Frailty in Older Adults: Evidence for a Phenotype

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Background. Frailty is considered highly prevalent in old age and to confer high risk for falls, disability, hospitalization, and mortality. Frailty has been considered synonymous with disability, comorbidity, and other characteristics, but it is recognized that it may have a biologic basis and be a distinct clinical syndrome. A standardized definition has not yet been established.

Methods. To develop and operationalize a phenotype of frailty in older adults and assess concurrent and predictive validity, the study used data from the Cardiovascular Health Study. Participants were 5,317 men and women 65 years and older (4,735 from an original cohort recruited in 1989–90 and 582 from an African American cohort recruited in 1992–93). Both cohorts received almost identical baseline evaluations and 7 and 4 years of follow-up, respectively, with annual examinations and surveillance for outcomes including incident disease, hospitalization, falls, disability, and mortality.

Results. Frailty was defined as a clinical syndrome in which three or more of the following criteria were present: unintentional weight loss (10 lbs in past year), self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity. The overall prevalence of frailty in this community-dwelling population was 6.9%; it increased with age and was greater in women than men. Four-year incidence was 7.2%. Frailty was associated with being African American, having lower education and income, poorer health, and having higher rates of comorbid chronic diseases and disability. There was overlap, but not concordance, in the cooccurrence of frailty, comorbidity, and disability. This frailty phenotype was independently predictive (over 3 years) of incident falls, worsening mobility or ADL disability, hospitalization, and death, with hazard ratios ranging from 1.82 to 4.46, unadjusted, and 1.29–2.24, adjusted for a number of health, disease, and social characteristics predictive of 5-year mortality. Intermediate frailty status, as indicated by the presence of one or two criteria, showed intermediate risk of these outcomes as well as increased risk of becoming frail over 3–4 years of follow-up (odds ratios for incident frailty = 4.51 unadjusted and 2.63 adjusted for covariates, compared to those with no frailty criteria at baseline).

Conclusions. This study provides a potential standardized definition for frailty in community-dwelling older adults and offers concurrent and predictive validity for the definition. It also finds that there is an intermediate stage identifying those at high risk of frailty. Finally, it provides evidence that frailty is not synonymous with either comorbidity or disability, but comorbidity is an etiologic risk factor for, and disability is an outcome of, frailty. This provides a potential basis for clinical assessment for those who are frail or at risk, and for future research to develop interventions for frailty based on a standardized ascertainment of frailty.

FRAILTY is considered to be highly prevalent with increasing age and to confer high risk for adverse health outcomes, including mortality, institutionalization, falls, and hospitalization (1–3). Numerous geriatric interventions have been developed to improve clinical outcomes for frail older adults (3–7). A major obstacle to the success of such interventions has been the absence of a standardized and valid method for screening of those who are truly frail so as to effectively target care (1,3).

Potential definitions of frailty abound, defining frailty as synonymous with disability (1,8,9), comorbidity (8), or advanced old age (3). Increasingly, geriatricians define frailty as a biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, and causing vulnerability to adverse outcomes (9–13). This concept distinguishes frailty from disability (9,10,14,15). There is a growing consensus that markers of frailty include age-associated declines in

lean body mass, strength, endurance, balance, walking performance, and low activity (9,10,14–17), and that multiple components must be present clinically to constitute frailty (9,14). Many of these factors are related (18–31) and can be unified, theoretically, into a cycle of frailty associated with declining energetics and reserve (Figure 1). The core elements of this cycle are those commonly identified as clinical signs and symptoms of frailty (9,10,14–16). Frailty likely also involves declines in physiologic complexity or reserve in other systems, leading to loss of homeostatic capability to withstand stressors and resulting vulnerabilities (2,9,11,12).

We hypothesized that the elements identified in Figure 1 are core clinical presentations of frailty, and that a critical mass of phenotypic components in the cycle would, when present, identify the syndrome. We evaluated whether this phenotype identifies a subset at high risk of the adverse health outcomes clinically associated with frailty. To do this, we operationalized a definition of frailty, as suggested by prior research and clinical consensus (Figure 1), and, in a population-based study of older adults, evaluated its prevalence and incidence, cross-sectional correlates, and its validity in terms of predicting the adverse outcomes geriatricians associate with frail older adults.

METHODS

Population

This study employed data from the Cardiovascular Health Study, a prospective, observational study of men and women 65 years and older. The original cohort ($N = 5201$) was recruited from four U.S. communities in 1989–90. An additional cohort of 687 African American men and women was recruited in 1992–93 from three of these sites. Participants were recruited from age- and gender-stratified samples of the HCFA Medicare eligibility lists in: Sacramento County, California; Washington County, Maryland; Forsyth County, North Carolina, and Allegheny County (Pittsburgh), Penn-

sylvania (32,33). Both cohorts received identical baseline evaluations (except that the latter did not receive spirometry or echocardiograms at baseline) and follow-up with annual examinations and semiannual telephone calls and surveillance for outcomes including incident disease, hospitalizations, falls, disability, and mortality.

Baseline Evaluation

Standardized interviews ascertained self-assessed health, demographics, health habits, weight loss, medications used, and self-reported physician diagnosis of cardiovascular events, emphysema, asthma, diabetes, arthritis, renal disease, cancer, and hearing and visual impairment. A version of the Minnesota Leisure Time Activities Questionnaire (34) ascertained physical activities in the prior 2 weeks, plus frequency and duration. Physical function was ascertained by asking about difficulty with 15 tasks of daily life, including mobility, upper extremity, instrumental activities of daily living (IADL) and activities of daily living (ADL) tasks (35). Frequency of falls in the prior 6 months was assessed by self-report. The modified 10-item Center for Epidemiological Studies–Depression scale [CES–D; (36)] ascertained depressive symptoms.

