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Frailty, hospitalization, and progression of disability in a cohort of disabled older women

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ABSTRACT

PURPOSE: To determine the association between a previously validated frailty phenotype and the development of new-onset dependence in activities of daily living, independent of hospitalizations and other established predictors of disability.

SUBJECTS: Seven hundred and forty-nine women enrolled in the Women's Health and Aging Study-I who were independent in all activities in daily living when enrolled in the cohort.

METHODS: Assessments and interviews were conducted through home visits at 6-month intervals for 3 years. Frailty was classified using a validated phenotype (≥3 of the following: weight loss, exhaustion, slow walking, sedentariness, and weak grip), and hospitalizations were identified by self-report. Grouped-time proportional hazard models assessed associations among frailty, hospitalization, and the development of dependence in activities in daily living, adjusting for other factors.

RESULTS: Twenty-five percent of the cohort (186/749) were frail at baseline; 56% (104/186) of frail versus 20% (23/117) of nonfrail women developed dependence in activities in daily living ($P < .001$). In multivariate analysis, frailty was independently associated with the development of dependence in activities in daily living (hazard ratio [HR] = 2.2; 95% confidence interval [CI]: 1.4 to 3.6), adjusting for hospitalization status, age, race, education, baseline functional status, cognition, depressive symptoms, number of chronic diseases, and self-reported health status. Additionally, a dose-response relationship existed between the number of frailty criteria that a woman had and the hazard of subsequent dependence in activities in daily living.

CONCLUSION: Frailty, conceptualized as an underlying vulnerability, and hospitalization, which marks an acute deterioration in health, were strongly and independently associated with new-onset dependence in activities in daily living. Additional research is needed to determine if dependence can be minimized by targeting resources and programs to frail older persons.

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Frailty has been proposed as a state of decreased physiologic reserve conferring increased vulnerability to stressors, such as acute illness or hospitalization.[1-8] Recent research indicates that frailty is not synonymous with disability, comorbidity, or old age but is an identifiable syndrome common in older adults.[9] A recently validated phenotype of frailty has been shown to predict incident and worsening disability, hospitalization, and death in the Cardiovascular Health Study (CHS).[2]

Although frailty has been shown to predict hospitalization and disability, hospitalization has also been shown to increase the risk of functional decline and disability in older adults.[2,10-13] Functional decline that is temporally associated with hospitalization may be caused by both the illness itself, as well as by the "hazards of hospitalization."[14] The purpose of this study was to assess the effect of frailty, independent of the effect of hospitalization, on the development of dependence in activities of daily living in a prospective cohort of community-dwelling, moderately disabled older women who were independent in activities in daily living at enrollment.

Methods

Study sample

The Women's Health and Aging Study I (WHAS-I) is a population-based, prospective, observational study of moderately to severely disabled community-dwelling older women, described in detail elsewhere.[15-17] The WHAS-I cohort was derived from an age-stratified random sample using 1992 Medicare data of 32 538 women aged ≥65 years living in eastern Baltimore city and county. Of 5316 randomly selected women, 4137 (78%) agreed to an in-home screening interview. Inclusion criteria were both of the following: self-report of difficulty or dependence with tasks in two or more of the following four functional domains: mobility, upper extremity function, higher functioning tasks, and self-care tasks; and Mini-Mental State Exam score ≥18.[18]

A total of 1002 women (78% of those eligible) provided written informed consent and enrolled in WHAS-I. Participation rates did not vary based on severity of disability. The sample for the study presented here was restricted to women who were independent in five activities in daily living (toileting, bathing, transferring, eating, and dressing) at study enrollment, and therefore at risk for new-onset dependence in activities in daily living during follow-up. The Johns Hopkins Medicine Institutional Review Board approved WHAS-I.

