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Preliminary Evidence for Subdimensions of Geriatric Frailty: The MacArthur Study of Successful Aging

Catherine A. Sarkisian, MD, MSPH[*,†], **Tara L. Gruenewald, PhD, MPH**[†], **W. John Boscardin, PhD**[‡,§], and **Teresa E. Seeman, PhD**[†]

[*] Veterans Affairs Greater Los Angeles Healthcare System Geriatric Research, Education, and Clinical Center, Los Angeles, California

[†] Division of Geriatrics, Department of Medicine, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, California

[‡] Department of Medicine, University of California at San Francisco, San Francisco, California

[§] Department of Epidemiology and Biostatistics, University of California at San Francisco, San Francisco, California

Abstract

OBJECTIVES—To identify frailty subdimensions.

DESIGN—Longitudinal cohort (MacArthur Study).

SETTING—Three U.S. urban centers.

PARTICIPANTS—One thousand one hundred eighteen high-functioning subjects aged 70 to 79 in 1988.

MEASUREMENTS—Participants with three or more of five Cardiovascular Health Study (CHS) frailty criteria (weight loss, weak grip, exhaustion, slow gait, and low physical activity) in 1991 were classified as having the CHS frailty phenotype. To identify frailty subdimensions, factor analysis was conducted using the CHS variables and an expanded set including the CHS variables, cognitive impairment, interleukin-6 (IL-6), C-reactive protein (CRP), subjective weakness, and anorexia. Participants with four or more of 10 criteria were classified as having an expanded frailty phenotype. Predictive validity of each identified frailty subdimension was assessed using regression models for 4-year disability and 9-year mortality.

RESULTS—Two subdimensions of the CHS phenotype and four subdimensions of the expanded frailty phenotype were identified. Cognitive function was consistently part of a subdimension including slower gait, weaker grip, and lower physical activity. The CHS subdimension of slower

Address correspondence to Catherine A. Sarkisian, MD, MSPH, VA Greater Los Angeles Healthcare System, Geriatric Research Education Clinical Center (GRECC), Building 220, Room 315 (11G), 11301 Wilshire Blvd., Los Angeles, CA 90073. E-mail: csarkisian@mednet.ucla.edu.

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gait, weaker grip, and lower physical activity predicted disability (adjusted odds ratio (AOR) =1.7, 95% confidence interval (CI) =1.3–2.2) and mortality (AOR =1.5, 95% CI =1.3–1.8). Subdimensions of the expanded model with predictive validity were higher IL-6 and CRP (AOR =1.2 for mortality); slower gait, weaker grip, lower physical activity, and lower cognitive function (AOR =1.8 for disability; AOR =1.5 for mortality), and anorexia and weight loss (AOR =1.2 for disability).

CONCLUSION—This study provides preliminary empirical support for subdimensions of geriatric frailty, suggesting that pathways to frailty differ and that subdimension-adapted care might enhance care of frail seniors.

Keywords

frailty; disability; aged; comorbidity

Many investigators have embraced a model in which frailty represents a state of decreased physiological reserves and dysregulation of multiple physiological systems.[1] In 2001, Fried et al.[2] used data from the Cardiovascular Health Study (CHS) and defined a phenotype of frailty that included three or more of the following: weight loss, weak grip, exhaustion, slow gait, and low physical activity level. A subsequent study used latent class analyses in the Women's Health and Aging Study to demonstrate that the selected dichotomized CHS criteria occur together across individuals.[3]

At the 2004 National Institute on Aging/American Geriatrics Society Research Conference on Frailty, identifying frailty subdimensions was identified as a research priority.[4] Identifying subdimensions with different prognostic profiles could offer insights into the varied pathways by which older adults become frail and proceed from frailty to bad outcomes. Ultimately, identifying different pathways could lead to the development of different or adjusted interventions to prevent and treat frailty. Scientists at the second International Frailty Conference in 2006 concurred that identification of subdimensions was a research priority and stated that a "broader definition of frailty may be useful, and even crucial, in research to understand the causes and consequences of the variety of traits subsumed under the general idea of frailty."[5] For example, many geriatricians believe that cognitive impairment is intrinsic to geriatric frailty.[6–10] It has also been hypothesized that inflammation characterizes frailty,[11] and high interleukin-6 (IL-6) levels are associated with the CHS frailty phenotype.[12]

