluated²⁷ using methods to test specifically for biologic interactions. In a study of 620 older women, 2 pairs of diseases or conditions were found to have significant biologic interactions that increased the risk of frailty: anemia and depression, and anemia and pulmonary disease. The proportions of the association between the diseases and frailty attributable to an interaction of the 2 diseases were substantial at 56% and 61%, respectively. Smaller interactions may have been detected by a larger study. A similar question has also been studied at the level of continuous physiologic function, rather than binary disease status, with a focus on exercise capacity as the outcome and frailty status as a potential modifier of physiologic reserves.²⁸ The study examined whether the systems involved in converting energy into lower extremity exercise capacity interact; that is, whether they responded differently to each other, in frail adults, compared with nonfrail, using interactive regression models. The results suggested that key physiologic impairments in lung function, leg strength, and frailty all caused diminished exercise capacity, cumulatively, in disabled older women. Furthermore, and more specifically, the positive effects of pulmonary function on better exercise capacity were significant in the absence of frailty but were muted in frailty, suggesting that integrated functioning could be degraded or uncoupled in frailty. Modulation by frailty status of the cumulative effects of pulmonary function and leg strength on exercise capacity was not statistically significant, possibly because of power limitations imposed by exclusion criteria for exercise testing.

INTERRELATIONSHIPS AMONG FRAILTY AND CHRONIC DISEASES

Empirical Models to Provide Further Support for Theory

The available data derived from the phenotypic approach to frailty support many aspects of the prespecified theory, a benefit and bane of hypothesis-driven research. Frailty meets criteria for a geriatric syndrome because it does not fit within a discrete disease definition category, but is substantially prevalent and involves several organ systems.^{12,29} Multidimensionality, or involvement of several physiologic subsystems, is a core characteristic of frailty, such that more than 1 impaired type of function is present.^{1,3} However, the data still leave unanswered many questions related to frailty's essential features. The list of physiologic subsystems that should be measured to capture frailty is potentially long,^{25,30,31} suggesting that there may be several subtypes of frailty.³² Unlike many conventional medical disease syndromes, frailty is likely to have multiple potential triggers, or points of entry, some of which correspond closely with advanced chronic disease complicated by malnutrition. As an alternative to the idea that there are subtypes of frailty, it is possible that there are different physiologic states, some dynamic, some suspended, on a frailty pathway. As an example of shifting among physiologic states, frailty may be both a wasting syndrome akin to failure to thrive and coexist with obesity.³³ Similarly, the reduction in heart rate variability recently associated with frailty may have different implications in differing physiologic conditions.³⁴

Because of frailty's multidimensionality, attempts to explain its causes are increasingly turning to a nonlinear, complex adaptive systems modeling approach that can provide new analyses of the relationship between frailty and chronic diseases. There has been a call to measure dynamics in response to a stressor,² making sure to

compare frail and nonfrail individuals responding to the same stressor. Such research should provide critical information because responses to stress engage feedback loops involving more than 1 physiologic system, some of which will be impaired in older adults with chronic diseases. These feedback loops may behave differently because of setpoint alterations caused by disease or the level of stressful stimulus. In such a system, small differences in starting levels can lead to divergent outcomes because a small stressor can be either diminished or magnified. Frailty is therefore an emergent property in a complex nonlinear system.³⁵ The important components are the dynamics, not just the individual functions, so interdependent risk factors and nonlinearity are expected. Instead of searching for mechanisms by holding everything except 1 variable constant, in a traditional experimental mindset, in the case of frailty it is expected that studying specific elements in isolation or one at a time cannot lead to a true understanding of the system, just as studying different cars and drivers in isolation cannot lead to a prediction of when or where traffic jams will occur.