Data collection

Participants were interviewed in their homes every 6 months for 3 years. At baseline, each participant identified a proxy who would be contacted if the participant was unable to be interviewed or contacted for any reason. The overall response rate remained stable over follow-up, at 93% of surviving participants. However, the percentage of proxy interviews increased from 3% at the first follow-up interview to 16% at the last follow-up interview. At baseline, data were collected on demographic factors and medical diagnoses of chronic conditions. Validation of the baseline presence of 17 chronic conditions was performed using state-of-the-art disease algorithms.[17] Cognitive function was measured by the Mini-Mental State Examination.[18] Depressive symptoms were assessed by the Geriatric Depression Scale.[19]

Data on hospitalizations occurring during the interval between visits was obtained by self report, a method demonstrated to correlate well with actual hospitalizations.[20-24] To maximize the sensitivity of these inquiries, hospitalizations were assessed in two contexts. First, participants were asked if they had been hospitalized for any reason in the previous 6 months. Second, for each chronic condition that a participant had, she was asked explicitly whether she had been hospitalized for this condition in the preceding interval.

Physical performance measures included a standardized 4-meter measured walk at usual pace, timed to 0.1 second, and grip strength, measured in kilograms by a hand-held Jamar dynamometer.[17] New-onset dependence in activities in daily living was defined as requiring the help of another person for any activity in daily living and was assessed at follow-up visits with five questions of the format: "Do you usually receive help from another person in 'toileting' (bathing, transferring, eating, dressing)?"

Definition of frailty

Frailty was defined according to the construct previously validated in the CHS,[2] which includes the following five components: "shrinking" (weight loss), self-report of "exhaustion," low physical activity, slowness, and weakness. An ordinal measure was created, as in CHS, with those with 0 criteria defined as nonfrail, those with 1 to 2 criteria considered "intermediate", and those with ≥3 criteria defined as frail. The metrics used to define individual frailty criteria were slightly different in WHAS-I than in CHS, and definitions of individual criteria used here are described in detail (Table 1). Shrinking was defined here by us as present if the participant's baseline measured weight was 10% less than their self-report of weight at age 60. Exhaustion was defined by any of 3 self-reported criteria. Low physical activity was measured using a subset of the Minnesota Leisure Time Activities Questionnaire[25] to determine the weekly kilocalories expended. The items used in WHAS-I were condensed from the original 18 activities used in CHS to assess participation in the 6 most frequently subscribed to by older women: walking, doing strenuous household chores, doing strenuous outdoor chores, dancing, bowling and exercise. Thus, low physical activity was defined in WHAS-I using an equilibrated threshold for low physical

Table 1 Frailty-defining criteria: The Women's Health and Aging Study I

Shrinking
Self-report of weight at age 60 years – weight at baseline exam ≥10% of weight at age 60 years
Exhaustion: any of
A score of 3 or less on a visual analog scale of energy from 0 (no energy) to 10 (most energy you have ever had)
Felt unusually tired in last month most or all of the time
Felt unusually weak in the past month most or all of the time
Low physical activity: ≤ 90 kilocalories per week on activity scale of six items, including:
Walking for exercise
Moderately strenuous household chores
Moderately strenuous outdoor chores
Dancing
Bowling
Participating in a regular exercise
Slowness
Timed walk over 4 m (or 3 m, as space allowed in the participant's home)
≤0.65 m/sec for height ≤159 cm
≤0.76 m/sec for height >159 cm
Weakness
Grip strength (strongest of three trials, dominant hand, dynamometer)
≤17 kg for body mass index ≤23 kg/m^2
≤17.3 kg for body mass index 23 to 26 kg/m^2
≤18 kg for body mass index 26 to 29 kg/m^2
≤21 kg for body mass index ≥29 kg/m^2

activity set at one third of the threshold used in CHS because WHAS-I only assessed one third of the tasks. Slowness was ascertained by slow walking speed in the first of two trials of a measured walk at usual pace. WHAS-I slowness criterion rescaled the CHS criterion (15 feet) to apply to the 4-meter (or 3 meter, as space allowed in the participant's home) distance used in WHAS-I. Weakness was assessed by weak grip strength and was measured, according to the CHS protocol, by dynamometer in the dominant hand, using the strongest of 3 trials. Cut points for both slow walking speed and weak grip strength were equivalent to those used to define frailty in women in CHS.

