Transitions Between Frailty States Among Community-Living Older Persons

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Background: Little is known about the natural course of frailty. We performed a prospective study to determine the transition rates between frailty states and to evaluate the effect of the preceding frailty state on subsequent frailty transitions.

Methods: We studied 754 community-living persons, aged 70 years or older, who were nondisabled in 4 essential activities of daily living. Frailty, assessed every 18 months for 54 months, was defined on the basis of weight loss, exhaustion, low physical activity, muscle weakness, and slow walking speed. Participants were classified as frail if they met 3 or more of these criteria, as prefrail if they met 1 or 2 of the criteria, and as nonfrail if they met none of the criteria.

Results: Of the 754 participants, 434 (57.6%) had at least 1 transition between any 2 of the 3 frailty states during 54 months. The rates were 36.8%, 21.5%, and 9.2% for 1, 2, and 3 transitions, respectively. During the 18-month intervals, transitions to states of greater frailty were more common (rates up to 43.3%) than transitions to states of lesser frailty (rates up to 23.0%), and the probability of transitioning from being frail to nonfrail was very low (rates, 0%-0.9%), even during an extended period. The likelihood of transitioning between frailty states was highly dependent on one's preceding frailty state.

Conclusions: Frailty among older persons is a dynamic process, characterized by frequent transitions between frailty states over time. Our findings suggest ample opportunity for the prevention and remediation of frailty.

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FRAILTY IS INCREASINGLY RECognized as a geriatric syndrome, distinct from disability and comorbidity, that results from a multisystem reduction in reserve capacity, confers high risk for an array of adverse outcomes, and is potentially amenable to prevention and remediation.[1] An important impediment to the development of frailty-specific interventions has been an incomplete understanding of the epidemiology of frailty. Until recently, research on frailty has been slowed by the absence of a standardized and valid operational definition. In a seminal report, Fried et al[2] proposed that frailty be defined on the basis of the following 5 features: unintentional weight loss, exhaustion, low physical activity, muscle weakness, and slow walking speed, with the presence of 3 or more of these features denoting frailty, 1 or 2 denoting prefrailty, and none denoting no frailty. This 3-level definition for frailty had strong concurrent validity, as evidenced by expected associations with age, chronic conditions, cognitive function, and depressive symptoms, and was independently predictive of several relevant outcomes, including incident falls, hospitalization, worsening disability, and death.[2]

To date, little is known about the likelihood of transitions between these different frailty states over time. In the Cardiovascular Health Study,[2] the 4-year incidence of frailty was 7.2% among participants who were initially nonfrail. In the Hispanic Established Populations for Epidemiological Studies of the Elderly,[3] the cumulative incidence of frailty among nonfrail participants was 3.6% at 2 years, 6.6% at 5 years, and 7.9% at 7 years. Neither study reported transition rates between nonfrail and prefrail states or evaluated how often frail older persons transition to less frail states. We have recently demonstrated that disability, a key frailty-related outcome, is a reversible, and often recurrent, event.[4-6] On the basis of these findings, we postulated that frailty may also be a dynamic process, as illustrated in **Figure 1**. To improve our understanding of frailty among older persons, we set out in the current study to determine the transition rates between frailty states over time and to evaluate the effect of the preceding frailty state on subsequent frailty transitions.

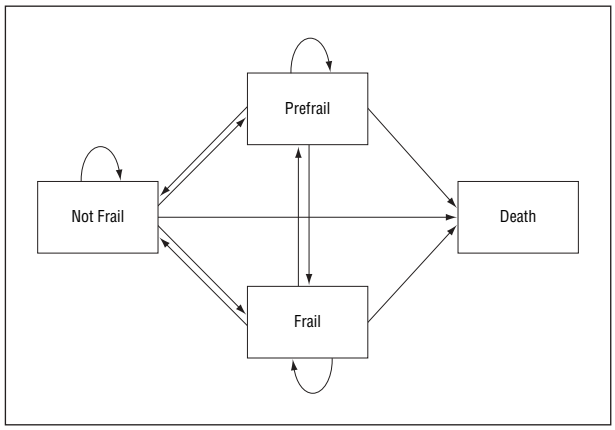

Figure 1. Multistate model depicting possible transitions between frailty states and death.