Cardiovascular diseases [myocardial infarction (MI), congestive heart failure (CHF), angina, peripheral vascular disease, and stroke] were validated by ascertaining medications used and through standardized examinations: electrocardiogram, echocardiogram, and posterior tibial–brachial artery systolic (ankle–arm) blood pressure ratio (32,37,38). These data and medical records were then reviewed by clinicians for consensus-based adjudication of the presence of these diseases, based on standardized algorithms (37).

Additional examinations ascertained weight; blood pressure; carotid ultrasound measuring maximal stenosis of the internal and common carotid arteries (39); phlebotomy, under fasting conditions, with blood analyzed by the Laboratory for Clinical Biochemistry Research (University of Vermont) for fasting glucose, serum albumin, creatinine,
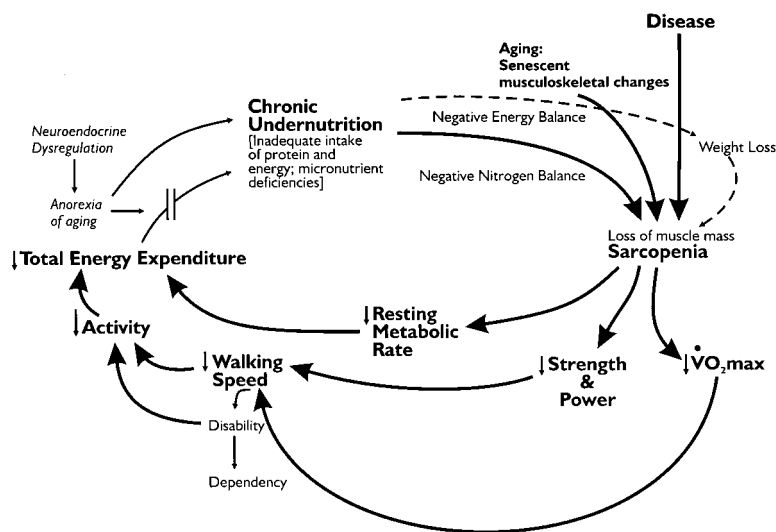

Figure 1. Cycle of frailty hypothesized as consistent with demonstrated pairwise associations and clinical signs and symptoms of frailty. Reproduced with permission from (14).

Table 1. Operationalizing a Phenotype of Frailty

A. *Characteristics of Frailty*	B. *Cardiovascular Health Study Measure**
Shrinking: Weight loss (unintentional) Sarcopenia (loss of muscle mass)	Baseline: >10 lbs lost unintentionally in prior year
Weakness	Grip strength: lowest 20% (by gender, body mass index)
Poor endurance; Exhaustion	"Exhaustion" (self-report)
Slowness	Walking time/15 feet: slowest 20% (by gender, height)
Low activity	Kcals/week: lowest 20% males: <383 Kcals/week females: <270 Kcals/week
	C. *Presence of Frailty*
	Positive for frailty phenotype: ≥3 criteria present
	Intermediate or prefrail: 1 or 2 criteria present

*See Appendix.

and fibrinogen (32). Fasting plasma lipid analyses were performed, and low-density lipoprotein cholesterol was calculated (32). Cognitive function was assessed with the Mini-Mental State Examination (40) and the Digit Symbol Substitution test (41). Standardized performance-based measures of physical function included time (seconds) to walk 15 feet at usual pace and maximal grip strength (kilograms) in the dominant hand (3 measures averaged), using a Jamar hand-held dynamometer (32).

Mortality

Deaths were identified at semi-annual contacts and confirmed through intensive surveillance (37,42). Mortality ascertainment was 100% complete through the eighth year.

Operationalization of the frailty phenotype in CHS.—Based on the scientific rationale above, a phenotype of frailty was proposed to include the elements summarized in Table 1, column A. It was operationalized utilizing data collected in CHS at baseline for Cohort 1 and years 3 (baseline for Cohort 2) and 7 for both cohorts (Figure 2 and Table 1, column B). We specified that a phenotype of frailty was identi-

fied by the presence of three or more of the following components (see Appendix) of the hypothesized cycle of frailty (Figure 1):

1. Shrinking: weight loss, unintentional, of ≥10 pounds in prior year or, at follow-up, of ≥5% of body weight in prior year (by direct measurement of weight).
2. Weakness: grip strength in the lowest 20% at baseline, adjusted for gender and body mass index.
3. Poor endurance and energy: as indicated by self-report of exhaustion. Self-reported exhaustion, identified by two questions from the CES–D scale (36), is associated with stage of exercise reached in graded exercise testing, as an indicator of $\dot{V}O_2$ max (43), and is predictive of cardiovascular disease (44).
4. Slowness: The slowest 20% of the population was defined at baseline, based on time to walk 15 feet, adjusting for gender and standing height.
5. Low physical activity level: A weighted score of kilocalories expended per week was calculated at baseline (34,45), based on each participant's report. The lowest quintile of physical activity was identified for each gender.

For measures that identified the lowest quintile, the level established at baseline was applied to follow-up evaluations. A critical mass of characteristics, defined as three or more, had to be present for an individual to be considered frail. Those with no characteristics were considered robust, whereas those with one or two characteristics were hypothesized to be in an intermediate, possibly prefrail, stage clinically.