Data analysis

Analyses were performed using SPSS (SPSS Inc., Chicago, Ill) and Stata version 7.0 (Stata Corp., College Station, Tex). Categorical variables were examined with contingency tables and the chi-squared or Fisher exact test, as appropriate. All P values were two-sided and considered statistically significant if $<.05$. Dependence in activities in daily living was ascertained at each 6-month visit (maximum of 7 months over 3 years of follow-up). To assess whether multiple intervals with hospitalizations further increased the risk of dependence in activities in daily living beyond a single interval with a hospitalization, we compared the percentage of patients who had become dependent in activities in daily living by 1.5 and 3 years according to ordinal group (0 intervals with a hospitalization, 1 interval with a hospitalization, and ≥2 intervals with a hospitalization), stratifying by frailty status at baseline.

To obtain estimates of the risks of dependence in activities in daily living associated with frailty and hospitalizations, we used grouped-time proportional hazard models, which are appropriate when outcomes are determined within intervals of time rather than at points of time.[26] Frailty, defined at baseline, and hospitalization, handled as a time-dependent variable for each follow-up interval, were included in all models. Other covariates that were assessed included age, race, number of validated chronic medical conditions, self-reported health status, depressive symptoms, cognitive status, and baseline functional status. Baseline functional status was characterized by self-report of difficulty with activities in daily living at baseline (note: women were required to be independent in activities in daily living for inclusion in this study, but they could have reported "difficulty" with the activities); and by self-report of difficulty with mobility, defined as any difficulty in walking one quarter of a mile or climbing 10 steps.[27] Covariates were included in models if they were statistically significantly associated with dependence in activities in daily living, substantially confounded the association between the variables of interest and dependence in activities in daily living, or have been found to be associated with dependence in activities in daily living in other published studies.

To determine if our results were overly influenced by hospitalizations for conditions that would be extremely likely to precipitate dependence in activities in daily living regardless of underlying frailty, we conducted a separate sensitivity analysis, excluding women hospitalized for stroke, amputation, hip fracture, coronary artery bypass grafting, carotid endarterectomy, lower extremity vascular surgery, or joint or back surgery during the study follow-up (n = 129).

Results

Baseline characteristics

Seven hundred eighty-four women (78% of WHAS-I) were independent in activities of daily living at baseline, and 749 (96%) of these eligible women had data on activities of daily living available for at least 1 follow-up interview and were thus included in the analysis. Of these women, 186 (25%) were frail, 446 (59%) were intermediate, and 117 (16%) were nonfrail (Table 2). Although the prevalence of frailty increases with older age, 13% (40/309) of younger (65 to 74 years) women were frail, suggesting that frailty is not synonymous with old age (Figure 1).

Bivariate analyses

Overall, 37% (n = 277) of women developed new-onset dependence in activities in daily living at some point over 3 years of follow-up. Frailty status at baseline was strongly associated with development of dependence in activities in daily living: 56% (104/186) of those women who were frail developed dependence in activities in daily living, compared with 34% (150/446) of those who were intermediate, and 20% (23/117) of those who were nonfrail ($P < .005$, all pair-wise comparisons). Women who were frail were also more likely to become permanent nursing home residents than women who were intermediate (17% [31/186] vs 7% [32/446]; $P = .001$) or women who were nonfrail (5% [6/117], $P = .003$). Women who were hospitalized in at least 1 interval were significantly more likely to develop dependence in activities in daily living compared with those who were not hospitalized by the end of follow-up (48% [198/414] vs 24% [79/335], $P < .0001$). Women who were both frail and hospitalized had the highest rates of new-onset dependence in activities in daily living over 3 years of follow-up (68%, [75/111]). At 18-month follow-up (Figure 2), chosen as an illustrative example, rates of developing new-onset dependence in activities in daily living increased as both number of intervals with hospitalization increased and as frailty status worsened. Women who were frail were not significantly more likely to report any intervals with hospitalization over 3 years of follow-up (60% [111/186] of frail women vs 54% [240/446] of intermediate women [$P = .188$] vs 54% [63/117] of nonfrail women [$P = .341$]).

