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Phenotype of Frailty: Characterization in the Women's Health and Aging Studies

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Background. "Frailty" is an adverse, primarily gerontologic, health condition regarded as frequent with aging and having severe consequences. Although clinicians claim that the extremes of frailty can be easily recognized, a standardized definition of frailty has proved elusive until recently. This article evaluates the cross-validity, criterion validity, and internal validity in the Women's Health and Aging Studies (WHAS) of a discrete measure of frailty recently validated in the Cardiovascular Health Study (CHS).

Methods. The frailty measure developed in CHS was delineated in the WHAS data sets. Using latent class analysis, we evaluated whether criteria composing the measure aggregate into a syndrome. We verified the criterion validity of the measure by testing whether participants defined as frail were more likely than others to develop adverse geriatric outcomes or to die.

Results. The distributions of frailty in the WHAS and CHS were comparable. In latent class analyses, the measures demonstrated strong internal validity *vis à vis* stated theory characterizing frailty as a medical syndrome. In proportional hazards models, frail women had a higher risk of developing activities of daily living (ADL) and/or instrumental ADL disability, institutionalization, and death, independently of multiple potentially confounding factors.

Conclusions. The findings of this study are consistent with the widely held theory that conceptualizes frailty as a syndrome. The frailty definition developed in the CHS is applicable across diverse population samples and identifies a profile of high risk of multiple adverse outcomes.

In recent literature, frailty has been conceptualized as an outcome of declines across multiple molecular, cellular, and physiologic systems which is highly prevalent in older persons and has severe consequences (1–8). Although clinicians claim that frailty can be easily recognized, definition has proved elusive. There have been proposals to identify older adults who are frail, or at risk for frailty, by their disability status (9), functional performance (10), or a combination of either with comorbidity, neurosensory problems, or adverse geriatric outcomes (11–15). Relatively little work has attempted to implement the theoretical construct of accelerated declines across multiple physiological systems into operational criteria for frailty identification (4,7,8,16,17). At a recent American Geriatrics Society/National Institute on Aging-sponsored national conference, Fried and colleagues (3) presented an operational definition of frailty based on their work in the Cardiovascular Health Study (CHS). The definition conceptualizes frailty as a syndrome of decreased resiliency and reserves, in which a mutually exacerbating cycle of declines across multiple systems results in negative energy balance, sarcopenia, and diminished strength and tolerance for exertion. Accordingly, it proposes exhaustion, weight loss, weak grip strength, slow walking speed, and low energy expenditure as frailty-identifying characteristics. It is the focus of this report.

Because frailty has no gold standard measure, validating its definition is intrinsically complex. The CHS definition derives face and content validity by tying its definitional criteria to the above-mentioned theoretical framework. Its validity for predicting frailty-related outcomes was demonstrated within the CHS data set. In this report, we use data from the Women's Health and Aging Studies (WHAS) to strengthen the validation of the frailty definition in two important ways. First, we cross-validate the criteria for frailty that were originally developed and validated in the CHS in a different, independent data set. Second, we evaluate whether CHS criterion co-occurrence is consistent with a medical syndrome. Doing so, we believe, provides the first internal validation of any extant frailty measure with respect to its conceptualizing theory; it also assesses whether the CHS algorithm of combining clinical criteria into an additive score is reasonable or, rather, invalidly masks aggregation of distinct subgroups of frailty characteristics, inconsistent with a clinical syndrome.

Methods

Study Population and Measures

Our analyses used merged data from complementary prospective studies of older women: WHAS I and II (18,19). WHAS I studied 1002 women aged 65 and older who, at baseline, represented the one third most disabled older women living in the community. WHAS II is studying 436 women initially among the two third least disabled women aged 70–79 years in the community. Besides disability status, the studies' eligibility criteria were identical, except that WHAS I required a Mini-Mental State Examination (20) score above 17, whereas WHAS II required a score above 23. All evaluations,