Data Analysis

Using CHS data, we identified the number of frailty characteristics present, as per definitions above. Those considered evaluable for frailty had three or more nonmissing frailty components among the five criteria (Table 1). We excluded those with a history of Parkinson's disease ($n = 47$), stroke ($n = 245$), or Mini-Mental scores <18 ($n = 84$), and those who were taking Sinemet, Aricept, or antidepressants ($n = 235$), as these conditions could potentially present with frailty characteristics as a consequence of a single disease. There were 4,735 in the original and 582 in the African American cohort who were eligible; the total baseline sam-
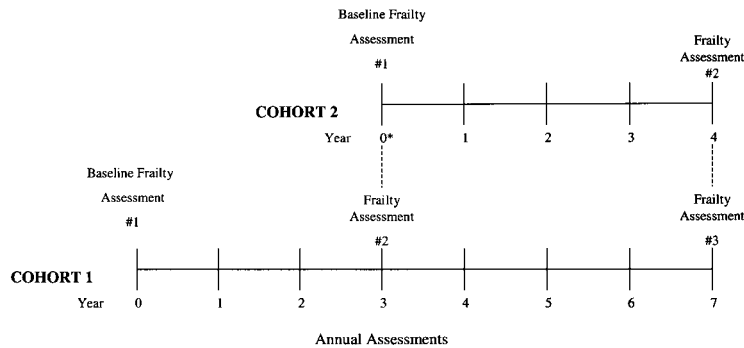
Figure 2. Timing of assessments of frailty components for both cohorts in the Cardiovascular Health Study. *Note that Cohort 2 was recruited and their baseline examination occurred 3 years after that of Cohort 1. Although clinic visits were done annually, frailty was evaluated less frequently.

ple size after applying the exclusion criteria was 5,317. For the first cohort, frailty components were ascertained at baseline, and then 3 years and 7 years into the study. The second cohort, recruited 3 years after the initial cohort, had frailty components ascertained 4 years later (corresponding to year 7 for the first cohort; Figure 2).

For associations of frailty with other factors, the trend *p* value based on the Cochran-Mantel-Haenszel (CMH) test was used. Comorbidity was defined as the presence of two or more of nine conditions: self-reported claudication, arthritis, cancer, hypertension, chronic obstructive pulmonary disease (COPD), and validated diabetes (ADA definition), CHF, angina, or MI. A Venn diagram illustrates the overlap of disability and comorbidity with frailty at baseline; percentages are based on all frail subjects.

Kaplan-Meier estimates were used to determine the percentage of subjects free of an event (e.g., hospitalization, fall, death) at 3 years after study entry and 7 years after study entry. Cohort 1 had a longer follow-up period (median 79 months, range 73–84) than Cohort 2 (median 38 months, range 37–43), so estimates at 7 years were based only on Cohort 1. The *p* values reported for the difference in survival curves between frailty phenotype groups were based on the logrank test.

Predictive Validity

Cox proportional hazard models were used to assess the independent contribution of baseline frailty status to incidence of major geriatric outcomes over 3 and 7 years, including: (a) incident falls (evaluated every 6 months); (b) worsening mobility or ADL function (evaluated annually); (c) incident hospitalization: from time of study entry to discharge date for the first confirmed overnight hospitalization; (d) death. Indicators for frail (3 or more frailty components) and at-risk (1 or 2 frailty components) were created, with the nonfrail group (0 frailty components) serving as the reference group. Unadjusted instantaneous hazard ratios (referred to as relative risk [RR] estimates) were estimated for each outcome. Covariate-adjusted Cox models were also fit, utilizing baseline covariates shown to be predictive of mortality in this cohort (42): age, gender, income, smoking status, diuretic use without a history of hypertension or congestive heart failure, fasting glucose, albumin, creatinine; objective measures of subclinical disease, including: brachial and tibial systolic blood pressure, abnormal left ventricular ejection fraction (LVEF; by echocardiography), major ECG abnormality, forced vital capacity (FVC), and maximal stenosis of the internal carotid artery (by ultrasound), congestive heart failure (validated history), digit symbol substitution score, depressive symptoms (CES–D score excluding the two questions utilized in the frailty definition), and difficulty in ≥1 IADL. Weight and physical activity were also found to be independent predictors of survival, but they were not included in the covariate-adjusted models, as they are components of the overall frailty score. Covariates selected were based on analyses performed on the first cohort; external validation using the second cohort showed good agreement. However, FVC and LVEF abnormality were not available at study entry for the second cohort, so they were not included in the covariate-adjusted

frailty models. Adding these two covariates to models based only on the first cohort did not alter the frailty results.

Finally, a logistic model was used to evaluate whether the intermediate frailty group (1,2 criteria) was at higher risk of incident frailty than those who were not frail (0 criteria) at study entry. Only subjects who were alive, eligible (satisfied exclusion criteria), and evaluable (at least 3 nonmissing frailty components) at the subsequent visit were included in the analysis. The covariate-adjusted logistic model includes the same covariates described for the proportional hazards models (above).

RESULTS

The 5,317 people evaluated were 65 to 101 years of age; 58% were female and 15% African American, with a broad range of socioeconomic, functional, and health status (Table 2, column A). Frailty markers present at baseline are shown in Table 3. Overall, 7% of the cohort had ≥3 frailty criteria, and 46% had none. Six percent of the initial cohort and 12% of the African American cohort were frail. Prevalence of frailty increased with each 5-year age group, and was up to twofold higher for women than men by age group (Table 4). The exception was those 90 years and older, where prevalence was lower in both subgroups of women and men in the minority cohort.

Three-year incidence of frailty was 7% for years 0–3 and was 7%, as well, for 4-year incidence of frailty from years 3–7, for the first cohort. The second cohort had a 4-year incidence rate of 11%. These incidence rates are likely underestimates, as they do not include loss to mortality or those who were not evaluable for frailty at follow-up due to missing data.

