The Frailty Syndrome: Definition and Natural History

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KEYWORDS

• Clinical phenotype • Hazard ratio • Frailty
• Latent class analysis

Frailty is a common clinical syndrome in older adults, which carries an increased risk for poor health outcomes, including falls, incident disability, hospitalization, and mortality.[1–5] Elucidating its cause and natural history is therefore critical for identifying high-risk subsets and new arenas for frailty prevention and treatment.

In an attempt to standardize and operationalize the definition of frailty, Fried and colleagues[2] proposed a clinical phenotype of frailty as a well-defined syndrome with biologic underpinnings. These investigators hypothesized that the clinical manifestations of frailty are related in a mutually exacerbating cycle of negative energy balance, sarcopenia, and diminished strength and tolerance for exertion. Building on this conceptual framework, preliminary evidence has now been obtained on the natural history of the clinical phenotype of frailty.[3,6] This article reviews the current state of knowledge regarding the epidemiology of frailty by focusing on 6 specific areas: (1) clinical definitions of frailty, (2) evidence of frailty as a medical syndrome, (3) prevalence and incidence of frailty by age, gender, race, and ethnicity, (4) transitions between discrete frailty states, (5) natural history of manifestations of frailty criteria, and (6) behavior modifications as precursors to the development of clinical frailty.

DEFINITION OF FRAILTY

Frailty is theoretically defined as a clinically recognizable state of increased vulnerability, resulting from aging-associated decline in reserve and function across multiple physiologic systems such that the ability to cope with everyday or acute stressors is compromised. In the absence of a gold standard, frailty has been operationally defined by Fried and colleagues[2] as a condition meeting 3 of the 5 phenotypic criteria indicating compromised energetics, namely, low grip strength, low energy, slowed waking speed, low physical activity, and unintentional weight loss (**Table 1**). A prefrail stage, in which 1 or 2 criteria are present, identifies a subset at high risk of progressing to frailty. Various adaptations of the clinical phenotype described by Fried have

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Table 1
Comparison of the frailty-defining criteria defined by the Cardiovascular Health Study and the Women's Health and Aging Studies

Characteristics	Cardiovascular Health Study	Women's Health and Aging Studies
Weight loss	Baseline: lost >4.5 kg unintentionally in the last year Follow-up: ([weight in previous year − current weight]/[weight in previous year])≥0.05 and the loss was unintentional	Baseline: either of the following: ([weight at age 60 y − weight at examination]/[weight at age 60 years])≥0.1 BMI at examination<18.5 Follow-up: either of the following: BMI at examination<18.5 ([weight in previous year − current weight]/[weight in previous year])≥0.05 and the loss was unintentional
Exhaustion	Self-report of either Feeling that everything the person did was an effort in the last week Inability to get going in the last week	Self-report of any of the following: Low usual energy level[a] (≤3, range 0–10) Felt unusually tired in the past month[b] Felt unusually weak in the past month[b]
Low physical activity	Women: energy<270 kcal on activity scale (18 items) Men: energy<383 kcal on activity scale (18 items)	Women: energy<90 kcal on activity scale (6 items) Men: energy<128 kcal on activity scale (6 items)
Slowness	Observed when walking 4.57 m at usual pace Women Time≥7 s for height≤159 cm Time≥6 s for height>159 cm Men Time≥7 s for height≤173 cm Time≥6 s for height>173 cm	Observed when walking 4 m at usual pace Women Speed≤4.57/7 m/s for height≤159 cm Speed≤4.57/6 m/s for height>159 cm Men Speed≤4.57/7 m/s for height≤173 cm Speed≤4.57/6 m/s for height>173 cm

Weakness	Grip strength Women ≤17 kg for BMI≤23 ≤17.3 kg for BMI 23.1–26 ≤18 kg for BMI 26.1–29 ≤21 kg for BMI>29 Men ≤29 kg for BMI≤24 ≤30 kg for BMI 24.1–26 ≤30 kg for BMI 26.1–28 ≤32 kg for BMI>28	Grip strength: same as in CHS

BMI: Body mass index; calculated as the weight in kilograms divided by the height in meters squared.

[a] Rated on 0–10 scale, where 0 indicated "no energy" and 10 indicated "the most energy that you have ever had."