Table 1. Frailty-Defining Criteria: WHAS and CHS

Characteristics	WHAS		CHS	
	Definition	%*	Definition	%*
Weight loss	Either of: i) Weight at age 60 – weight at exam ≥10% of age 60 weight or ii) BMI at exam < 18.5 kg/m^2	12.7	Lost >10 pounds unintentionally in last year	7.3
Exhaustion	Self-report of any of: i) low usual energy level (≤3, range 0–10)[†], ii) felt unusually tired in last month[‡], or iii) felt unusually weak in the past month[‡]	14.1	Self-report of either of: i) felt that everything I did was an effort in the last week, or ii) could not get going in the last week	21.3
Low energy expenditure[§]	90 on activity scale (6 items)	19.8	270 on activity scale (18 items)	24.1
Slowness[§]	Walking 4 m: Speed ≤ 4.57/7 for height ≤159 cm or Speed ≤ 4.57/6 for height >159 cm	31.3	Walking 15 feet (4.57 m): Time ≥ 7 for height ≤ 159 cm or Time ≥ 6 for height >159 cm	38.0
Weakness[§]	Grip strength: As for CHS	20.8	Grip strength ≤17 for BMI ≤23, ≤17.3 for BMI 23.1–26, ≤18 for BMI 26.1–29, or ≤21 for BMI >29 kg/m^2	26.2
Overall frailty status	Robust	44.9	Robust	33.2
	Intermediate	43.8	Intermediate	55.2
	Frail	11.3	Frail	11.6

Notes: *% with criterion among women ages 70–79 years: weighted in WHAS, $n = 786$; CHS, $n = 1741$.
[†]Rated on 0–10 scale, where 0 = ''no energy'' and 10 = ''the most energy that you have ever had.''
[‡]If yes, there followed questioning ''how much of the time'' the feeling persisted; responses ''most'' or ''all'' of the time were considered indicative of exhaustion.
[§]Based on original CHS, female-specific criterion.
WHAS = Women's Health and Aging Study; CHS = Cardiovascular Health Study; BMI = body mass index.

interviews, and physical examinations were conducted using the same rigorously standardized methods.

Disease burden and physical disability.—Presence or absence of major chronic conditions was adjudicated by physicians based on predefined criteria (21) and included: angina pectoris, myocardial infarction, and congestive heart failure (CHF); degenerative disc disease, spinal stenosis, hip fracture, and osteoporosis; osteoarthritis of the knee, hip, and hand and rheumatoid arthritis; stroke, Parkinson's disease, pulmonary disease, diabetes mellitus, peripheral arterial disease, and cancer. The number of ''definite'' conditions, of 17, was considered as an index of disease burden.

Physical function.—Instrumental activities of daily living (IADL: doing light house work, preparing meals, shopping, managing money) and basic activities of daily living (ADL: bathing, transferring from bed or chair, dressing, eating, toileting) were assessed. For analyses, women were categorized as having ''severe IADL (respectively, ADL) disability'' who reported ''any difficulty'' in three or more IADL (ADL) tasks.

Frailty Phenotype

Application of CHS frailty phenotype in WHAS.—The CHS frailty criteria (3) were adjudicated in WHAS participants using available WHAS baseline measures (Table 1). Grip strength was measured in WHAS exactly as in CHS, using a Jamar dynamometer (model BK-7498; Fred Sammons, Inc., Burr Ridge, IL). Usual pace walking speed (m/s) was measured in WHAS over 4 meters, instead of 15 feet as in CHS. Energy expenditure was measured for both populations using the Minnesota Leisure Time Activity Questionnaire (22), but in WHAS we used a threshold of low energy expenditure one third that in CHS because only 6 of the 18 activities considered in CHS were evaluated in WHAS (walking, doing strenuous household chores, doing strenuous outdoor chores, dancing, bowling, exercise). We defined exhaustion in WHAS by using questions similar to those in CHS. Weight loss was defined in CHS as self-report of having unintentionally lost more than 10 pounds in the last year, and in WHAS as at least 10% weight loss compared to the weight at age 60 or having measured body mass index below 18.5 kg/m^2. As in CHS, women meeting 3 or more criteria were classified as frail; those meeting 1 or 2 as intermediate; and those meeting none as robust.

Data Analysis

We used data from WHAS I and II participants 70–79 years old. Analyses were probability-weighted, thus referenced to the population of community-dwelling older women. We compared the prevalence of each frailty criterion in the WHAS to that among CHS women aged 70–79 years.