Those who were frail were older, more likely to be female and African American, and had less education, lower income, poorer health, and higher rates of comorbid chronic diseases and of disability than those who were not frail or were in the intermediate group (*p* <.05 for each comparison; Table 2). They also had significantly higher rates of cardiovascular and pulmonary diseases, arthritis, and diabetes. There was no significant difference in cancer, possibly a result of recruitment criteria that excluded those under active treatment for cancer. The intermediate frailty group was intermediate between those who were frail and those not frail in all of these measures (*p* for trend <.05 in each case except cancer). Notably, 7% of those who were frail had none of these chronic diseases, and 25% had just one; they were: 56% arthritis, 25% hypertension, 8% diabetes, and less than 5% each of angina, congestive heart failure, cancer, and pulmonary disease. Both lower cognition and greater depressive symptomatology were associated with frailty (despite exclusion of those being treated with antidepressants or with MMSE <18).

Further analyses explored the association between the frailty phenotype and self-reported physical disability. In Table 2, 72% and 60% of those who were frail reported difficulty in mobility tasks or IADLs, respectively, while only 27% of those who were frail had difficulty in ADLs. There was a step-wise increase in disability with increasing frailty status (*p* for trend <.001). Separately, among those with disability in ADLs, often considered synonymous with

Table 2. Baseline Association of Demographic and Health Characteristics With Frailty, in Percentages: the Cardiovascular Health Study

Factor	A Total (5317)	B Not Frail ($n = 2469$)	C Intermediate ($n = 2480$)	D Frail ($n = 368$)	E Trend p Value	F Age Adjusted Trend p Value
Age						
65–74	67.3%	76.1%	62.9%	38.0%	<.001	—
75–84	29.1	22.6	32.7	48.9		
85+	3.6	1.3	4.5	13.0		
Sex						
Female	57.9	56.4	57.7	68.5	<.001	<.001
Male	42.1	43.6	42.3	31.5		
Race						
Caucasian	84.5	89.7	81.1	71.7	<.001	<.001
African American	14.8	9.6	18.1	27.5		
Other	0.7	0.7	0.8	0.8		
Education						
≤9th grade	18.2	12.7	22.2	28.3	<.001	<.001
10–11th grade	9.9	8.8	10.9	10.6		
HS grad/GED	28.3	29.5	27.8	24.8		
>12 years	43.5	49.0	39.2	36.2		
Income						
<12K	25.6	18.7	29.9	44.3	<.001	<.001
12–<24K	35.4	34.8	36.3	32.9		
24–50K	25.7	30.0	23.3	13.4		
>50K	13.2	16.5	10.6	9.3		
Self-Assessed Health						
Excellent	14.3	19.5	10.7	3.5	<.001	<.001
Very good	25.2	31.1	21.3	11.4		
Good	37.1	36.1	39.4	28.3		
Fair	20.0	12.6	24.4	40.3		
Poor	3.4	0.7	4.1	16.4		
Live Alone	14.1	10.9	15.5	27.5	<.001	<.001
Prevalent Disease at Baseline						
MI	9.1	7.3	10.3	13.3	<.001	<.001
Angina	18.5	14.5	21.0	28.8	<.001	<.001
CHF	4.0	2.0	4.5	13.6	<.001	<.001
PVD	2.2	1.5	2.7	3.8	<.001	.002
Arthritis	51.2	44.8	54.7	70.6	<.001	<.001
Cancer	14.6	14.2	14.7	15.8	.42	1.00
Diabetes	15.8	12.1	18.2	25.0	<.001	<.001
Hypertension	42.9	38.8	45.9	50.8	<.001	<.001
COPD*	7.8	5.8	8.8	14.1	<.001	<.001
Number of Chronic Diseases						
0	18.5	23.2	15.4	7.3	<.001	<.001
1	33.3	36.8	31.0	24.7		
2	25.6	24.0	27.0	26.9		
3–4	19.8	14.5	23.2	32.9		
≥5	2.9	1.5	3.5	8.2		
Self-Reported Disability						
≥1 mobility task	28.7	16.0	35.2	71.7	<.001	<.001
≥1 IADL task	23.8	13.5	28.8	59.7	<.001	<.001
≥1 ADL task	6.8	2.2	8.5	27.4	<.001	<.001
Any Disability	36.8	23.5	44.1	76.4	<.001	<.001
Cognitive Function						
(Mini-Mental score range: 0–30)						
18–23	6.3	3.0	8.3	15.1	<.001	<.001
>23	93.7	97.0	91.7	84.9		
Depressive Symptoms						
CES–D ≥10	9.9	2.6	14.0	31.0	<.001	<.001

Note: MI = myocardial infarction; CHF = congestive heart failure; PVD = peripheral vascular disease; IADL = instrumental activity of daily living; ADL = activity of daily living; CES–D = Center for Epidemiological Studies–Depression scale.
*Chronic emphysema, bronchitis, or asthma confirmed by doctor.