[b] If yes, there followed the question, "How much of the time?" the feeling persisted; responses "Most" or "All" of the time were considered indicative of exhaustion.

emerged in the literature, which were often motivated by available measures in specific studies rather than meaningful conceptual differences.

Alternatively, frailty has been operationalized as a risk index by counting the number of deficits accumulated over time, termed frailty index (FI), including disability, diseases, physical and cognitive impairments, psychosocial risk factors, and geriatric syndromes (eg, falls, delirium, and urinary incontinence).[7] Compared with the Fried frailty phenotype, the FI is a more sensitive predictor of adverse health outcomes because of its finer graded risk scale and its robustness in clinical inferences with regard to the number and actual composition of the items in it.[8]

However, the discussion of the epidemiology of frailty in this article focuses on the Fried definition of frailty phenotype for several reasons. First, there is increasing consensus that frailty is a definable clinical state involving multiple signs and symptoms. Second, the clinical manifestations of frailty, in theory, may be organized into a self-perpetuating cycle of naturally progressing events (**Fig. 1**) consistent with clinical observations.[2,9] Third, converging lines of evidence suggest that these manifestations exhibit associations[10–15] that are consistent with a syndromal presentation.[1] Fourth, all the 3 reasons mentioned earlier provides a priori theoretical framework that facilitates the investigation of mechanisms underlying the development of frailty.[16] Last, it could be argued that the 5-component phenotype is more appealing for use in a clinical setting than the FI that typically contains 30 to 70 items.

NATURAL HISTORY OF MANIFESTATIONS OF FRAILTY CRITERIA

Understanding the points of onset of frailty is vital to early identification of at-risk individuals and intervention on those components that are first affected, when reversal

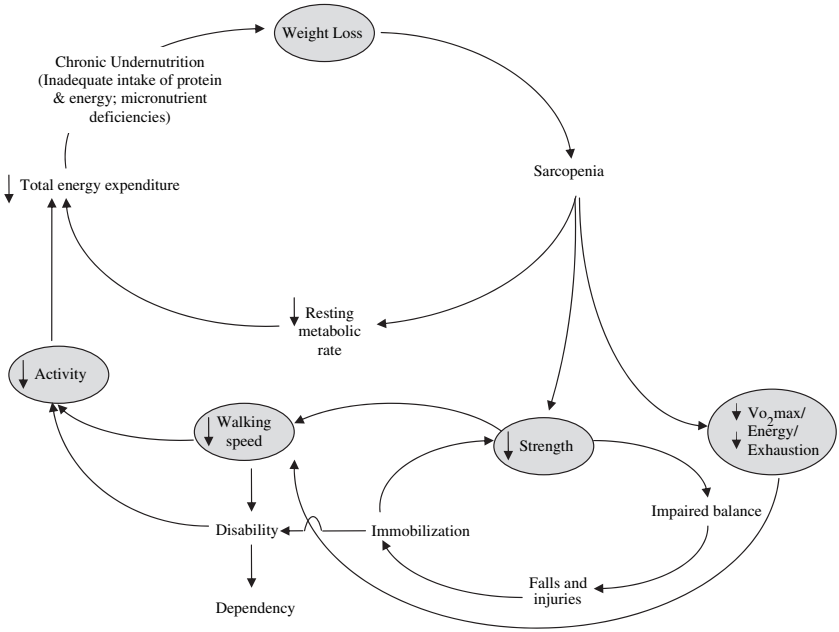

Fig. 1. Cycle of frailty. (Xue QL, Bandeen-Roche K, Varadhan R, et al. Initial manifestations of frailty criteria and the development of frailty phenotype in the Women's Health and Aging Study II. J Gerontol A Biol Sci Med Sci 2008;63(9):984–90, by permission of the Gerontological Society of America.)

may be most possible. Preclinical detection of early manifestations leading to the frailty syndrome requires an understanding of the natural history of frailty development. The author suggests 2 potential hypotheses as to the natural history of frailty initiation and progression. The author hypothesized that the cycle of frailty could be initiated via any of the clinical manifestations, which could then precipitate a vicious cycle culminating in an aggregate syndrome; and different initial manifestations may lead to differential rates of progression to frailty. Based on a 7.5-year longitudinal study of 420 participants of the Women's Health and Aging Studies (WHAS) II who were defined as nonfrail using the Fried definition of frailty phenotype at baseline, the author found initial evidence of a partially hierarchical order in the onset of frailty manifestations over time.[6] Although there was notable heterogeneity in the initial manifestations of frailty, weakness was the most common first manifestation, and occurrence of weakness, slowness, and low physical activity preceded exhaustion and weight loss in 76% of the women who were nonfrail at baseline.