METHODS

STUDY POPULATION

Participants were members of the Precipitating Events Project, a longitudinal study of 754 community-living persons, aged 70 years or older, who were nondisabled (ie, required no personal assistance) at baseline in 4 essential activities of daily living: bathing, dressing, walking inside the house, and transferring from a chair.[7] Exclusion criteria included significant cognitive impairment with no available proxy,[8] inability to speak English, diagnosis of a terminal illness with a life expectancy of less than 12 months, and a plan to move out of the New Haven, Conn, area during the next 12 months.

The cohort was assembled between March 23, 1998, and October 26, 1999. Eligibility was determined during a screening telephone interview and was confirmed during an in-home assessment. Participants were enrolled in a 4:2:1 ratio for low, intermediate, and high risk of disability, using a model developed and validated in an earlier study.[9] Participants were classified as low risk if they scored 10 seconds or less on the rapid gait test (ie, walk back and forth over a 10-ft [3-m] course as quickly as possible); as intermediate risk if they scored greater than 10 seconds on rapid gait, scored 24 or better on the Folstein Mini-Mental State Examination,[10] and were younger than 85 years; and as high risk if they scored greater than 10 seconds on rapid gait and if they either scored less than 24 on the Mini-Mental State Examination or were aged 85 years or older. A complete description of our stratified sampling technique is provided elsewhere.[7] Only 4.6% of the 2753 health plan members who were alive and could be contacted refused to complete the screening telephone interview, and 75.2% of the eligible members agreed to participate in the project. Persons who refused to participate did not differ significantly from those who were enrolled for age or sex. The study protocol was approved by the Yale Human Investigation Committee, New Haven; all participants provided oral informed consent.

DATA COLLECTION

Comprehensive home-based assessments were completed by trained nurse researchers at baseline and at 18, 36, and 54 months. Data were collected on demographic characteristics; cognitive status[10]; 13 self-reported, physician-diagnosed chronic conditions[7]; and frailty as described in the next section. Deaths were ascertained by review of the local obituaries and/or from an informant. Two hundred twelve participants (28.1%) died after a median follow-up of 40 months, and 30 (4.0%) dropped out of the study after a median follow-up of 22 months.

Table 1. Specific Modifications to the Frailty Criteria

Criterion	Modification
Weight loss	Intentional vs unintentional cause was not determined
Exhaustion	Original response categories to fulfill this criterion were "moderate amount of time (3-4 days)" or "most of the time"
Low physical activity	Short version of Minnesota Leisure Time Activity questionnaire was originally used, and sex-specific cutoff points (for worse quintile) were established based on kilocalories of physical activity expended per week
Muscle weakness	Body mass index (calculated as weight in kilograms divided by the square of height in meters) was based on self-reported, rather than observed, height and weight; Jamar hand dynamometer was originally used
Slow walking speed	Sex- and height-specific cutoff points (for worse quintile) were originally established based on usual gait speed over 15-ft course

ASSESSMENT OF FRAILTY

Data from the comprehensive assessments were used to define each of the 5 criteria for frailty: weight loss, exhaustion, low physical activity, muscle weakness, and slow walking speed. Because the instruments were not identical, our operational definitions differed modestly from those previously described by Fried et al[2] for use in the Cardiovascular Health Study. The specific modifications are described in **Table 1**. Comparable modifications have been successfully implemented in the Women's Health and Aging Studies.[11]

In the current study, the weight loss criterion was met if the participant answered "Yes" when asked, "In the past year, have you lost more than 10 pounds?" The exhaustion criterion was met if the participant answered "Much or most of the time" when asked, "How often in the last week did you feel this way" to either of the following 2 statements from the Center for Epidemiologic Studies Depression Scale[12]: "I felt that everything I did was an effort" and "I could not get going." The physical activity criterion was met for men who scored less than 64 and women who scored less than 52 on the Physical Activity Scale for the Elderly.[13,14] These sex-specific cutoff points denote the worse quintile of scores among the first 356 enrolled participants, who had been selected randomly from our source population of health plan members.[7] The Physical Activity Scale for the Elderly, which assesses several occupational, household, and leisure activities during a 1-week period, has been shown to be both valid and reliable.[13,15,16] The muscle weakness criterion was met when grip strength, assessed as the average of 3 readings by a handheld dynamometer (Chatillon 100; Ametek Inc, Largo, Fla), was less than or equal to the sex- and body mass index–specific cutoff points provided by Fried et al.[2] Finally, the slow walking speed criterion was met if the participant scored more than 10 seconds on the rapid gait test, as previously described. This cutoff point delineated a threshold response (at the worst quartile) between rapid gait scores and the development of disability in an earlier population-based cohort of older persons.[17,18]