Internal construct validity.—A medical syndrome is ''a group of signs and symptoms that occur together and characterize a particular abnormality'' (23). Thus two patterns of criteria co-occurrence are consistent with frailty being a syndrome: 1) manifestation in a critical mass; and 2) aggregation in a specific order, as would occur in a cycle in which dysregulation in a sentinel system spurs a cascade of alterations across other systems. To evaluate our measure's convergent validity with such co-occurrence, we first tabulated the frequencies of the 32 possible frailty criteria combinations. Then, we applied latent class analysis (LCA; 24), fit in MPlus (25). The LCA hypothesis is that the population of community-dwelling older women comprises discrete subpopulations characterized by sentinel patterns of frailty criteria co-occurrence and exhibiting frailty criteria homogeneously excepting purely random variability about the sentinel pattern (technically: ''conditionally independent'').

Table 2. Frailty Criteria Patterns and Latent Class Analysis* Fit: WHAS I and II

	Criteria (In Order): Weight Loss/Weak/Slow/Exhausted/ Low Activity Has Criterion: No (N) or Yes (Y)	Observed	Pattern Frequencies Expected		
			1-Class Model	2-Class Model	3-Class Model
8 most	NNNNN	310	247.8	339.5	341.2
frequently	NNYNN	76	107.2	74.9	72.4
observed	NNNNY	40	61.9	36.0	34.1
nonfrail	NYNNN	36	63.9	39.7	38.5
patterns	NNYNY	32	26.8	22.8	28.7
	NYYNN	31	27.6	23.1	26.8
	NNNYN	28	40.0	25.4	24.4
	YNNNN	25	35.1	28.7	30.3
8 most	NYYNY	16	6.9	18.8	14.5
frequently	NYYYY	12	1.1	9.5	8.2
observed	NNYYY	10	4.3	9.5	7.3
frail	YYYYY	10	0.2	3.3	7.6
patterns	YYYNY	9	1.0	6.4	7.0
	YNYNY	8	3.8	6.6	5.0
	YYYNN	7	3.9	6.5	5.5
	NYNYY	6	2.6	4.3	3.4
Latent class model fit statistics					
Pearson chi square			568 ($p < .0001$)	24.4 ($p = .22$)	13.1 ($p = .52$)
AIC			3560	3389	3390
BIC			3583	3440	3467

Notes: *Probability-weighted WHAS I and II; $n = 740$.
WHAS = Women's Health and Aging Studies; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion.

LCA aims to determine (i) the number of such subpopulations (''classes''); (ii) each subpopulation's prevalence in the overall population; and (iii) per subpopulation and criterion, the proportion having the criterion (''conditional probabilities''—here, five per class).

Validation of the theory that our frailty criteria are syndromic in their occurrence involves the number of latent classes and patterns of conditional probabilities across classes. We evaluated the number of latent classes needed to satisfy the LCA hypothesis by comparing goodness-of-fit of models with different numbers of classes, using Pearson's chi square (24), Akaike Information Criterion (AIC) (26), and Bayesian Information Criterion (BIC) (27). Models imposed no external conditions (e.g., no requisite number of criteria in ''frailer'' subpopulations). If frailty is a syndrome there must be two or more classes, as a one-class model indicates independent criteria thus no syndromic aggregation. Fits requiring two or more classes support that the CHS frailty criteria aggregate in a syndrome, so long as criteria either have similar probabilities of being manifested per each class [see (1) in last paragraph], or are hierarchical [less sensitive criteria rarely manifested unless more sensitive criteria also are, per (2) in last paragraph]. Propensity for criteria to co-occur in distinct subgroups would suggest the effects of distinct biologic processes rather than a syndrome.

Criterion validity.—We used discrete-time proportional hazards models (28) to analyze association of frailty status with incidence (first self- or proxy-reported) of: 1) falling; 2) severe IADL or ADL disability; 3) hospitalization; and 4) nursing home entry (''permanent,'' counting only entries with no discharge by study close-out). For our analysis, each outcome was assessed every 18 months for both studies, corresponding to rounds 1, 4, and 7 of WHAS I and rounds 1, 2, and 3 of WHAS II, yielding 3 years follow-up. Cox proportional hazards models (28) were used to analyze mortality (age, by death certificate). In each analysis we calculated instantaneous hazards ratios comparing frail, and intermediately frail, to robust women, adjusting for baseline age, race, education (grades completed), smoking (pack-years), Mini-Mental State Examination (20) score, depressive symptoms (Geriatric Depression Scale; 29), CHF presence, disease burden, ankle-arm blood pressure, and use of diuretics without history of hypertension or CHF (previously shown to be an independent predictor of mortality; 30). Additional adjustment for albumin and creatinine levels had negligible impact, hence is not shown.