The fact that weakness should presage frailty onset is consistent with earlier reports that suggest that loss of muscle strength begins in midlife.[17–19] The decline in muscle strength has been attributed to the loss of muscle mass and muscle quality, which is referred to as sarcopenia, resulting from anatomic and biochemical changes in the aging muscle.[20] The causal mechanisms underlying sarcopenia are many, including oxidative stress, dysregulation of inflammatory cytokines and hormones, malnutrition, physical inactivity, and muscle apoptosis,[21,22] all of which have been hypothesized to contribute to frailty through interactive pathways at multiple temporal and spatial scales.[16]

The finding of heterogeneity in initial criteria is consistent with the hypothesis that the cycle of frailty may be initiated by insults at many points in a hypothesized cycle of dysregulated energetics.[2,9] It was not the number of early manifestations (ie, 1 or 2) but the specific manifestations initially present that distinguished the risk and rate of onset of frailty. Specifically, women with exhaustion or weight loss as initial presenting symptoms were 3 to 5 times more likely to become frail than were women without any criterion, after adjusting for baseline age, race, education, and comorbidity. Weakness was moderately predictive of frailty onset (hazard ratio = 2.6). Neither slow walking speed nor low activity at baseline was significantly associated with incident frailty. It remains to be determined whether the different patterns of initial accumulation of frailty criteria represent different causative pathways with different rates of progression to frailty, either organ-specific or representing systemic physiologic dysregulations of aging. Alternatively, certain criterion measures may be more sensitive than others to changes associated with normal aging, for instance, performance-based criteria as opposed to self-reported criteria.

Despite heterogeneous entry points into the cycle of frailty, 80% of transitions to frailty involved adding exhaustion and/or weight loss. This finding raises the possibility that decreased energy production or increased use, as in wasting conditions, may be involved in the threshold transition in a final common pathway toward frailty. Weight loss and exhaustion rarely developed alone, but rather co-occurred with other manifestations. This co-occurrence is consistent with the reliability theory,[23] whereby an emergent aggregation of multiple frailty manifestations result from the depletion of system redundancy or compensatory mechanisms, such that any new deficit leads to the failure of the whole organism.[24–27] Then, early detection of subclinical changes or deficits at the molecular, cellular, and/or physiologic level is key to preventing or delaying the development of frailty.

The clinical utility of these findings lies in the fact that weakness was the most common initial manifestation of the frailty phenotype. It evidenced only moderate

predictive validity for incident frailty. However, according to the author's conceptualization, the development of frailty is progressive and multisystemic and any 1 specific criterion alone, especially at an early stage in the process as in the case of weakness, may be neither sufficient nor specific for frailty prediction. Given that the criteria defining thresholds for grip strength are known to be associated with a greater risk of adverse outcomes, including disability and mortality,[28] weakness may nevertheless be a clinically meaningful indicator of increasing vulnerability at a relatively early stage of the frailty process, when preventive intervention could be easiest to implement and theoretically most effective. Although the subsequent or concurrent onset of weight loss or exhaustion with the other criteria may better predict frailty onset, by the time someone experiences weight loss or exhaustion, it may be too late to implement frailty interventions. Therefore, consideration should be given to the possible trade-off between risk prediction and potential for benefits in deciding the proper timing and targets of interventions.