Participants were classified as frail if they met 3 or more of the aforementioned criteria, as prefrail if they met 1 or 2 of the

Table 2. Characteristics of Study Participants*

Characteristic	Baseline (n = 754)	18 Months (n = 679)	36 Months (n = 626)	54 Months (n = 557)
Age, mean ± SD, y	78.4 ± 5.3	79.7 ± 5.2	81.0 ± 5.1	82.2 ± 5.0
Sex, No. (%) F	487 (64.6)	442 (65.1)	415 (66.3)	376 (67.5)
Race, No. (%) non-Hispanic white	682 (90.5)	613 (90.3)	562 (89.8)	501 (89.9)
Lives alone, No. (%)	298 (39.5)	275 (40.5)	253 (40.4)	209 (37.5)
Education level, mean ± SD, y	12.0 ± 2.9	12.0 ± 2.9	12.0 ± 2.8	12.0 ± 2.8
No. of chronic conditions,† mean ± SD,	1.9 ± 1.3	2.0 ± 1.3	2.2 ± 1.3	2.2 ± 1.3
Mental status‡				
Score, mean ± SD	26.8 ± 2.5	26.3 ± 3.3	26.1 ± 3.9	25.2 ± 4.6
Significant cognitive impairment, No. (%)	6 (0.8)	29 (4.3)	31 (5.0)	51 (9.2)
Frailty group, No. (%)				
Nonfrail	172 (22.8)	130 (19.1)	125 (20.0)	84 (15.1)
Prefrail	386 (51.2)	326 (48.0)	265 (42.3)	235 (42.2)
Frail	194 (25.7)	216 (31.8)	230 (36.7)	226 (40.6)
Missing data	2 (0.3)	7 (1.0)	6 (1.0)	12 (2.2)

*The number of decedents was 49 at 18 months, 98 at 36 months, and 166 at 54 months.

†The 13 self-reported, physician-diagnosed chronic conditions included hypertension; myocardial infarction; congestive heart failure; stroke; diabetes mellitus; arthritis; hip fracture; fracture of wrist, arm, or spine since age 50 years; amputation of leg; chronic lung disease; cirrhosis or liver disease; cancer (other than minor skin cancers); and Parkinson disease.

‡As assessed by the Mini-Mental State Examination; significant cognitive impairment was defined as a score of less than 20.

criteria, and as nonfrail if they met none of the criteria. Among a subgroup of 24 participants who were examined independently within a 3-day period by different nurse researchers, we found that the reliability of our frailty assessment was substantial,[19] with a weighted $\kappa = 0.78$. For participants who had significant cognitive impairment, information on weight loss and physical activity was obtained from a proxy informant, as previously described.[8]

STATISTICAL ANALYSIS

We calculated descriptive statistics for participants who completed the comprehensive assessments at baseline and at 18, 36, and 54 months. Next, we evaluated the predictive validity for each of the modified frailty criteria by the Kaplan-Meier method, with survival over 72 months as the outcome,[20] and calculated unadjusted hazard ratios by the Cox proportional hazards method.[21]

We determined the number and rate of all participants who had at least 1 transition between any 2 of the 3 frailty states during the 54-month follow-up period. We then determined the numbers who had 1, 2, and 3 transitions and calculated the corresponding rates, including only participants who had complete frailty data for the corresponding number of transitions.

Next, we calculated rates for each of the transitions depicted in Figure 1 between baseline and 18 months, 18 and 36 months, and 36 and 54 months, respectively, including participants who had data on frailty or death at each of the 2 time points defining the relevant follow-up interval. Using data from the first 356 randomly selected and enrolled participants, we repeated these analyses to ensure that the overall results were not dependent on our stratified sampling strategy.