To identify therapeutic targets in a complex dynamic system like frailty, it is necessary to distinguish compensatory mechanisms from primary derangements caused by disease. This distinction is particularly important because frailty may emerge when several diseased physiologic subsystems begin to operate semiautonomously. A strategy that is optimal for a physiologic subsystem (eg, preservation of the kidney's ability to filtrate) may have effects that are not optimal for the organism (eg, an increase in systemic vascular resistance and left ventricular end-diastolic pressure).³⁶ This example is discussed later. The uncoupling of benefit to the whole organism from compensatory strategies that, in isolation, provide benefits on a smaller scale provides refinement for the general hypothesis that frailty is the result of impaired homeostasis in several systems.

Punished Inefficiency as a Conceptual Framework for Frailty and Chronic Disease

Based on a complex dynamic systems approach, attention to the central importance of fatigue and exhaustion for frailty, and an understanding of physiologic costs and gains, punished inefficiency proposes that having several physiologic impairments leads not simply to loss of ability and proportional disadvantages but to physiologic inefficiencies. These inefficiencies may become manifest as frailty, often in the presence of disease. As a consequence, frail older adults may perform less external work to avoid spending more out of a smaller pool of internal resources. Stress imposed on frail older adults can strengthen this negative feedback on activity, and lead to disuse and to worsening of chronic disease states.³⁷

Impaired energy flow has been recognized as a prime candidate for changes caused by aging. Physiologic functioning is counterentropic because it provides a stimulus that sustains supporting physiologic structures through healthy feedback.³⁸ Conversely, age-associated blunted or reduced physiologic function leads to a loss of supporting physiologic structures, and even a restructuring of homeostasis.³⁹ This theory has been hypothesized to also apply to changes that occur because of chronic diseases, leading to frailty.³²

Punished inefficiency proposes, first, that energy should not be studied as a rate using time as the denominator, as is most commonly done in an energy expenditure approach (eg, mL O₂/kg/time elapsed). Energy flow should also be measured as a rate using work achieved as a denominator, an energy efficiency approach, sometimes also referred to as energy economy or energy cost (eg, mL O₂/kg/m traveled). Usual or preferred gait speed, a frailty criterion, provides an example of how energy efficiency provides critical guidance. Among frailty criteria, slowed gait speed is the strongest predictor of functional dependence or disability.⁴⁰⁻⁴² It is now believed

that the energy efficiency of walking explains preferred walking speed. The brain selects the most energy efficient speed as its preferred speed, also identifiable as the nadir in a curve expressing the relationships between energy costs on the y-axis and gait speed on the x-axis.^{43–45} This relationship illustrates that reduced function, an obvious consequence of physiologic impairments, may not be as important as inefficiency for identifying the optimal physiologic setpoint for an individual. Reduced function on an external and nonbiologic per-unit-time scale may not provide information that leads to an understanding of how homeostatic relationships were reorganized.

Frail older adults with impairments, compared with nonfrail older adults, can consume more energy to achieve normal levels of work, and thereby slow down to both normalize energy expenditure and, perhaps more importantly, perform tasks with as little loss of efficiency as possible. Although, to a casual observer, it may appear to be doing less, walking with physiologic impairments is inefficient, as anyone who has tried to walk up stairs with an injured leg or foot can attest. In addition, because disease-related pathologies create a smaller pool of available energy, behavior is affected by conditions of scarcity. In this way, it may be possible to better explain the behavior of frail individuals. They walk more slowly, arrive at their destination later, and use more energy to cover the same distance.