EVIDENCE OF FRAILTY AS A MEDICAL SYNDROME

A medical syndrome is "a group of signs and symptoms that occur together and characterize a particular abnormality." To formally evaluate the degree to which the frailty phenotype conforms to the definition of a medical syndrome, Bandeen-Roche and colleagues[1] analyzed patterns of co-occurrence of the 5 frailty-defining criteria based on data from a combined sample of women aged 70 to 79 years from the WHAS I and WHAS II. Patterns of criteria co-occurrence that would support the syndrome definition are "(1) manifestation in a critical mass and (2) aggregation in a hierarchical order, as would occur in a cycle in which dysregulation in a sentinel system may trigger a cascade of alterations across other systems."[1] Propensity for criteria to co-occur in distinct subgroups would suggest the effects of distinct biologic processes rather than a syndrome. Using latent class analysis,[29] 3 population subsets (also termed classes) with similar profiles of frailty criteria co-occurrence were identified; each criterion's prevalence increased progressively across the population subsets, indicating increase in frailty severity. These findings supported the internal validity of the frailty criteria vis-à-vis the stated theory characterizing frailty as a medical syndrome and provided justification to the current counting strategy for defining frailty categories (ie, nonfrail, prefrail, and frail).

PREVALENCE AND INCIDENCE OF FRAILTY

Based on the frailty criteria developed in the Cardiovascular Health Study (CHS), the overall prevalence of frailty in community-dwelling older adults aged 65 years or older in the United States ranges from 7% to 12%. In the CHS, prevalence of frailty increased with age from 3.9% in the age group of 65 to 74 years to 25% in the age group older than 85 years and was greater in women than in men (8% vs 5%).[2] African Americans were more than twice as likely to be frail than Whites in the CHS (13% vs 6%) and the WHAS (16% vs 10%). The 1996 estimate for Mexican Americans from the Hispanic Established Populations for Epidemiologic Studies of the Elderly was 7.8%, similar to those of Whites.[4]

Similar age trends and gender differences have been reported for older adult populations in European and Latin American countries (**Table 2**). A recent survey of 7510 community-dwelling older adults in 10 European countries found that the prevalence of frailty ranged from 5.8% in Switzerland to 27% in Spain, with an overall prevalence of 17% and was higher in southern than in northern Europe, consistent with an unexplained north-south health risk gradient previously reported in the same population.[30,31]

The geographic variation in frailty prevalence among these European countries persisted after adjusting for age and gender, which led the investigators to speculate that there may be differences in cultural characteristics, influencing the perception of health and/or interpretation of the frailty questions.[30] According to a survey of 7334 older adults who were 60 years or older living in 5 large Latin American and Caribbean cities, including Bridgetown, Barbados (n = 1446); Sao Paulo, Brazil (n = 1879); Santiago, Chile (n = 1220); Havana, Cuba (n = 1726); and Mexico City, Mexico (n =1063), prevalence of frailty varied from 30% to 48% in women and from 21% to 35% in men, which was much higher than their American and European counterparts.[32]

FRAILTY TRANSITIONS

Epidemiologic data on transitions between frailty states (ie, nonfrail, prefrail, frail) were first reported by Gill and colleagues[3] in a 4.5-year longitudinal study of 754 community-living older adults who were 70 years or older. Of the 754 participants, 58% had at least 1 transition between any 2 of the 3 frailty states at one of the 3 follow-up visits 18-months apart during the study; 37%, 22%, and 9% of the participants had 1, 2, and 3 transitions. About one-third (35%) of all 18-month transitions were from states of greater frailty to states of less frailty (calculated based on data in **Table 3** of Gill and colleagues[3]). However, the likelihood of transitioning from being frail to nonfrail was extremely rare during each of the 18-month intervals.

In WHAS II, frailty status of 405 women representing two-thirds of least-disabled community-dwelling women aged 70 to 79 years was repeatedly assessed at baseline and at least one of the 4 follow-up visits spanning 7.5 years (approximately 18 months apart except for the interval between the third and the fourth examination, which was, on average, 3 years). Of the 405 women, 72% had at least 1 transition between frailty states over 7.5 years; 37%, 24%, 16%, and 2% had 1, 2, 3, and 4 transitions. Consistent with the finding of Gill and colleagues,[3] most of the transitions occurred between adjacent frailty status; one-third (34%) of all 18-month transitions were from states of greater frailty to states of less frailty. In WHAS II, the rate of transition from frail to nonfrail was noticeably higher (17%) during the first 18 months than that of the previous study, which could be because of the small sample size of the frailty group (see **Table 3**). It was also found that two-thirds of the 24 (n = 15) women who were nonfrail at baseline and became frail during the course of the study did so slowly and progressively, whereas one-third (n = 9) had rapid onset of frailty without progressing through any identified prefrail stage. This observation suggests that the rate at which frailty progresses may vary dramatically among older adults, that is, more sudden and catastrophic in some people and slowly progressive among others. Similar findings have been reported by Gill and colleagues[3] and for severe mobility disability, with the rate of progression depending on the level of comorbidity as well as specific disease types.[33] Owing to low frailty incidence, the author had limited power in detecting factors differentiating the pace of frailty development.