To determine the effect of the preceding frailty state, we stratified the results for 18 to 36 months by the baseline frailty state and those for 36 to 54 months by the frailty state at 18 months, using data from all available participants. We formally tested the independent effect of the preceding frailty state by using a cumulative logit model,[22] with frailty (3 levels) at baseline and 18 months, respectively, as independent variables and frailty (3 levels) at 36 months as the dependent variable. These results were confirmed in a separate model that included frailty at 18 and 36 months, respectively, as independent variables and frailty at 54 months as the dependent variable (results available on request).

All statistical tests were 2 tailed, and $P<.05$ was considered to indicate statistical significance. All analyses were performed with SAS version 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

The characteristics of the study participants at each time point are provided in **Table 2**. At baseline, most participants were female, were non-Hispanic white, and did not live alone. On average, participants had a high school education and 2 chronic conditions. Only a few had significant cognitive impairment. About half of the participants met the criterion for prefrailty, while comparable proportions were classified as nonfrail and frail. Over time, as the cohort aged, the proportion of participants who were frail increased, while the proportions who were nonfrail or prefrail decreased. As shown in **Figure 2**, each of the frailty criteria was strongly associated with the probability of survival.

Among the 754 participants, 434 (57.6%) had at least 1 transition between any 2 of the 3 frailty states during the 54-month follow-up period. The corresponding results for 1, 2, and 3 transitions, including only participants who had complete frailty data as described in the "Methods" section, were 252 (36.8%), 133 (21.5%), and 49 (9.2%), respectively. **Table 3** provides the transition rates between the 3 frailty states and death for each of the 18-month follow-up intervals. While transitions were observed between each of the states, most participants remained in their current frailty state for each of the follow-up intervals. For participants who were nonfrail or prefrail, the transition rates did not change appreciably over time. For participants who were frail, the probability of transitioning to the prefrail state decreased over time, while the probability of dying increased. With only 2 exceptions, participants who were frail did not transition to the nonfrail state. Similarly, few participants transitioned from being nonfrail to frail dur-