Table 2 Sample characteristics: The Women's Health and Aging Study I

Baseline characteristic	Value (n = 749) Number (%), mean ± SD
Age (years)	78.0 ± 7.9
African-American race	206 (28)
Frail	186 (25)
Intermediate	446 (59)
Nonfrail	117 (16)
Education of 9 or more years	432 (58)
Mini-Mental State Examination score	
18–24	151 (20)
>24	598 (80)
Geriatric depression scale ≥14	107 (14)
Self-reported health status:	
Fair/poor	362 (49)
Hip or knee osteoarthritis	373 (50)
Heart disease (myocardial infarction, angina, or heart failure)	259 (35)
Peripheral arterial disease	159 (21)
Diabetes	102 (14)
≥4 chronic conditions	133 (18)
Difficulty walking one quarter mile or up 10 steps	590 (79)
Difficulty with ≥1 activities of daily living (but no dependency)	455 (61)
Number of Intervals with hospitalization over 3 years	
0	335 (45)
1	211 (28)
2	127 (17)
≥3	76 (10)

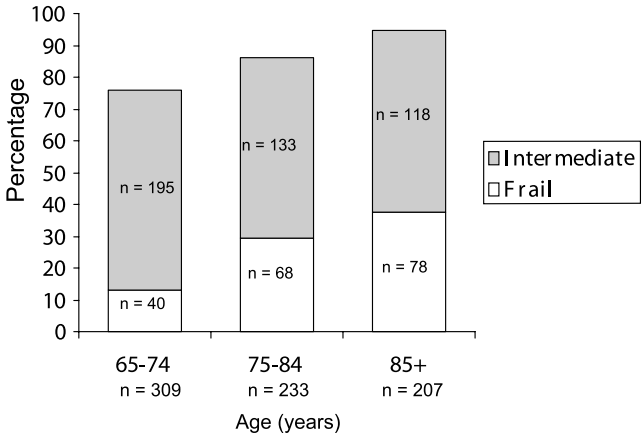

Figure 1 Percent of women who met 1 or 2 frailty criteria (intermediate) or ≥3 frailty criteria (frail) at baseline, stratified by age.

Multivariate analyses

In a multivariate grouped-time proportional hazard model, women who were frail had significantly greater risk of developing dependence in activities in daily living compared with women who were nonfrail (hazard ratio [HR] = 2.2; 95% confidence interval [CI], 1.4 to 3.6) (Table 3). Hospitalization within the previous 6 months was strongly and independently associated with activities of daily living dependency (HR = 4.4; 95% CI, 3.5 to 5.6). Other factors statistically significantly associated with developing dependence in activities in daily living included age and education.

A separate sensitivity analysis, excluding women hospitalized for stroke, amputation, hip fracture, coronary artery bypass grafting, carotid endarterectomy, lower extremity vascular surgery, or joint or back surgery, did not apprecia-

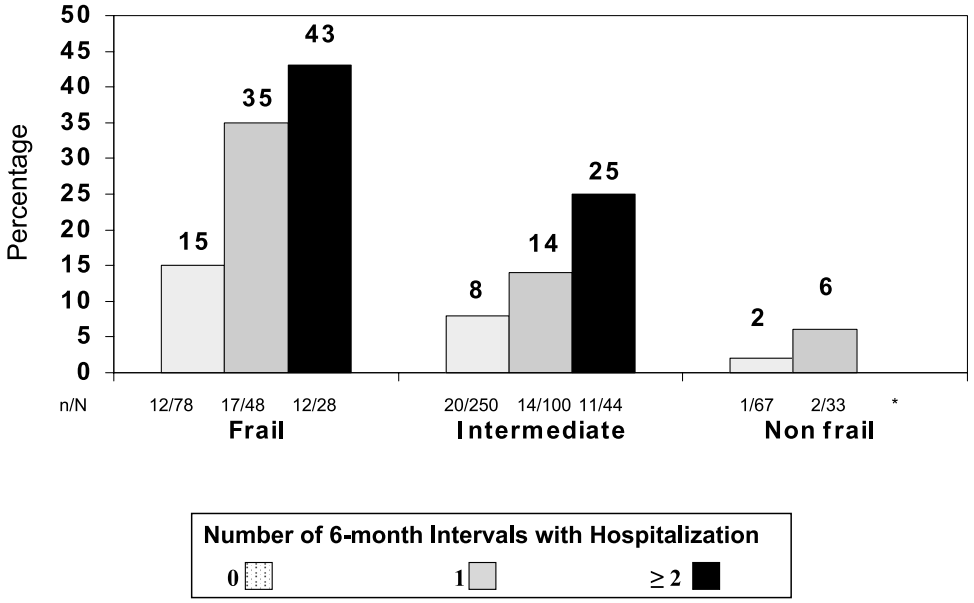

Figure 2 Percent developing dependence in activities of daily living at 18 months, stratified by hospitalization and frailty status. *Only 4 women were both nonfrail and hospitalized in 2 or more intervals. No estimate is drawn from this group.