The implications of this theory, if it is further validated, are that frailty comprises a synergistic interaction whereby individuals with loss of reserves also experience loss of efficiency in a manner that is detrimental to maintaining adequate physiologic function. Many physiologic relationships are consistent with this idea. For example, the heart muscle performs more work (cardiac output, on a conventional per-unit-time basis) as end-diastolic pressure in the left ventricle increases. However, physiologic impairments related to heart failure lead to the well-known shift off the Frank-Starling curve, whereby muscle fibers are no longer at optimal length. Increased demand on the heart muscle is not translated as efficiently into increased cardiac output. The amount of oxygen consumed to achieve the same amount of oxygen delivery is increased. In a possible example of homeostatic rearrangement, there are data to suggest that adaptation in this manner can even fail to occur in older adults, which constitutes a further worsening of efficiency than a shift in the curve.⁴⁶ Loss of efficiency is a general phenomenon, because physiologic impairments in exercise capacity lead to an increase in the number of muscle fibers that need to be recruited to create the same amount of force. These changes result in recruitment of larger muscle units that are more susceptible to fatigue.⁴⁷ Research using an efficiency model, such as usual gait speed^{48,49} or the oxygen uptake efficiency slope that examines the milliliters of oxygen taken up per volume of air moved through the lungs,⁵⁰ has identified elegant predictors of physiologic reserve. **Fig. 2** provides a general form for studying physiologic function through the use of an efficiency index comprising units of cost (eg, oxygen consumed) per amount gained (eg, meters traveled, ions transported). Studying changes in efficiency should provide a way to assess when a compensatory strategy improves function. This assessment is especially important in frail older adults with diseases because of the potential for opposing effects from similar responses whose physiologic context is incompletely understood.⁵¹ In addition, although it has been suspected that many geriatric syndromes are self-sustaining,²⁹ physiologic inefficiency, especially if it is punished, provides a framework for specifying testable hypotheses related to physiologic changes associated with diseases and aging.

Reduced efficiency may often be confronted uncharitably by conditions of increased external demand, or *punished*, creating a feedback loop that further

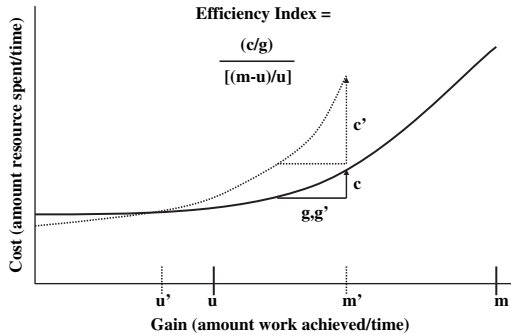


Fig. 2. Efficiency index that can be used to understand loss of optimization in frailty. Physiologic function can be studied in terms of efficiency, not simply expenditure over time. The units of this efficiency index are resource spent/work gained. c , cost in response to stimulus to increase function; g , gain in response to stimulus to increase function; M , function at maximum; u , usual function. The m , u , g , c , and solid line correspond with the healthy state. In the frail state identified by prime variables and the dotted line, maximum function is lowered ($m-m'$); usual function is lowered to a lesser degree ($u-u'$) to maintain similar physiologic expenditures on the y -axis; proportional function $[(m'-u')/u']$ can be preserved; and more resources are spent to achieve the same gain, that is, the cost slope is greater ($c'/g' > c/g$).

promotes inefficiency. Most older adults with a major chronic disease have at least 2 of them.⁵² Many physiologic examples of inefficiency are available for an older adult with at least 2 chronic diseases, and expanding the scope of investigation from physiology to behaviors and treatments will further exemplify this phenomenon.

However, even though most frail older adults have, and receive treatments for, chronic diseases, the effects of care received from a system that was not designed for the frail have received little attention in frailty research. An incomplete or distorted understanding of frailty on the part of health care providers can lead to perverse responses, whereby the level of demands placed on a person by the health care system are inversely proportional to physiologic reserves. **Table 2** presents a construct of how frail older adults with chronic diseases experience more formal care stressors, contributing to punished inefficiency. In conditions of low physiologic reserve (as can be expected in individuals with several chronic diseases), increased demands can dissipate limited resources and lead to an amplification of physiologic inefficiency. **Fig. 3A, B** illustrate this phenomenon in older adults in the National Health and Nutrition Examination Survey (1999–2001), a sample representing community-dwelling people. Hospitalization rates in **Fig. 3A**, and number of prescribed medications in **Fig. 3B**, increase synergistically according to one criterion of frailty (slower usual gait speed) and the presence of chronic diseases. In the real-world context of receiving health care, frailty can have a feed-forward negative effect on activity.⁵³