This team hypothesized that the construct of frailty would subsume two or more subdimensions —one or more of which would include the CHS criteria, as well as cognitive impairment, subclinical inflammation, and subjective weakness and anorexia. The specific aims of this study were to use the MacArthur Study of Successful Aging to test empirically for the existence of subdimensions of frailty, using the CHS and an expanded set of criteria from vulnerability-based models, and to test the predictive and discriminant validity of identified subdimensions.

METHODS

Subjects

The MacArthur Study of Successful Aging (MSSA) was a longitudinal cohort study of 1,189 adults, aged 70 to 79 in 1988. MSSA participants were selected from the National Institute on Aging's Established Populations for Epidemiologic Studies of the Elderly (EPESE). Selection criteria were employed to exclude subjects with disability.[13] A cohort of 1,313 subjects met eligibility criteria; 1,189 (90.6%) agreed to participate. Wave 1 data collection was completed in 1988 and 1989. Wave 2 data collection began in 1991, with face-to-face interviews, physical examinations, and performance measures completed between 24 and 32 months after baseline. Of the original cohort, 71 died by Wave 2. Because information on weight loss was not available

at Wave 1, Wave 2 (n =1,118) was selected as the baseline analytical sample. Subjects who did not complete measures necessary to measure frailty (108 for the CHS model; 115 for the expanded model) were excluded, leaving analytical samples of 1,010 for analyses examining the CHS frailty model and 1,003 for analyses examining the expanded frailty model. For analyses using component scores as predictors, only participants with complete data on candidate criteria were included (n =967 for the CHS analyses; n =695 for the expanded model analyses). For analyses using disability as the outcome, persons without an interview in 1995 were excluded (disability analyses n =762 and 563 for CHS and expanded models respectfully). All subjects provided informed consent, and institutional review boards approved the project.

Measures

CHS Frailty Criteria—Representative or identical measures of all CHS frailty criteria were available at Wave 2. Weight loss (or gain) was calculated as percentage of body weight lost (or gained) between Waves 1 and 2. Grip strength (average of 3) was measured using a handheld dynamometer. Exhaustion was measured using the Hopkins Symptom Checklist:[14] "During the past week, how much have you been distressed by feeling low in energy or slowed down?" (not at all, a little, quite a bit, extremely). Gait speed was measured using the timed 10-foot walk (usual pace). Physical activity was measured using energy expenditure–weighted assessments of engagement in recreational, exercise, housework, and yard-work activities from the Yale Physical Activity Survey[15] and other physical activity surveys.[16,17]

Expanded-Model Frailty Measures—In selecting candidate criteria for an expanded model of frailty (one that includes not only the CHS criteria, but also additional criteria), this team considered criteria that were included in the biological model of geriatric frailty presented and embraced at the 2006 International Congress on Geriatric Frailty:[5]

- *Cognitive Impairment*. Cognitive function was assessed using reliable tests of language, executive function, spacial ability, and verbal and nonverbal memory. A previously tested well-distributed summary score[18] was used.
- *IL-6 and CRP*. At Wave 2, 80.3% of participants provided blood samples, which were analyzed for IL-6 and CRP using standard protocols. Values were measured in duplicate with averages reported.
- *Subjective weakness*. Subjective weakness was assessed using the Hopkins Symptom Checklist:[14] "During the past week, how much have you been distressed by weakness in parts of your body?" (not at all, a little, quite a bit, extremely).
- *Anorexia*. Anorexia was measured using the Hopkins Symptom Checklist:[14] "During the past week, how much have you been distressed by poor appetite?" (not at all, a little, quite a bit, extremely).