Because some misconstrue frailty as a premorbid state defining the end of life, the findings reported earlier suggest that frailty is not an irreversible process, certainly not an inevitable trajectory to death. Therefore, the development and evaluation of interventions designed to prevent or ameliorate frailty should remain as one of the top priorities in frailty research.

BEHAVIORAL PRECURSORS TO THE DEVELOPMENT OF FRAILTY

An overt state of frailty is believed to be preceded by behavioral adaptation made in response to declining physiologic reserve and capacity with which to meet

Table 2
Frailty prevalence and criteria in various countries

Source	Country	Number of Patients	Frailty Prevalence		Frailty Criteria
Fried et al,[2] 2001	United States	5317	Age		CHS criteria (see **Table 1**)
			65–74 y	3.9%	
			75–84 y	11.6%	
			Older than 85 y	25.0%	
			Sex		
			Women	8.2%	
			Men	5.2%	
			Race		
			White	5.9%	
			African American	12.9%	
Bandeen-Roche et al,[1] 2006	United States	786	Age		WHAS criteria (see **Table 1**)
			70–79 y	11.3%	
			Race		
			White	9.8%	
			African American	15.8%	
Santos-Eggimann et al,[30] 2009	10 European countries:	7510	Older than 65 y	17.0%	Three or more of the following 5 criteria: *Weight loss*: self-report of a diminution in the desire for food in response to the question, "What has your appetite been like?" *Exhaustion*: responding "Yes" to the question, "In the last month, have you had too little energy to do things you wanted to do?" *Weakness*: same as in CHS *Slowness*: self-report of having either "Difficulty (expected to last more than 3 months) walking 100 m" or "Climbing one flight of stairs without resting" because of health reasons *Low activity*: responding "1 to 3 times a month" or "Hardly ever or never" to the question, "How often do you engage in activities that require a low or moderate level of energy, such as gardening, cleaning the car, or going for a walk?"
	Sweden			8.6%	
	Denmark			12.4%	
	Netherlands			11.3%	
	Germany			12.1%	
	Austria			10.8%	
	Switzerland			5.8%	
	France			15.0%	
	Italy			23.0%	
	Spain			27.3%	
	Greece			14.7%	

Graham et al,[4] 2009	United States	1996	Older than 65 y Race Mexican American	7.8%	Three or more of the following 5 criteria: *Weight loss*: unintentional weight loss of ≥4.5 kg in the last year *Exhaustion*: same as in CHS *Weakness* by grip strength: Weakest 20% for men: ≤21 kg for BMI≤24.2 ≤24.5 kg for BMI 24.3–26.8 ≤25.4 kg for BMI 26.9–29.5 ≤25.5 kg for BMI>29.5 Weakest 20% for women: ≤13.5 kg for BMI≤24.7 ≤14.2 kg for BMI 24.8–28.3 ≤15.0 kg for BMI 28.4–32.1 ≤15.0 kg for BMI>32.1 *Slowness* by 4.9-m–timed walk at fast pace Slowest 20% for men: ≥11.2 s for height ≤168 cm ≥9.7 s for height >168 cm Slowest 20% for women: ≥12.0 s for height ≤154 cm ≥11.2 s for height >154 cm *Low activity*: lowest 20th percentile on the basis of gender on the Physical Activity Scale for the Elderly Lowest 20% for men: ≤30[47] Lowest 20% for women: ≤27.5[47]