Table 3. Prevalence of Frailty Phenotype Components in Percentages: Cardiovascular Health Study

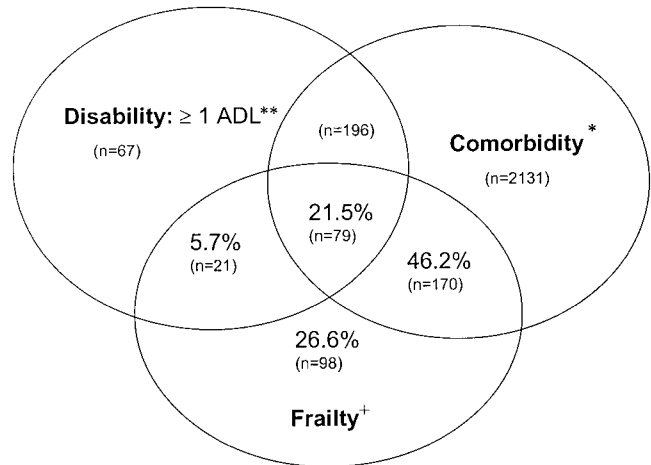|	Total (N = 5317)	Men (n = 3077)	Women (n = 2240)
Frequency of Frailty Components	%	%	%
Exhaustion	17	19	12
Weight loss	6	6	6
Low activity (kcals)	22	20	20
Slow walk (s)	20	20	20
Grip strength (kg)	20	20	20
Number of Frailty Components Present			
0	46	45	48
1	32	32	33
2	15	15	14
3	6	6	6
4	1	2	1
5	0.2	0.1	0.2

Figure 3. Venn diagram displaying extent of overlap of frailty with ADL disability and comorbidity ($\geq$2 diseases). Total represented: 2,762 subjects who had comorbidity and/or disability and/or frailty. *n* of each subgroup indicated in parentheses. + Frail: overall *n* = 368 frail subjects (both cohorts). *Comorbidity: overall *n* = 2,576 with 2 or more out of the following 9 diseases: myocardial infarction, angina, congestive heart failure, claudication, arthritis, cancer, diabetes, hypertension, COPD. Of these, 249 were also frail. **Disabled: overall *n* = 363 with an ADL disability; of these, 100 were frail.

frailty, only 28% were in the frail group (Table 5). Figure 3 displays the overlap between these characteristics, as well as with the presence of two or more comorbid diseases. There was only modest concordance between frailty and disability. Of those who were frail, 46% had comorbid disease, 6% had ADL disability, 22% had both comorbid disease and ADL disability, and 27% had neither ADL disability nor comorbidity.

Frailty is considered to be a high-risk state predictive of a range of adverse health outcomes (9,10,14–16). The incidence of each of these outcomes is displayed (Table 6) by frailty status and length of follow-up. In those who met the criteria for frailty at baseline, mortality was sixfold higher (18%) than that for the nonfrail (3%) for 3-year cumulative survival, and was over threefold higher (43% compared to 12%), compared to the nonfrail group, for 7-year survival. Figure 4 provides the unadjusted survival curves for each frailty group, over the 7-year interval. After 84 months, 43% of those who were frail had died, compared to 23% of those who were intermediate and 12% of those who were robust at baseline.

To assess whether three criteria predicted mortality significantly better than two, Kaplan-Meier survival curves (similar to Figure 4) were created, where each of the 10 possible combinations of three phenotype criteria were consid-

ered as the definition of frailty. The predictive power of each combination of three criteria being present was contrasted with only two of these being present. In each of 10 survival analyses, each group with three components positive for frailty had significantly worse survival than those with two components, or the "no frailty" groups ($p < .05$; data not shown). Based on these models, it was concluded that criteria that were based on three, rather than two, components, provided improved predictive power in identifying mortality risk.

To assess the independent predictive validity of this frailty phenotype, we evaluated its association, prospectively, with five important adverse health outcomes ascertained in prospective follow-up, using Cox proportional hazards models. As seen in Table 7, the RR ratio estimate, or hazard ratio, for the outcomes of interest over 3 and 7 years of follow-up is displayed for those who were in the intermediate and frail groups at baseline, each relative to

Table 4. Prevalence of Frailty at Baseline: Cardiovascular Health Study

			Original Cohort (1989–1990)		Minority Cohort (1992–1993)	
Age Group	(n)	Overall % Frail	Women (n = 2710) % Frail	Men (n = 2025) % Frail	Women (n = 367) % Frail	Men (n = 215) % Frail
65–70	(2308)	3.2	3.0	1.6	11.0	5.8
71–74	(1271)	5.3	6.7	2.9	9.7	3.1
75–79	(1057)	9.5	11.5	5.5	13.8	17.9
80–84	(490)	16.3	16.3	14.2	30.6	15.4
85–89	(152)	25.7	31.3	15.5	60.0	25.0
90+	(39)	23.1	12.5	36.8	0.0	0.0
Total	(5317)	6.9	7.3	4.9	14.4	7.4

Table 5. Distribution of Frailty Status Among Those With a Disability at Baseline

	CHS Baseline: Both Cohorts		
	Not Frail (n = 2469) %	Intermediate (n = 2480) %	Frail (n = 368) %
Distribution in population	46.4	46.6	6.9
Difficulty			
$\geq$1 Mobility task	25.9	57.1	17.0
$\geq$1 IADL task	26.4	56.3	17.2
$\geq$1 ADL task	14.6	57.9	27.5

Note: CHS = Cardiovascular Health Study; ADL = activities of daily living; IADL = instrumental activities of daily living.