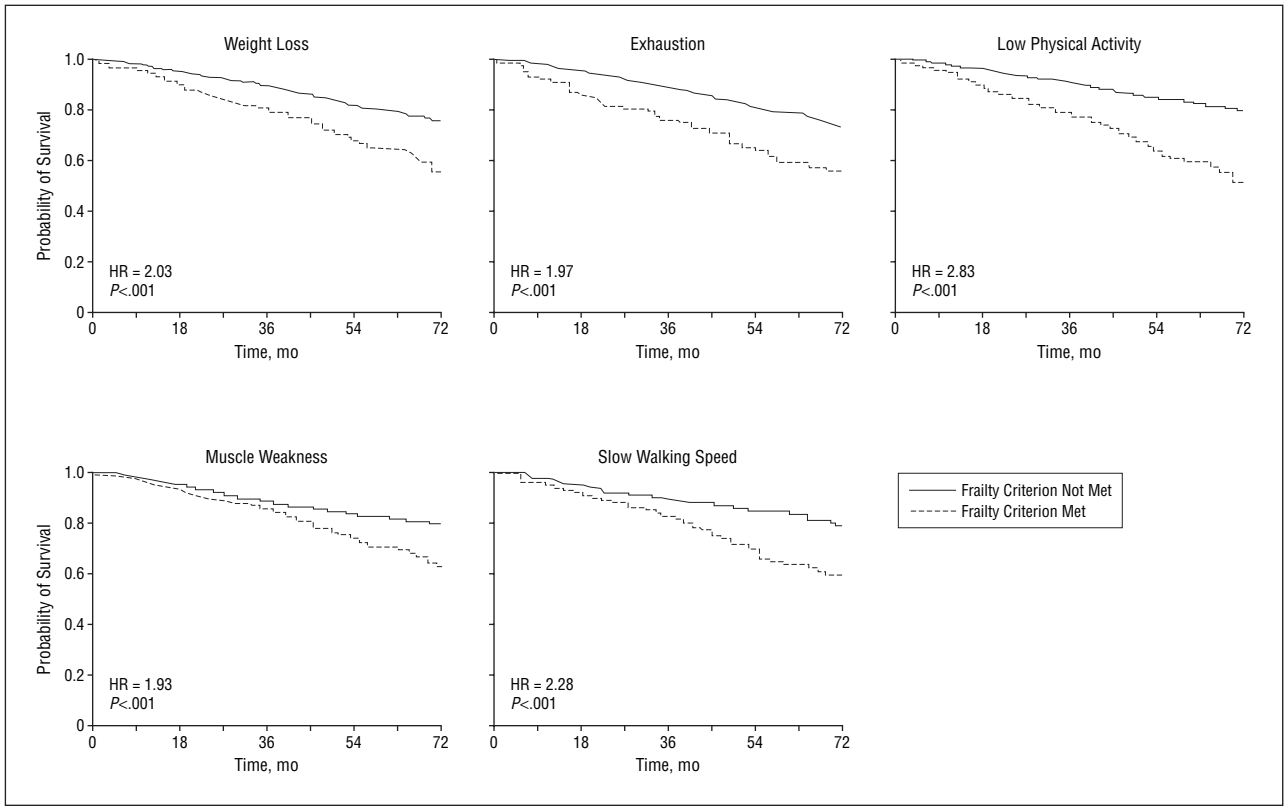

Figure 2. Kaplan-Meier curves for survival over 72 months according to each of the 5 modified frailty criteria at baseline. Unadjusted hazard ratios (HRs) were calculated by the Cox proportional hazards method.

ing a single follow-up interval. When an expanded follow-up interval of 36 to 54 months was considered, no additional participant transitioned from being frail to nonfrail. Finally, depending on the follow-up interval, the likelihood of dying was approximately 3 to 5 times greater among participants who were frail than among those who were either nonfrail or prefrail. When these analyses were restricted to the first 356 enrolled participants, the results did not differ substantively (available on request).

The transition rates between frailty states over 18 months differed according to the participants' preceding frailty state. This finding is illustrated in **Table 4**, which shows the transition rates from the prefrail state at 18 months to each of the 4 possible states at 36 months according to the participants' baseline state. While the overall transition rate from prefrail at 18 months to nonfrail at 36 months was 16.5%, the transition rates were 31.8%, 14.8%, and 0% for participants who were nonfrail, prefrail, and frail, respectively, at baseline. In the cumulative logit model, frailty state at baseline and 18 months were each independently associated with frailty state at 36 months ($P<.001$), confirming the stratified results in Table 4.

COMMENT

In this prospective cohort study, we found that frailty among older persons is a dynamic process, characterized by frequent transitions between frailty states over time. Transitions to states of greater frailty were more common than transitions to states of lesser frailty, and the probability of transitioning from being frail to nonfrail was very low, even over an extended period. Importantly, the likelihood of transitioning between frailty states was highly dependent on one's preceding frailty state.

In 2003, the Institute of Medicine identified frailty as 1 of 20 priority areas, selected from several hundred potential candidates, in need for improvement in health care quality.[23] To achieve this objective, clinicians and policymakers will require an enhanced understanding of the epidemiology of frailty, including its natural course. Our results provide strong evidence to support a model of frailty that involves frequent transitions over time. These transitions occur most commonly between adjacent frailty states, suggesting a gradual progression in, or resolution of, the underlying etiologic disorder(s). In future studies, we plan to evaluate the risk factors and precipitants for the onset and progression of frailty and to identify the factors that may facilitate transitions to less frail states. Together, the results of the current and future research will help to inform the development of preventive and restorative interventions for frailty[24] and, ultimately, to enhance the quality of care for older persons who are frail or at risk for frailty.[1]

Our assessment of frailty included modified versions of the 5 criteria that were initially operationalized by Fried et al[2] using data from the Cardiovascular Health Study. While these modifications may have modestly affected our point estimates of frailty, they should have had little effect on the transition rates, which reflect changes in frailty over time. Each of our modified criteria was strongly associated with survival, providing evidence of their validity. The high reliability of our assessment suggests that

Table 3. Numbers and Rates of Transitions According to Follow-up Interval*

Transition	Baseline to 18 mo		18 to 36 mo		36 to 54 mo	
	No.	Rate, %	No.	Rate, %	No.	Rate, %
Nonfrail to	n = 167		n = 126		n = 120	
Nonfrail	86	51.5	69	54.8	57	47.5
Prefrail	67	40.1	47	37.3	52	43.3
Frail	7	4.2	8	6.3	7	5.8
Death	7	4.2	2	1.6	4	3.3
Prefrail to	n = 369		n = 316		n = 253	
Nonfrail	44	11.9	52	16.5	24	9.5
Prefrail	215	58.3	174	55.1	146	57.7
Frail	92	24.9	79	25.0	66	26.1
Death	18	4.9	11	3.5	17	6.7
Frail to	n = 183		n = 212		n = 224	
Nonfrail	0	0.0	0	0.0	2	0.9
Prefrail	42	23.0	38	17.9	29	12.9
Frail	117	63.9	140	66.0	148	66.1
Death	24	13.1	34	16.0	45	20.1

*Transition rates were calculated on the basis of participants who had data on frailty or death at each of the 2 time points defining the relevant follow-up interval.