bly change the association of frailty (HR = 2.1; 95% CI, 1.2 to 3.6) or hospitalization (HR = 4.2; 95% CI, 3.1 to 5.6) with dependence in activities in daily living.

The number of criteria for frailty (out of 5) was associated with the development of dependence in activities in daily living in a dose-response relationship. Compared with participants who did not meet any frailty criteria at baseline, the adjusted risk of dependence in activities in daily living was 1.33 (95% CI, 0.82 to 2.16) in those with 1 frailty criterion, 1.62 (95% CI, 1.00 to 2.60) in those with 2, 2.23 (95% CI, 1.34 to 3.71) in those with 3, and 2.38 (95% CI, 1.33 to 4.25) in those with 4 or 5 criteria (Table 4). Of the specific frailty criteria, shrinking, slowness, and low physical activity were significantly connected with the development of dependence in activities in daily living but weakness and exhaustion were not.

Table 3 Association of frailty and other factors with development of new-onset dependency in activities of daily living

Predictor	Hazard ratio (95% confidence interval)
Frail (vs. nonfrail)	2.2 (1.4–3.6)
Intermediate (vs. nonfrail)	1.5 (0.9–2.3)
Hospitalization	4.4 (3.5–5.6)
Age (per 10-year increase)	1.6 (1.3–2.0)
African-American race	1.3 (1.0–1.7)
Education of ≥9 years	1.4 (1.1–1.8)
≥4 chronic diseases	0.8 (0.6–1.1)
Self-reported health status: fair/poor	1.1 (0.9–1.5)
Difficulty with ≥1 activities of daily living	1.2 (0.9–1.5)
Difficulty walking one quarter mile or up 10 steps	1.1 (0.8–1.6)
Mini-Mental State Examination score 18-24 (vs. >24)	1.3 (1.0–1.8)
Geriatric depression scale ≥14	0.9 (0.6–1.3)

Discussion

Dependence in activities in daily living is a crucial health outcome for older patients and their families; it is strongly linked with quality of life, increases the demands on caregivers and the likelihood of transfer to a nursing home, and is associated with future hospitalizations and mortality.[28-30] As population demographics change, an increasing number of patients will be at risk for dependence in activities in daily living. In this study, frailty, as defined by a validated phenotype at baseline, was strongly associated with the likelihood of developing dependence in activities in daily living over 3 years of follow-up, adjusting for a broad range of demographic, clinical, and psychosocial covariates, including hospitalization. Additionally, in agreement with our prior work,[10] intervals in which a hospitalization occurred were associated with over a 4-fold increased risk of dependence in activities in daily living.

Although there is not a universally accepted definition of frailty, it is a concept that is familiar to clinicians who care for older patients. Frailty is sometimes equated with age. Although frailty was significantly more common in older women in our study, it was common in all age groups and remained strongly associated with dependence in activities in daily living after adjustment for age. We used a previously validated definition of frailty, based on 5 domains that can easily be measured in clinical practice. From a conceptual standpoint, frailty has been proposed as a manifestation

Table 4 Association of frailty criteria with development of new-onset dependence in activities of daily living