Results

Excepting weight loss, lower percentages met individual frailty criteria in WHAS than CHS. For all 5 criteria, percentages agreed across the two studies to within 7% (Table 1). The greater percentage with weight loss in WHAS is expected, given the WHAS assessment method. The lower percentages meeting exhaustion and low-energy-expenditure criteria in WHAS are consistent with the lower percentages meeting slowness and weakness criteria. To reference comparison across studies: Compared to their WHAS counterparts, women aged 70–79 years who participated in CHS tended to be more frequently white (82% vs 78%) and better educated (69% vs 57% completing high school or more) and reported less ADL task difficulty (prevalence ranging from 1% to 7% across tasks, vs 3%–17% in WHAS). Yet, perceived health status was reported similarly across the studies. Notably, (ascending) prevalence rank order across criteria was the same in CHS and WHAS: weight loss, exhaustion, low energy expenditure, weakness, and slowness.

Percentages meeting our definition of ''frail'' were remarkably similar in CHS and WHAS (11.6% vs 11.3%). There were fewer ''robust'' women in CHS (33.2%, vs 44.9% in

Table 3. Conditional Probabilities of Meeting Criteria Within Latent Frailty Classes: WHAS*

	2-Class Model		3-Class Model		
	Class 1	Class 2	Class 1	Class 2	Class 3
Criterion	Nonfrail	Frail	Robust	Intermediate	Frail
Weight loss	.073	.26	.072	.11	.54
Weakness	.088	.51	.029	.26	.77
Slowness	.15	.70	.004	.45	.85
Low physical activity	.078	.51	.000	.28	.70
Exhaustion	.061	.34	.027	.16	.56
Class prevalence (%)	73.3	26.7	39.2	53.6	7.2

Note: *Per class and criterion: Estimated proportion in class exhibiting the criterion.

WHAS = Women's Health and Aging Studies.

Table 4. Association of Baseline Frailty Status and Risk of Incident Adverse Events, Combined WHAS I (Rounds 1, 4, 7) and WHAS II (Rounds 1, 2, 3) Cohorts ($N = 784$)*

	Adjusted HRs (95% CIs)†	
Outcome	Intermediate‡	Frail‡
Fall ($n = 560$)	0.92 (0.63, 1.34)	1.18 (0.63, 2.19)
Severe ADL disability ($n = 612$)	5.68 (2.41, 13.42)	15.79 (5.83, 42.78)
Severe IADL disability ($n = 698$)	3.53 (1.20, 10.35)	10.44 (3.51, 31.00)
Hospitalization ($n = 715$)	0.99 (0.67, 1.47)	0.67 (0.33, 1.35)
Permanent nursing home entry ($n = 750$)§	5.16 (0.81, 32.79)	23.98 (4.45, 129.2)
Death ($n = 766$)	3.50 (1.91, 6.39)	6.03 (3.00, 12.08)

Note: *Excluding participants with stroke or Parkinson's disease.

†Adjustments: Baseline age, race, grades completed, smoking (pack-years), disease-related variables—history of congestive heart failure, Mini-Mental State Examination score, Geriatric Depression Scale score (≥14), number of adjudicated diseases (modeled by natural splines with 3 *df*), ankle-arm blood pressure, use of diuretics without history of hypertension or congestive heart failure.

‡Risk ratios were calculated relative to the nonfrail group.

§Not known to have returned to community dwelling following entry.

WHAS = Women's Health and Aging Study; ADL = activities of daily living; IADL = instrumental activities of daily living; HRs = hazard ratios; CIs = confidence intervals.

WHAS) and, correspondingly, more in the ''intermediate'' category (55.2% vs 43.8%). As expected, the more disabled WHAS I cohort had a higher percentage of women meeting each frailty criterion than did the WHAS II or CHS cohort, by 25%–40% for exhaustion, low energy expenditure, and weakness, and by as high as 62% for slowness. In WHAS I, 25.4% were frail, 60.6% were in the intermediate group, and only 14.0% were robust.

Internal construct validity.—We analyzed patterns of co-occurrence of the diagnostic criteria (Table 2). The one-class model did not adequately predict the frequencies of the observed patterns. The concordance between predicted and observed frequencies improved substantially with the two- and three-class models, both of which provided an adequate fit (chi-square p values = .22 and .52). The two-class model was slightly favored by AIC and BIC criteria, achieving adequate fit with fewer parameters. These findings indicate that the frailty criteria aggregate, as required for the elements of a syndrome.