The motivation for understanding punished inefficiency is to reverse frailty, possibly by improving energy efficiency in older individuals through appropriate therapies that augment compensatory strategies. As an example, resistance training holds the potential to improve efficiency during real-life activities in older adults.⁵⁴ It is imperative to target treatment among frail older adults because a treatment can be administered in the wrong physiologic context can contribute to a rearrangement of interactions among physiologic systems that is harmful. In good health, such a rearrangement of processes is unlikely for complex, highly redundant physiologic processes, with are exceptions where there is a crucial gate mechanism, such as cardiac pacemaking.⁵⁵ In contrast, some physiologic processes and many behaviors

Table 2

How frail older adults with chronic diseases experience more formal care stressors, causing punished inefficiency

Individual Health Status	Involvement with Formal Health Care	Combined Result
In frail with chronic diseases, the intrinsic physiologic reserves listed are decreased	In frail with chronic diseases, the extrinsic stressors imposed by disease care are increased	Intrinsic resilience and extrinsic stressors are related inversely through bidirectional feedback
Structural Changes (Examples)		
Communication (rods and cones in eyes, hair cells in ears, nerve cells)	Number of people providing care (primary care, subspecialists, mental health)	Decreased ability to receive an increased amount and variety of sensory input
Dimensionality across scales (loglinear hormonal relationships)	Number and type of visits (urgent, follow-up)	
Coupling connections across systems (nutrient availability, oxygen use and thermogenesis)	Number and type of tests and interventions (diagnostic procedures)	
Functional Changes (Examples)		
Range of stimulus that can be processed (levels of light, sound waves)	Emergency care (emergency room, hospital) Duration of illness episodes (deconditioning)	Decreased ability to reconcile and create targeted response to an increased amount and variety of stressors
Dynamic range of function (tendon elasticity, renal clearance, gas ventilation, blood oxygen carrying capacity, mental multitasking)	Locations of care and health care information iatrogenic complications and conflicting therapies (nosocomial infections, delirium, deep vein thrombosis)	
Dimensionality (maintenance of muscle mass, salt and water balance, life space)	Reversals of improving trajectory (exacerbations of coexisting conditions)	
Ability to qualitatively change processing (speed up, walk on different surfaces, efficiency)		
Anatomic integrity (ulcerations, tooth loss, amputations)		
Emergent Manifestations (Examples)		
Impairments are synonymous with diminished adaptive capacity (falls causing injuries) Integrative ability is also impaired leading to energetic inefficiency (early fatigue)	Increased use and spending	Diminished therapeutic effectiveness, and increased disability and death

Formal health care refers to paid activities that an older adult would not do if they were healthy. Informal health care by unpaid caregivers is important and not illustrated here because of space constraints.