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Table 2
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Source	Country	Number of Patients	Frailty Prevalence		Frailty Criteria
Alvarado et al,[32] 2008			Older than 60 y		Three or more of the following 5 criteria:
	Barbados	1446	Women	30.0%	*Weight loss*: self-report of loss of >4.5 kg
			Men	21.5%	unintentionally during the previous 3 months
	Cuba	1726	Women	46.7%	*Exhaustion*: responding "No" to the question,
			Men	26.2%	"Do you have lots of energy?" and/or
	Mexico	1063	Women	45.5%	responding "Yes" to the question, "Have your
			Men	30.4%	dropped many of your activities or interests?"
	Chile	1220	Women	48.2%	*Weakness*: same as in CHS
			Men	31.7%	*Slowness*: self-report of difficulty in walking 100
	Brazil	1879	Women	44.1%	yd and/or in climbing one flight of stairs
			Men	35.4%	*Low activity*: responding, "No" to the question, "In the last 12 mo, have your exercised regularly or participated in vigorous physical activity, such as playing a sport, dancing, or doing heavy housework, 3 or more times a week?"
Avila-Funes et al,[44] 2009	France	6030	Older than 65 y	7.0%	Three or more of the following 5 criteria: *Weight loss*: self-report of recent loss of $\geq$3 kg unintentionally or BMI <21 kg/m^2 *Exhaustion*: same as in CHS *Weakness*: responding "Yes" to the question, "Do you have difficulty rising from a chair?" *Slowness*: gender- and height-adjusted lowest quantile on a timed 6-m walking test at usual pace *Low activity*: denied doing daily leisure activities, such as walking or gardening or participating in athletic activity at least once a week

BMI: Body mass index; calculated as the weight in kilograms divided by the height in meters squared.

Table 3
Numbers and rates of transitions according to follow-up interval

Transition	Number	Rate (%)	Number	Rate (%)	Number	Rate (%)	Number	Rate (%)
	Baseline to 18 mo		18–36 mo		36–72 mo		72–90 mo	
Nonfrail to	N = 244		N = 222		N = 147		N = 129	
Nonfrail	179	73.4	132	59.5	93	63.3	66	51.2
Prefrail	61	25.0	86	38.7	40	27.2	58	45.0
Frail	3	1.2	4	1.8	6	4.1	2	1.6
Death	1	0.4	0	0	8	5.4	3	2.3
Prefrail to	N = 137		N = 130		N = 161		N = 130	
Nonfrail	48	35.0	26	20.0	36	22.4	22	16.9
Prefrail	75	54.7	89	68.5	92	57.1	85	65.4
Frail	9	6.6	11	8.5	15	9.3	15	11.5
Death	5	3.7	4	3.1	18	11.2	8	6.2
Frail to	N = 12		N = 13		N = 14		N = 28	
Nonfrail	2	16.7	1	0.8	2	14.3	0	0
Prefrail	7	58.3	10	76.9	5	35.7	10	35.7
Frail	2	16.7	2	15.4	7	50.0	13	46.4
Death	1	8.3	0	0	0	0	5	17.9

environmental challenges. The causes of this loss of physiologic reserve are likely to be multifactorial, including both environmental challenges (eg, area deprivation) and intraindividual challenges (eg, age-related physiologic changes). Observations of early behavioral changes during this preclinical phase in older adults in whom frailty is developing, but as yet undetected, could provide insight into the frailty development process and suggest means for early intervention. More importantly, such changes may not be captured by conventional measures of function such as fixed-distance or fixed-time walking tests for mobility function, which assess one's functional capacity under hypothetical or experimental conditions rather than enacted function in the real world.[34] Therefore, assessment of the changes in real life may reflect the net impact of declining reserve, taking into account the balance between internal physiologic capacity and external challenges older adults experience in daily life.