Table 4. Numbers and Rates of Transitions From Prefrail State at 18 Months to Subsequent State at 36 Months According to Baseline State*

Baseline State	No. of Participants	State at 36 Months							
		Nonfrail		Prefrail		Frail		Death	
		No.	Rate, %	No.	Rate, %	No.	Rate, %	No.	Rate, %
Nonfrail	66	21	31.8	31	47.0	10	15.2	4	6.1
Prefrail	209	31	14.8	133	63.6	40	19.1	5	2.4
Frail	41	0	0.0	10	24.4	29	70.7	2	4.9
Overall†	316	52	16.5	174	55.1	79	25.0	11	3.5

*For each set of results, the rates do not add up to 100% because of rounding and the small number of participants with missing data on frailty.
†The values for the overall results are identical to those provided in the middle data panel of Table 3.

most of the observed transitions represent true changes in frailty status rather than measurement error. However, some investigators[25] have cautioned that it would be premature to accept the Fried et al definition of frailty as the reference standard, despite evidence supporting its validity, given the clinical complexity of frailty and the omission of potentially important features such as cognitive impairment, depressive symptoms, and poor balance (among others).[26]

Our stratified sampling strategy yielded a study population with a much higher prevalence of frailty and a much lower prevalence of nonfrailty relative to the study populations in the Cardiovascular Health Study[2] and Women's Health and Aging Studies.[11] Nevertheless, because comparable transition rates were observed among the first 356 enrolled participants, who had been randomly sampled,[7] our estimates should accurately reflect those of our source population of health plan members. Whether our findings can be generalized more widely, however, may reasonably be questioned. As previously noted,[27] the demographic characteristics of our source population closely mirror those of persons aged 70 years or older in New Haven County, which, in turn, are comparable with those in the United States as a whole, with the exception of race (New Haven County has a larger proportion of non-Hispanic whites in this age group than the United States, 91% vs 84%).[28] The high participation rate, completeness of data collection, and low rate of attrition for reasons other than death all enhance the generalizability of our findings[29] and, at least partially, offset the absence of a population-based sample.

While our study population included an increasing proportion of participants over time with significant cognitive impairment, we have previously demonstrated the validity of our proxy assessments for disability in activities of daily living.[8] Because physicians are notoriously poor at identifying common geriatric problems[30,31] and at using this information effectively when it is available,[32,33] it is unlikely that our findings were appreciably affected by the provision of frailty-specific preventive or restorative interventions, which were not ascertained as part of the study.

Despite assessing frailty every 18 months, it is possible that we missed transitions that occurred during shorter intervals. We have previously demonstrated that older persons transition frequently between states of disability and independence.[4,6] While frailty and disability are distinct geriatric syndromes,[1] transitions in frailty and disability

are likely related. In future studies, we plan to elucidate the temporal, and potentially reciprocal, relationships between these transitions. Because the likelihood of a subsequent state is dependent not only on the current state, but also on the previous state, for disability[34] and, as demonstrated in the current study, for frailty, analytic strategies that assume a memoryless process, such as standard first-order Markov chain models, will not be valid.

To complement the exciting cross-sectional research that is exploring the biological underpinnings of frailty,[35-38] longitudinal studies are needed to more completely elucidate the epidemiology of frailty, including its natural course, risk factors, precipitants, and interrelationships over time with disability and comorbidity. By demonstrating that frailty, like disability, is a dynamic process, the results of the current study suggest ample opportunity for prevention and remediation and set the stage for a series of subsequent epidemiologic studies that will ultimately inform the development and evaluation of interventions designed to prevent frailty among at-risk individuals and to reduce vulnerability among those who are frail.[26]

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