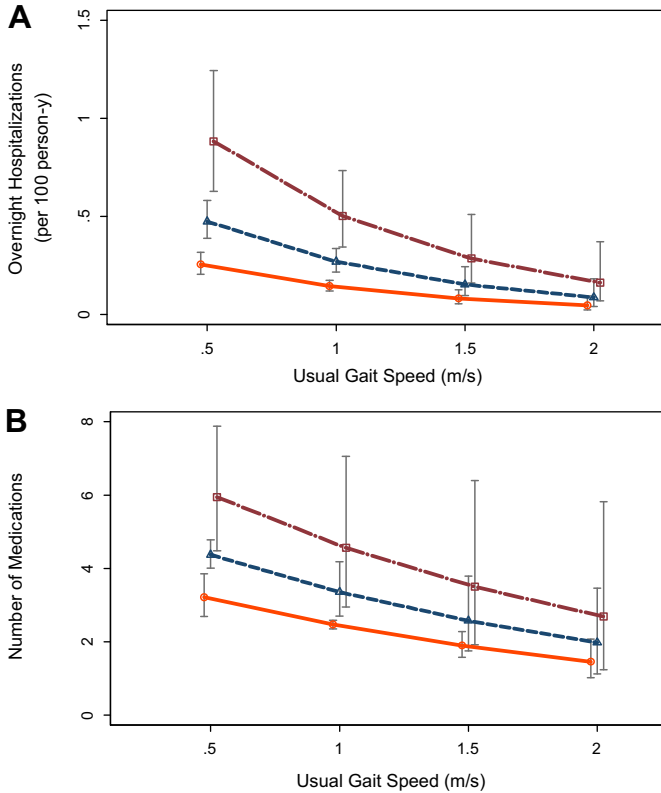


Fig. 3. (A) Rate of overnight hospitalization among older adults in NHANES 1999 to 2002, according to usual gait speed and presence of 1, 3, or 5 chronic diseases. (B) Number of medications taken by older adults in NHANES 1999 to 2002, according to usual gait speed and presence of 1, 3, or 5 chronic diseases. Circle/solid orange line, 1 chronic disease; triangle/dashed blue line, 3 chronic diseases; square/dot-dashed red line, 5 chronic diseases. Bars are 95% confidence intervals. Data are from people aged 65 years and older in NHANES 1999 to 2002 ($n = 3953$) and estimates are from multivariable negative binomial regression models using survey weights. Gait speed and chronic diseases were significant predictors of both outcomes ($P < .01$) and for number of medications an interaction term was also significant ($P = .003$). Residual age difference was not a significant contributor after adjustment for gait speed and chronic diseases and was removed from final models.

by frail people with chronic diseases are highly reflexive (ie, dependent on sensory input for deciding the type of response) and therefore more capable of shifts or reversals that short-circuit homeostatic mechanisms, resulting in a negative feed-forward effect. For this reason, future work on the interactions of frail older adults with the health care system appears to be highly important.

DO INTERVENTIONS THAT PREVENT OR TREAT CHRONIC DISEASES ALSO PREVENT FRAILITY?

The current standard is to treat geriatric syndromes, even when incomplete understanding complicates diagnosis and management must be directed at manifestations, not underlying causes.²⁹ However, caution seems warranted before approaching frailty this way because it is possible that there are physiologic subtypes of frailty,

and response to an intervention is likely to vary according to several factors, such as the level of functioning of several interdependent physiologic systems. Given current understanding, there is a limited basis for directly treating frailty. Exercise has been shown to have the potential to reverse several non-disease-specific characteristics of frailty.^{56,57} An important opportunity to improve current understanding of the causes of frailty would arise if frailty were measured as an outcome in randomized controlled trials of disease-based therapies. For example, observational data currently do not support the idea that use of statins, with their pleiotropic effects on lipid levels and inflammation, lowers incidence of frailty.⁵⁸ However, data from randomized trials are needed to gain a clearer understanding of whether statins, or other pharmacologic therapies, have a biologic effect on the development or prognosis of frailty. The major barrier to gaining such an understanding from randomized trials is a failure to measure frailty as an outcome in large trials of older adults.^{30,59} In particular, frailty holds promise as a treatment effect modifier that identifies a small but vulnerable subset in whom treatment can be more or less efficacious.⁵⁷

SUMMARY

The goal of geriatric medicine is to continually improve how older adults can avoid or be affected by the diseases and frailty that often accompany later life. Although it only affects a minority of older adults, frailty is highly predictive of adverse health outcomes. The associations between frailty and chronic diseases can inform a next generation of models to understand frailty as an emergent property in a complex adaptive system. Punished inefficiency may serve as one of these models to distinguish physiologic compensations from impairments and avoid feedback loops that cause or accelerate frailty. The effects on frailty of treatment directed at chronic diseases have received little attention thus far.

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