Although all continuous variables were kept continuous for factor analyses (see Analysis, below), to construct a categorical CHS frailty variable, each of the five CHS frailty indicators was dichotomized using the absolute values of the CHS criteria. Weight loss was defined as a decrease of 5% or more. Participants who scored below the CHS-derived cutpoints were classified as having weaker grip. Those who responded "quite a bit" or "extremely" to the exhaustion question were categorized as exhausted. Those scoring in the lowest quintile (CHS derived) on the 10-foot walk, stratified according to sex and height, were classified as having slower gait. Those scoring in the lowest quintile of physical activity, stratified according to sex, were classified as having lower physical activity. Participants with three or more of the five CHS criteria were classified as having the CHS phenotype of frailty; those with one or two criteria were classified as having the CHS phenotype of intermediate frailty.

Participants with scores in the lowest quintile in cognitive functioning score were classified as having lower cognitive function. Those with scores in the top quintile of CRP (>3.68) and IL-6 (>5.51) were classified as higher risk. Those responding "quite a bit" or "extremely" on the weakness and anorexia questions were classified as having subjective weakness and anorexia, respectively. To create categorical frailty variables for the expanded model, the distribution of total number of criteria prevalence was examined, and cutpoints were selected based on "stepping off" points that would result in frailty prevalence rates close to those of the CHS model. Participants with four or more of 10 possible frailty criteria (the 5 CHS criteria, high IL-6, high CRP, low cognitive function, subjective weakness, and anorexia) were classified as having an expanded (MSSA) phenotype of frailty; those with two or three criteria were classified as having an expanded (MSSA) phenotype of intermediate frailty.

Other Measures

Comorbidity was defined as the lifetime incidence of two or more of seven conditions. Disability was defined as self-reported difficulty in one or more of seven items from the Katz activity of daily living scale.[19] Mortality data was obtained from National Death Index searches through 2000.

Analyses

Identifying Subdimensions—Factor analysis refers to statistical techniques whose common objective is to represent a set of variables in terms of a smaller number of hypothetical variables, in this case, frailty subdimensions.[20] The hypothesis is that a selected group of variables can be defined as linear combinations of subdimensions, in this case, with one set of subdimensions identified using variables from the CHS model, and another set of subdimensions identified using variables from the 10-criteria expanded MSSA model of frailty. Principal components analysis (PCA) was selected to approximate factor analytical subdimensions as indices that explain as much of the total variance as possible. All continuous variables were kept continuous. Extracted components were selected based on eigenvalues and visual inspection of scree plots, including the Kaiser-Guttman rule of retaining components with eigenvalues greater than 1, as well as the common practice of retaining 100/P percent (P =number of variables) of the total variance.[21] Continuous component scores were constructed to estimate each identified frailty subdimension.

Assessing Predictive Validity—A series of logistic regression models was constructed to quantify the relationship between each frailty phenotype and PCA-identified subdimension and two outcomes: disability by 1995 and mortality by 2000. Models examining the subdimensions used the continuous component scores as predictors. Models were adjusted for age, sex, ethnicity (African American vs non-Latino white), education (high school graduate vs less than high school education), comorbidity, 1991 disability, and when applicable, presence of other frailty subdimensions. The percentage of participants classified as frail in 1991 who had neither disability nor comorbidity was calculated. To examine the extent to which the chosen cutpoints for defining frailty influenced findings, sensitivity analyses were conducted using different cutpoints (≥3 and ≥5 criteria in the expanded model of frailty =frail).

RESULTS

Mean age of the 1,189 study participants was 74; 55% were female, 19% were African American, and 46% were high school graduates.

PCA of the CHS criteria revealed two subdimensions (components) with eigenvalues greater than 1.0, explaining 48% of the variance. As illustrated in Table 1, the rotated factor-loading matrix indicates a two-component structure in which slower gait, weaker grip, and lower

physical activity define one component (subdimension), and exhaustion and weight gain (not loss) define the second component (subdimension). The correlation coefficient between components was 0.04. PCA of the expanded set of frailty criteria (the 5 CHS criteria and the 5 additional criteria) revealed four components with eigenvalues greater than 1.0. Higher IL-6 and CRP define the first of these components (subdimensions); exhaustion and subjective weakness the second; slower gait, weaker grip, lower physical activity, and lower cognitive function the third; and weight loss and anorexia the fourth. Total variance explained was 56%; correlations between components ranged from 0.02 to 0.12.