To evaluate whether criteria aggregated syndromically, we examined the (''conditional'') probabilities of having each criterion, within latent classes (Table 3). In neither two- nor three-class models was there evidence that some criteria co-occurred preferentially in specific classes; rather, each criterion's prevalence increased progressively across less-to-more-frail classes. The three-class fit estimated the mean number of criteria for ''intermediate'' and ''frail'' individuals as 1.26 and 3.42, well in line with the CHS definitions of 1–2 and ≥3 criteria. These analyses strongly support the notion that the frailty criteria aggregate in accordance with the a priori hypothesis that they are elements of a syndrome and are well summarized by the proposed counting strategy.

Criterion validity.—Consistently with analyses in CHS, frailty strongly predicted all considered outcomes except falls and first hospitalization (Table 4). Findings for nonmortality outcomes are cause-specific with respect to death; otherwise, there was only 5% loss to follow-up in WHAS I, and 1.4% in WHAS II. After adjustment for comorbidity and other key covariates, compared to robust individuals, frail women had 6-fold higher risk of death and more than 10-fold higher risk of incident IADL and ADL disability and nursing home entry.

Discussion

We evaluated the validity of the CHS frailty definition (3) in companion population-based cohorts, the WHAS I and II. The five frailty criteria and the overall frailty measure demonstrated similar distributions in CHS and WHAS. Concordant with CHS findings, frailty strongly predicted disability and mortality among WHAS participants, independently of disease and other measures. The CHS frailty definition showed internal construct validity *vis à vis* a medical syndrome. These findings indicate that the CHS frailty definition has internal and criterion validity and is generalizable.

To our knowledge, this is the first application of a LCA to internally validate a theoretical construct for frailty by its rigorous translation into predicted properties of frailty operational measurements. In this context, LCA was preferred to factor analysis because the former is consistent with investigating a syndrome and does not hypothesize an underlying continuum (31). LCA also addresses whether three phenotype categories better capture heterogeneity in frailty measurements than do two. Our analysis did not indicate so, but a larger sample is needed to convincingly address the question.

Some lingering questions should be acknowledged. First, there remain aspects of construct validity to be evaluated. For example, the CHS frailty phenotype includes measures of functional limitation (slow walking speed) and impairment (weakness), which may be in the same causal pathway to declining physical function. This may partially explain why our frailty measure strongly predicts adverse outcomes. More work to evaluate discriminant validity would be valuable. Second, how much value a ''phenotype'' adds for predicting adverse outcomes, above independent contributions of individual criteria, is of interest. A formal delineation remains to be accomplished. Third, our phenotype's definition entailed operational choices—cutoffs defining ''frail'' on each criterion and a requirement of three positive criteria for frailty categorization. Alternative choices could alter classification or improve prediction of selected outcomes. Fourth, the WHAS lacks men, so cross-validation and internal validation remain to be accomplished in this major subgroup of older adults. Finally, we acknowledge continuing debate over the biological underpinnings and component features of frailty. The criteria assessed by our measure reflect one theory, to which their content validity is tied. Other criteria plausibly reflect frailty and may prove

useful. Ultimately, scientists must adjudicate the worth of the theory (1–8) on which our work, hence its validity, relies.

Although we have operationalized frailty as a discrete ''abnormality,'' frailty may span one extreme of a health continuum and become normative as persons age. Discrete medical categories rarely reflect the complexity of processes that underlie diminished functioning. We do not propose to reify our classification (32) as such risks diminishing the quality of care (e.g., 33). Nor do we uphold it as the last or only frailty measure that should be considered. Nonetheless, the need for discrete classifications has long been recognized by the medical community. We consider ''frailty'' as a phenomenon that becomes clinically visible above a threshold of severity. Our approach aims to provide a useful tool for research and identification of those at high risk for health declines.

Summary

Our findings supported criterion validity of the proposed frailty phenotype similarly to that resulting from analyses conducted in CHS. LCA also supported the internal validity of the CHS frailty definition (3) for a syndromic outcome, as predicted by the theory that frailty results from aggregate declines in multiple molecular, cellular, and physiologic systems (7). Such definition appears to be applicable across populations, and identifies persons at increased risk for adverse health outcomes.

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