Frailty criteria		Incidence rate of dependency (per 100 person-years)	Unadjusted hazard ratio (95% confidence interval)	Adjusted hazard ratio* (95% confidence interval)
Number				
0		7.7	1.0	1.0
1		11.7	1.54 (0.96–2.48)	1.33 (0.82–2.16)
2		16.7	2.21 (1.40–3.49)†	1.62 (1.00–2.60)†
3		25.2	3.40 (2.12–5.45)†	2.23 (1.34–3.71)†
4–5		37.9	5.18 (3.09–8.67)†	2.38 (1.33–4.25)†
Specific criteria				
Shrinking	No	13.3	1.0	1.0
	Yes	27.9	2.15 (1.65–2.80)†	1.60 (1.20–2.12)†
Weakness	No	12.8	1.0	1.0
	Yes	18.7	1.47 (1.14–1.88)†	1.06 (0.81–1.39)
Slowness	No	8.6	1.0	1.0
	Yes	20.6	2.45 (1.83–3.28)†	1.96 (1.43–2.70)†
Low physical activity	No	12.0	1.0	1.0
	Yes	23.1	1.95 (1.54–2.48)†	1.44 (1.12–1.87)†
Exhaustion	No	15.5	1.0	1.0
	Yes	19.5	1.26 (0.94–1.70)	0.94 (0.67–1.31)

*Adjusted for age, race, education, self-reported health status, baseline difficulty with ≥ 1 activities of daily living, baseline difficulty walking one-quarter mile or up 10 steps, presence of ≥4 chronic conditions, Mini-Mental State Examination score, Geriatric Depression Scale score, and hospitalization.

†*P* value <.05.

of a patient's underlying vulnerability to acute illness, accident, or other stressor. Shrinking, slowness, and low physical activity had the strongest and most significant associations with dependence in activities in daily living, but no individual criterion is the dominating force behind frailty. We found that the number of frailty criteria that a participant had at baseline was associated with subsequent dependence in activities in daily living in a dose-response relation, supporting the concept of an aggregate syndrome of frailty. Previously, it has been shown that having 1 to 2 frailty criteria strongly predicted progression to frailty, suggesting that the intermediate status was a "prefrail" state.[2]

Our results contribute additional evidence to the literature showing that "vulnerable" older people are at the highest risk of developing dependence in activities in daily living following an acute stressor but that this mechanism is not driven only by age.[11,31] For example, underlying vulnerability, as determined by physical performance status, cognitive status, and age, increased the risk of dependence in activities in daily living following hospitalization in the Established Populations for the Epidemiologic Study of the Elderly and Project Safety cohorts.[11]

Functional decline following hospitalization is driven by both the underlying illnesses and sequelas that led to the hospitalization, as well as the stresses of the hospitalization experience itself, such as immobilization, indwelling catheters, polypharmacy, and disruption of routine.[14,32] It remains to be determined whether frail patients have a greater functional decline during hospitalizations, are less likely to recover functional ability, or both.

Our study has several limitations. First, the study was conducted in a cohort of moderately disabled women who were at high risk of subsequent dependence in activities in daily living, and our findings may not generalize to men or to groups that are markedly dissimilar from our cohort. Second, we relied on self-reported hospitalizations. Using self-report of hospitalization over a 6-month period in an older, disabled sample is reasonable based on current evidence in the literature,[20-24] although hospitalization may be somewhat under-reported.[33] Third, although we based our frailty construct on that developed and validated in the CHS, we used slightly modified definitions for the individual frailty criteria, because the primary data collection and measures used in WHAS-I were not identical to those used in CHS.

Our results suggest that frail patients are strikingly vulnerable to functional declines and dependence in activities in daily living following hospitalization. Targeting vulnerable hospitalized patients for prevention of functional decline might be key to improving patient outcomes.[34] Understanding the effect of frailty on functional change has implications for research on how to prevent and rehabilitate functional decline associated with hospitalization for acute illnesses. Among older adults with either slow walking speed or inability to rise from a chair without using their hands, an intervention incorporating a targeted combination of balance and strength training successfully prevented functional decline in community-dwelling older adults.[35] Similar interventions may also have applications to hospitalized older adults.

Recent innovations in the delivery of care for acutely ill older adults have shown encouraging results in improving functional outcomes for hospitalized patients.[34,36] Other interventions, such as home hospital, are being tested.[37,38] Our research suggests a scheme for identifying frail older adults, who are at the highest risk of developing dependence in activ-

ities in daily living over time, particularly following hospitalization. Research efforts are needed to understand how to remediate frailty and prevent the adverse consequences of the combination of acute events and vulnerability to such stressors.

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