The relationship between each frailty phenotype and subdimension and health outcomes is illustrated in Table 2. Subjects with the CHS frailty phenotype had an adjusted odds ratio (AOR) of 4.4 (95% confidence interval (CI) =2.1–9.4) of becoming disabled in 4 years and of 2.1 (95% CI =1.2–3.8) of dying in 9 years. Those with the expanded phenotype of frailty had an AOR of 5.9 (95% CI =3.0–11.7) of becoming disabled and of 2.7 (95% CI 1.6–4.7) of dying. The slowness, weak grip, low physical activity subdimension of the CHS model independently predicted disability and mortality, with AORs ranging from 1.5 (mortality) to 1.7 (disability). Subdimensions of the expanded model associated with poor outcomes included the higher inflammatory markers (AOR =1.2 for mortality); slower gait, weaker grip, lower physical activity, and lower cognitive function (AOR =1.8 for disability; 1.5 for mortality), and anorexia and weight loss (AOR =1.2 for disability). Neither subdimension including exhaustion was associated with disability or mortality. In sensitivity analyses using alternative cutpoints for the dichotomous operational definition of frailty (≥3 and ≥5 criteria), the expanded model of frailty was significantly associated with disability and mortality (AORs ranging from 1.9 to 6.0).

As illustrated in Table 3, 28% of participants with the CHS phenotype of frailty and 39% of with the expanded (MSSA) phenotype had neither disability nor comorbidity. Across frailty subdimensions, at least 42% had neither disability nor comorbidity. Correlations between subdimensions ranged from 0.03 to 0.21.

DISCUSSION

This study provides preliminary empirical support for the existence of subdimensions of geriatric frailty. Within the CHS model, two subdimensions were identified, and within an expanded model of frailty, four subdimensions were identified. These preliminary findings suggest that older adults experience a variety of pathways to frailty and that some subdimensions of frailty may carry worse prognosis than others.

The finding that cognitive impairment is part of a frailty subdimension including slower gait, weaker grip, and lower physical activity is consistent with increasing evidence that physical performance tests are sensitive indicators of cognitive impairment[22] and supports the hypothesis that cognitive impairment is intrinsic to geriatric frailty. Although some have referred to the CHS model of frailty as the “biological” model of frailty (in contrast to other models that include social and psychological criteria),[23] these findings call this into question, because several variables in the CHS phenotype of frailty appear to be integrally related to cognitive impairment.

That weight gain but not loss correlated with exhaustion as a subdimension is consistent with findings confirming that wasting, measured according to weight loss, is not a necessary component of frailty.[24] To attempt to shed light on the mechanisms by which wasting, obesity, and sarcopenia contribute to frailty, these analyses should be repeated in a longitudinal dataset containing reliable measures of sarcopenia.

Although exhaustion is undesirable in its own right, neither of the "exhaustion subdimensions" was independently associated with disability or mortality. This finding is inconsistent with a European study that showed that "tiredness" was associated with future disability.[25] Whether the differences between these study results are due to differences in measurement or the samples (maybe fatigue is only predictive of disability in lower-functioning persons) should be examined further in other cohorts.

Although the cutpoints used for "higher" levels of inflammation were conservative in this high-functioning sample, given previously demonstrated associations between these biomarkers and mortality,[26] it was notable that the inflammation subdimension had an independent association with mortality of only borderline significance. One possible explanation for this finding is that, although intra-individual increases in these biomarkers have strong associations with mortality, baseline levels of IL-6 are not always associated with mortalilty;[27] another possibility is that the inflammatory markers themselves act through causal pathways involving the other subdimensions, such as slower gait, weaker grip, lower physical activity, and lower cognitive function. Future studies in which these strongly correlated variables are measured at multiple time points should be conducted to attempt to elucidate these variables' pathways to disability and mortality.