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Table 6. Incidence of Adverse Outcomes Associated With Frailty: Kaplan-Meier Estimates at 3 Years and 7 Years* After Study Entry for Both of the Cohorts† (N = 5317)

Frailty Status at Baseline	(n)	Died		First Hospitalization		First Fall		Worsening ADL Disability		Worsening Mobility Disability	
		3 yr %	7 yr %	3 yr %	7 yr %	3 yr %	7 yr %	3 yr %	7 yr %	3 yr %	7 yr %
Not Frail	(2469)	3	12	33	79	15	27	8	23	23	41
Intermediate	(2480)	7	23	43	83	19	33	20	41	40	58
Frail	(368)	18	43	59	96	28	41	39	63	51	71
p‡		<.0001		<.0001		<.0001		<.0001		<.0001	

*7-year estimates are only available for the first cohort.
†Only those evaluable for frailty are included.
‡p value is based on the 2 degree of freedom log rank test using all available follow-up.

those who were nonfrail. Bivariate (unadjusted) associations were significant ($p < .05$) for the predictive association of frailty and intermediate frailty status with incident falls, worsened mobility or ADL disability, incident hospitalization, and death over 3 or 7 years, with hazard ratios ranging from 1.82–4.46 and 1.28–2.10 for the frail and intermediate groups, respectively. After adjustment for covariates (42), the frailty phenotype remained an independent predictor of all adverse outcomes at both 3 and 7 years, with 7-year hazard ratios ranging from 1.23–1.79 ($p < .05$ for all, except falls, where $p = .06$). The intermediate group also significantly ($p < .05$) predicted all outcomes after adjustment, but with lower strengths of association. Results for both 3 and 7 years follow-up were consistent. The proportional hazards assumption was found reasonable for each model.

Finally, we evaluated whether being in the intermediate group identified increased risk of frailty. Adjusting for covariates, those who were intermediate at baseline were at more than twice the risk of becoming frail over 3 years (or over 4 years for cohort 2), relative to those subjects with no frailty characteristics at baseline (odds ratio [OR] = 2.63, 95% confidence interval [CI] = 1.94, 3.56) (Table 8). The

results were nearly identical in separate analyses of just the first cohort (which had a 1-year shorter initial follow-up interval than the second cohort). Of incident frailty cases, 88% (254/290) came from the first cohort.

DISCUSSION

This work proposes a standardized phenotype of frailty in older adults and demonstrates predictive validity for the adverse outcomes that geriatricians identify frail older adults as being at risk for: falls, hospitalizations, disability, and death. Even after adjustment for measures of socioeconomic status, health status, subclinical and clinical disease, depressive symptoms, and disability status at baseline, frailty remained an independent predictor of risk of these adverse outcomes. The intermediate group with one or two frailty characteristics was at elevated, but intermediate, risk for these outcomes and at risk for subsequent frailty.

This study provides insight into frailty and its outcomes in a population-based sample of older adults who were neither institutionalized nor end-stage, characterizing both early presentation, correlates, and long-term outcomes. A standardized phenotype provides a basis for future comparison with other populations. The exact frequencies identified
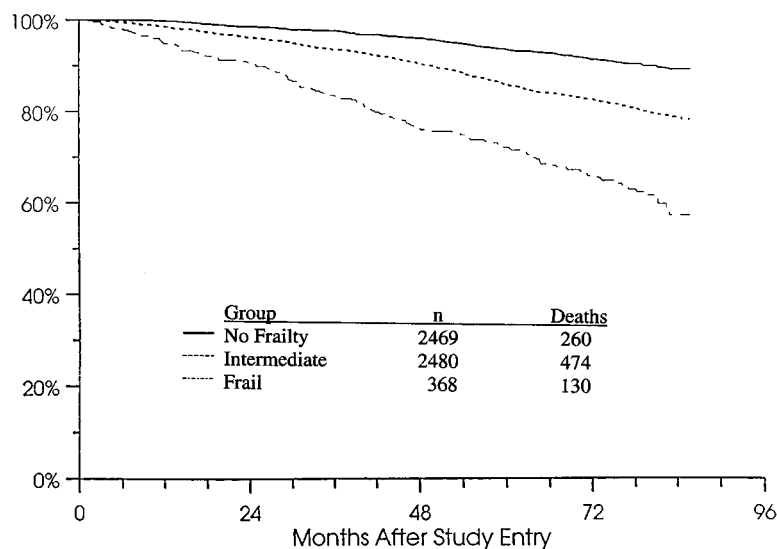

Figure 4. Survival curve estimates (unadjusted) over 72 months of follow-up by frailty status at baseline: Frail (3 or more criteria present); Intermediate (1 or 2 criteria present); Not frail (0 criteria present). (Data are from both cohorts.)

Table 7. Baseline Frailty Status Predicting Falls, Disability, Hospitalizations, and Death in Both Cohorts of CHS With a Maximum Follow-up Time of 7 Years for the First Cohort and 4 Years for the Minority Cohort