One example of such a behavioral precursor is life space, a measure of spatial mobility, defined as the size of the spatial area people purposely move through in their daily life as well as the frequency of travel within a specific time frame.[35,36] The author analyzed the 3-year cumulative incidence of frailty using the WHAS phenotype in relation to baseline life-space constriction among 599 community-dwelling women who were 65 years or older and not frail at baseline. Frailty-free mortality (ie, death before the observation of frailty) was treated as a competing risk. Multivariate survival models showed that when compared with women who left the neighborhood 4 or more times per week, those who left the neighborhood less frequently were 1.7 times (95% confidence interval [CI], 1.1–2.4; $P<.05$) more likely to become frail, and those who never left their homes experienced a 3-fold increase in frailty-free mortality (95% CI, 1.4–7.7; $P<.01$), after adjustment for chronic disease, physical disability, and psychosocial factors.[37] It is particularly intriguing to find that difficulty with mobility, instrumental activities of daily living, and activities of daily living alone did not necessarily lead to a reduction in life space. In fact, 97% of the participants in the study cohort had already reported mobility disability at baseline. Such discordance between functional capacity and actual performance has been reported in several other studies.[34,38,39] To explain the discrepancy, one could argue that some people may compensate for underlying functional decrements by adapting to a modified daily routine (eg, the use of assistive devices) to maintain the same level of performance in real life (ie, enacted function).[40] Although the exact reasons for this discrepancy remain unknown, the author hypothesizes that the employment of external (eg, social support) and internal (eg, using a cane) compensatory strategies (termed environmental supports and intraindividual supports, respectively, in **Fig. 2**) may help to minimize the impact of the loss of physiologic reserve and thereby preserve life-space mobility. On the other hand, the ability to compensate effectively for functional limitations may itself be a function of physiologic reserve. It may be the interplay of functional limitations and functional reserve, which determines actual function and behavior.

Obtaining empirical evidence of this association is the critical first step toward evaluating a broad conceptual framework about the cause of frailty (see **Fig. 2**). In the case of life space, it is theorized that constriction of life space is a marker of declines in physiologic reserve and that constriction of life space itself could lead to decreased physical activity and social engagement, accelerated deconditioning, and exacerbated decline in physiologic reserve, directly contributing, as these processes progress, to the development of clinical frailty and subsequent mortality. Future development of tools for the assessment of physiologic reserve and analysis of their relations to behavioral maladaptations could help in delineating the hypothesized causal pathway.

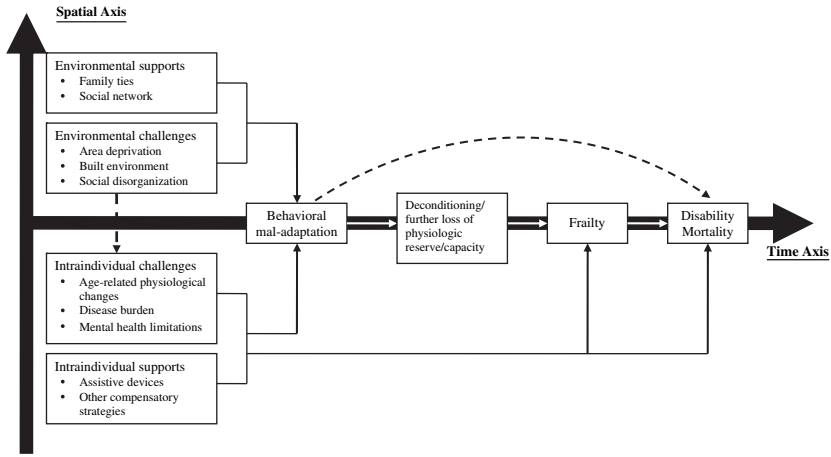

Fig. 2. Theoretical model of the association of life space with the clinical syndrome of frailty. Solid and dashed lines represent direct and indirect effects, respectively; arrows represent causal direction. (Xue QL, Fried LP, Glass TA, et al. Life-space constriction, development of frailty, and the competing risk of mortality: the Women's Health And Aging Study I. Am J Epidemiol 2008;167(2):240–8, by permission of Oxford University Press.)

SUMMARY

The recent work on the natural history of frailty has advanced the understanding of the aging process and its potential physiologic correlates. The ongoing debate on the operational definition of frailty, its subdomains (eg, physical vs cognitive), and its relationship with aging, disability, and chronic diseases[41–45] signals that more work is necessary to better define and quantify reserve and resilience, the hallmarks of frailty.[16,46] Despite this debate, researchers and clinicians have no disagreement on the severe impact of frailty on older adults, their caregivers, and on society as a whole. Although specific treatments for frailty are yet to be developed and tested, the existing clinical measures of frailty provide useful means for identifying high-risk individuals and, therefore, could lead to improved treatment, decision making, and management of care by taking into account individual vulnerabilities and propensity for adverse health outcomes.

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