Because EPESE participants who scored in the lower two-thirds on measures of physical and cognitive function were excluded from the sample, a strength of MSSA is that participants were unlikely to have had "occult" frailty at baseline. It is already known that older adults with existing disability and cognitive impairment are at high risk of incident frailty; it is important to learn about pathways to frailty in older adults one would not consider already to be at high risk. This strength is also a limitation of this dataset, in that conclusions from this data may not generalize to populations that include less-healthy older adults.

Another limitation of the MSSA is the paucity of older adults from ethnic groups other than non-Latino whites and African Americans. Because the 1991 (Wave 2) participants were the analytical sample, findings from this "survivor cohort" should be compared with findings from a true population-based sample. Additional limitations of the study include the fact that comorbidity was self-reported and that, like the CHS data, the MacArthur data are dated. Exhaustion and anorexia were suboptimally measured using single items; future studies should attempt to repeat these preliminary findings in datasets with more-robust measures of exhaustion and anorexia.

Correlation coefficients between factors on the oblique rotation were 0.04 for the CHS model and 0.02 to 0.12 for the expanded model, raising the possibility that some sub-dimensions might be better considered to be different constructs rather than frailty subdimensions, especially those with pairs of conceptually tightly linked variables such as IL-6 and CRP. Although many of the selected criteria measured overlapping constructs, none of the items correlated with each other more than a coefficient of determination of 0.26 (CRP with IL-6). Regardless, although latent class analyses done previously support the construct validity of the five-item CHS model,[3] similar analyses should be conducted on the expanded model to build on the preliminary findings shown here.

By including several additional markers of geriatric frailty, the expanded model offers additional insight into the potential role of a larger number of these highly correlated risk factors for poor outcomes in older adults. The fact that there were a greater number of potential criteria drove in part the finding that there were four subdimensions in the expanded model of frailty (vs 2 in the CHS model). It is important to keep in mind that the five additional criteria were selected conservatively based on existing theoretical biologically focused models (and the data available in MSSA) and by no means represent the world of potential frailty criteria. How to

"best" define frailty is a complicated issue in geriatrics,[28] with some scientists publishing broad models that include a large number of "deficits"[29] and others selecting a small number of criteria that it might be possible to measure in a single office visit.[3,8] Appreciating the value of both approaches, this team did not set out to take sides in this debate but rather to identify theoretically grounded and empirically supported subdimensions that warrant further investigation.

In conclusion, this study provides preliminary empirical support for the existence of subdimensions of geriatric frailty. These findings should inform future interventions aimed at preventing or addressing frailty in older adults. As interventions to prevent and treat geriatric frailty are developed and tested, it makes sense to examine whether some subdimensions are more likely to respond than others so that, ultimately, clinicians can provide customized care that is most likely to have an impact.

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Table 1

Principal Component Analysis: Pattern Matrix-Rotated Loadings*

	Five Cardiovascular Health Study Frailty Criteria Components†		Ten Expanded MacArthur Study of Successful Aging Frailty Criteria Components‡			
Criterion	**1**	**2**	**1**	**2**	**3**	**4**
Slower gait	0.71				0.75	
Weaker grip	0.61			0.37	0.50	
Lower physical activity	0.60				0.44	− 0.33
Weight loss	0.27	0.77				0.69
Exhaustion	0.31	− 0.63		0.81		
Lower cognitive function				− 0.36	0.56	
Subjective weakness				0.73		
Anorexia						0.71
Higher IL-6			0.85			
Higher CRP			0.85			
Initial eigenvalue	1.4	1.0	1.8	1.5	1.2	1.1
Percentage of variance explained	28	20	18	15	12	11

*Loadings <0.20 are omitted from the table.

†The rotated factor-loading matrix of the five Cardiovascular Health Study frailty criteria indicates a two-component structure in which slower gait, weaker grip, and lower physical activity define one component (subdimension), and exhaustion and weight gain (not loss) defined the second component (subdimension).