	No Frailty (reference)	Hazard Ratios Estimated Over 3 Years		Hazard Ratios Estimated Over 7 Years	
		Intermediate	Frail	Intermediate	Frail
Incident Fall					
Unadjusted	HR* = 1.0	HR = 1.36 CI = (1.18,1.56) $p < .0001$	HR = 2.06 CI = (1.64,2.59) $p < .0001$	HR = 1.28 CI = (1.15,1.43) $p < .0001$	HR = 1.82 CI = (1.50,2.21) $p < .0001$
Covariate Adjusted	HR = 1.0	HR = 1.16 CI = (1.00,1.34) $p = .056$	HR = 1.29 CI = (1.00,1.68) $p = .054$	HR = 1.12 CI = (1.00,1.26) $p = .045$	HR = 1.23 CI = (0.99,1.54) $p = .064$
Worsening Mobility†					
Unadjusted	HR = 1	HR = 1.94 CI = (1.75,2.15) $p < .0001$	HR = 2.68 CI = (2.26,3.18) $p < .0001$	HR = 1.72 CI = (1.58,1.87) $p < .0001$	HR = 2.45 CI = (2.11,2.85) $p < .0001$
Covariate Adjusted	HR = 1	HR = 1.58 CI = (1.41,1.76) $p < .0001$	HR = 1.50 CI = (1.23,1.82) $p < .0001$	HR = 1.41 CI = (1.29,1.54) $p < .0001$	HR = 1.36 CI = (1.15,1.62) $p = .0003$
Worsening ADL‡ Disability					
Unadjusted	HR = 1.0	HR = 2.54 CI = (2.16,3.00) $p < .0001$	HR = 5.61 CI = (4.50,7.00) $p < .0001$	HR = 2.14 CI = (1.92,2.39) $p < .0001$	HR = 4.22 CI = (3.55,5.01) $p < .0001$
Covariate Adjusted	HR = 1.0	HR = 1.67 CI = (1.41,1.99) $p < .0001$	HR = 1.98 CI = (1.54,2.55) $p < .0001$	HR = 1.55 CI = (1.38,1.75) $p < .0001$	HR = 1.79 CI = (1.47,2.17) $p < .0001$
First Hospitalization					
Unadjusted	HR = 1.0	HR = 1.38 CI = (1.26,1.51) $p < .0001$	HR = 2.25 CI = (1.94,2.62) $p < .0001$	HR = 1.34 CI = (1.25,1.43) $p < .0001$	HR = 2.14 CI = (1.89,2.42) $p < .0001$
Covariate Adjusted	HR = 1.0	HR = 1.13 CI = (1.03,1.25) $p = .014$	HR = 1.29 CI = (1.09,1.54) $p = .004$	HR = 1.11 CI = (1.03,1.19) $p = .005$	HR = 1.27 CI = (1.11,1.46) $p = .0008$
Death					
Unadjusted	HR = 1.0	HR = 2.42 CI = (1.84,3.19) $p < .0001$	HR = 6.47 CI = (4.63,9.03) $p < .0001$	HR = 2.01 CI = (1.73,2.33) $p < .0001$	HR = 4.46 CI = (3.61,5.51) $p < .0001$
Covariate Adjusted	HR = 1	HR = 1.49 CI = (1.11,1.99) $p < .0001$	HR = 2.24 CI = (1.51,3.33) $p = .0001$	HR = 1.32 CI = (1.13,1.55) $p = .0006$	HR = 1.63 CI = (1.27,2.08) $p = .0001$

Note: Covariate adjustment includes: age, gender, indicator for minority cohort, income, smoking status, brachial and tibial blood pressure, fasting glucose, albumin, creatinine, carotid stenosis, history of CHF, cognitive function, major ECG abnormality, use of diuretics, problem with IADLs, self-report health measure, CES–D modified depression measure.

*HR = hazard ratio, the ratio of risk of frailty group (either frail or intermediate) relative to the nonfrail group with regards to the event of interest (e.g., first fall, death).

†Defined as an increase in 1 unit of mobility score relative to baseline.

‡Defined as an increase in 1 unit of ADL score relative to baseline.

are a function of the definitions of each criterion selected, and would (obviously) change if definition shifted. However, the approach selected indicates that frailty is not rare in a community-dwelling population, and is a meaningful predictor when people are relatively functional.

Prior to this, frailty has primarily been evaluated in hospitalized or nursing home populations (3,4,7,8,24,46,47). Such studies, due to the selection process by which their participants arrive in these settings, are likely to characterize persons with late-stage frailty, after the occurrence of related adverse outcomes, and having highly selected correlates. One recent study in a community-dwelling population in The Netherlands used a subset of the phenotype studied here, inactivity and weight loss over 5 years of >4 kg (48). They found a similar prevalence of 6% (26/440), and similar unadjusted associations with mortality and disability, providing evidence for consistency of findings across popu-

lation. The phenotype proposed here offers greater predictive validity, compared with using only two criteria.

The characterization of frailty offered here also provides new insights into potential etiologies. Frailty in this study was strongly associated with a number of major chronic diseases, including cardiovascular and pulmonary diseases and diabetes, suggestive of etiologic associations with these single diseases. However, there was a greater likelihood of frailty when two or more diseases were present than with any one. Conversely, the observation that a subset of those who were frail reported none of the diseases assessed supports the hypothesis that there may be two different pathways by which individuals become frail: one, a result of physiologic changes of aging that are not disease-based (e.g., aging-related sarcopenia [16] or anorexia of aging [30,31,49,50]), and the other a final common pathway of severe disease or comorbidity, as suggested by the higher

Table 8. Association of "Intermediate" Status at Baseline With Frailty Status at Follow-up*

	Baseline Status	
Incident Frailty	Intermediate vs No Frailty Using Both Cohorts (*n* = 3882)	Intermediate vs No Frailty Only Cohort 1 (*n* = 3546)
Unadjusted	OR = 4.51 CI = (3.39,6.00) *p* < .0001	OR = 4.29 CI = (3.19,5.78) *p* < .0001
Covariate Adjusted†	OR = 2.63 CI = (1.94,3.56) *p* < .0001	OR = 2.42 CI = (1.76,3.32) *p* < .0001

Note: OR = odds ratio of intermediate frailty group (at baseline) becoming frail, relative to the not frail group; CI = confidence interval.

*Logistic regression predicting frailty, assessing subjects from both cohorts who were alive and evaluable at follow-up. Follow-up was after 3 years for Cohort 1 and 4 years for Cohort 2.

†Adjusting for covariates (described in Methods and bottom of Table 7).

rates of poor health status and greater extent of subclinical physiologic changes in the frail group. Individual or comorbid diseases could potentially initiate frailty via any point on the hypothesized cycle (Figure 1). These hypotheses remain to be confirmed.