‡The rotated factor-loading matrix of the expanded frailty criteria indicates a four-component structure in which higher interleukin (IL)-6 and C-reactive protein (CRP) define the first of these components (subdimensions), exhaustion and subjective weakness the second, slower gait, weaker grip, lower physical activity and lower cognitive function the third, and weight loss and anorexia the fourth.

Table 2
Predictive Validity of Frailty Phenotypes and Subtypes

	Incident Disability		Mortality	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Frailty Phenotype or Subtype	**Odds Ratio (95% Confidence Interval)**			
Cardiovascular Health Study Model*				
Intermediate frailty	1.9 (1.3–2.9)	1.8 (1.2–2.7)	1.6 (1.2–2.1)	1.5 (1.1–2.0)
Frailty	7.3 (3.7–14.5)	4.4 (2.1–9.4)	2.8 (1.7–4.8)	2.1 (1.2–3.8)
Subtype†				
Slower gait, weaker grip, and lower physical activity	1.8 (1.5–2.2)	1.7 (1.3–2.2)	1.3 (1.2–1.5)	1.5 (1.3–1.8)
Exhaustion and weight gain	1.0 (0.8–1.2)	1.0 (0.8–1.3)	0.8 (0.7–0.9)	0.9 (0.8–1.0)
Expanded MacArthur Study of Successful Aging Model‡				
Intermediate frailty	2.3 (1.5–3.4)	2.0 (1.3–3.0)	2.1 (1.6–2.7)	2.0 (1.4–2.6)
Frailty	8.9 (4.7–16.9)	5.9 (3.0–11.7)	3.3 (2.0–5.3)	2.7 (1.6–4.7)
Subtype†				
Higher inflammatory markers	1.1 (0.9–1.4)	1.0 (0.8–1.3)	1.4 (1.2–1.6)	1.2 (1.0–1.5)
Exhaustion, subjective weakness	1.0 (0.8–1.3)	1.0 (0.8–1.3)	0.9 (0.8–1.1)	1.1 (0.9–1.3)
Slower gait, weaker grip, lower physical activity, and lower cognitive function	1.9 (1.5–2.5)	1.8 (1.3–2.4)	1.3 (1.1–1.6)	1.5 (1.2–1.8)
; Anorexia and weight loss	1.3 (1.1–1.7)	1.2 (1.0–1.6)	1.3 (1.1–1.5)	1.1 (0.9–1.3)

*≥3 of 5 criteria needed to be classified as having frailty and one or more criteria needed to be classified as having intermediate frailty: slow gait, weak grip, low physical activity, exhaustion, and weight loss.

†Subtype scores represent continuous component scores derived from principal component analyses.

‡≥4 of 10 criteria needed to be classified as frail.

Table 3

Discriminant Validity of Frailty Phenotypes and Subtypes

Frailty Phenotype/Subtype	With Phenotype or Subtype, n	With Phenotype or Subtype Who Have Neither Comorbidity Nor Disability, n (%)
Cardiovascular Health Study model*	68	19 (28)
Subtypes		
Slower gait, weaker grip, and lower physical activity†	77	32 (42)
Exhaustion and weight gain‡	209	112 (54)
Expanded MacArthur Study of Successful Aging model§	75	29 (39)
Subtypes		
Elevated inflammatory markers‡	302	164 (54)
Exhaustion and subjective weakness‡	130	55 (42)
Slower gait, weaker grip, lower physical activity, and lower cognitive function‖	141	68 (48)
Anorexia and weight loss‡	222	111 (50)

*≥3 of 5 criteria needed to be classified as frail: slow gait, weak grip, low physical activity, exhaustion, and weight loss.

†≥2 of 3 criteria needed to be classified as having this subtype.

‡≥1 of 2 criteria needed to be classified as having this subtype.

§≥4 of 10 criteria needed to be classified as frail, including slow gait, weak grip, low physical activity, exhaustion, weight loss, elevated interleukin-6, elevated C-reactive protein, subjective weakness, low cognitive function, anorexia.

‖≥2 of 4 criteria needed to be classified as having this subtype.