The likelihood of frailty was also higher among women and/or those with lower socioeconomic status. Female gender could confer intrinsic risk of frailty due to women starting with lower lean mass and strength than age-matched men; thereafter, women losing lean body mass with aging might be more likely to cross a threshold necessary for frailty. Women could also have greater vulnerability to frailty via extrinsic effects on sarcopenia (e.g., because older women have a greater likelihood of inadequate nutritional intake, compared to men, due to living alone more often [19]).

This study offers support for geriatricians' contention that frailty is a physiologic syndrome (9–16), and it delineates frailty from comorbidity and disability—characteristics that are often treated as synonymous with frailty. Our findings support the hypothesis that frailty causes disability, independent of clinical and subclinical diseases (Table 7). The syndrome of frailty may be a physiologic precursor and etiologic factor in disability, due to its central features of weakness, decreased endurance, and slowed performance. The aspects of function likely affected by frailty are those dependent on energetics and speed of performance (e.g., mobility). It is notable that only 27% of those who were disabled in ADL tasks were also frail (Table 2), suggesting that frailty begins by affecting mobility tasks before causing difficulty in endstage function such as ADLs, or that there are additional pathways by which older adults can become disabled. For example, disability due to arthritis of the hands might very specifically affect ability to grasp or eat, without having any relationship to frailty. Thus, frailty does not appear to be synonymous with either disability or comorbidity. Given the findings here, the terms appear to apply to distinct, but related, entities and should not be used interchangeably.

The definition of frailty offered and validated here provides a standardized, physiologically based definition applicable to the spectrum of frailty presentations seen in community-dwelling older adults. The clear criteria (see Appendix) are relatively easy and inexpensive to apply, and offer a basis for standardized screening for frailty and risk of frailty in older adults. They can, potentially, be used to establish clinical risk of adverse outcomes. They also provide a phenotype applicable to future research on etiology and interventions to prevent or retard the progression of frailty.

The major limitation of this study is that the measures utilized to operationalize the phenotype of frailty were limited to those that were fortuitously collected 10 years ago for other purposes in this longitudinal study. In addition, weight loss prior to baseline was necessarily drawn from baseline self-report. On the other hand, few studies can offer the length of follow-up or the breadth of health and demographic characteristics available in this cohort for use in understanding frailty. A number of questions remain to be evaluated, including the role of frailty in health outcomes for different subgroups (e.g, African Americans and Caucasians). In this same issue, we separately examine the association of frailty with cardiovascular diseases (51).

Overall, these findings provide support for the hypotheses of a physiologic cycle of frailty (14) that serves as the basis for the phenotype considered here (Figure 1). This incorporates prior research demonstrating pairwise associations between each two components in the cycle (18–31). This hypothesized cycle of frailty, representing an adverse, potentially downward spiral of energetics, is consistent with the clinical markers of frailty identified by geriatricians and gerontologists (1–16) and our findings and others' proposals (46,52,53) of an intermediate and later stage of frailty in community-dwelling older adults. A more advanced stage may be observed in more debilitated populations, such as in nursing homes. This phenotype may not, however, fully explain the more subtle biologic underpinnings of decreased reserves and ability to maintain homeostasis (11–13), which may be latent prior to an insult, but be a basis for vulnerability to stressors (10,11,14). Further understanding of the basis for risk associated with frailty may ultimately be found in the alterations in multisystem function, complexity, and reserve with aging (12). It is possible that early frailty, or progression from the intermediate stage to frailty, might have one set of etiologic factors, whereas progression of the frailty observed here to a more end-stage point might be associated with others, such as declines in weight, albumin, or cholesterol as consequences of malnutrition or catabolism. This end stage has been reported to be irreversible and presage death (19,24,52,53).

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Appendix

Criteria Used to Define Frailty

- **Weight loss:** "In the last year, have you lost more than 10 pounds unintentionally (i.e., not due to dieting or exercise)?" If yes, then frail for weight loss criterion. At follow-up, weight loss was calculated as: (Weight in previous year – current measured weight)/(weight in previous year) = K. If K $\geq$ 0.05 and the subject does not report that he/she was trying to lose weight (i.e., unintentional weight loss of at least 5% of previous year's body weight), then frail for weight loss = Yes.
- **Exhaustion:** Using the CES–D Depression Scale, the following two statements are read. (a) I felt that everything I did was an effort; (b) I could not get going. The question is asked "How often in the last week did you feel this way?" 0 = rarely or none of the time (<1 day), 1 = some or a little of the time (1–2 days), 2 = a moderate amount of the time (3–4 days), or 3 = most of the time. Subjects answering "2" or "3" to either of these questions are categorized as frail by the exhaustion criterion.
- **Physical Activity:** Based on the short version of the Minnesota Leisure Time Activity questionnaire, asking about walking, chores (moderately strenuous), mowing the lawn, raking, gardening, hiking, jogging, biking, exercise cycling, dancing, aerobics, bowling, golf, singles tennis, doubles tennis, racquetball, calisthenics, swimming. Kcals per week expended are calculated using standardized algorithm. This variable is stratified by gender.
  Men: Those with Kcals of physical activity per week <383 are frail.
  Women: Those with Kcals per week <270 are frail.

- **Walk Time**, stratified by gender and height (gender-specific cutoff a medium height).

Men	*Cutoff for Time to Walk 15 feet criterion for frailty*
Height $\leq$ 173 cm	$\geq$7 seconds
Height > 173 cm	$\geq$6 seconds
Women	
Height $\leq$ 159 cm	$\geq$7 seconds
Height > 159 cm	$\geq$6 seconds

- **Grip Strength**, stratified by gender and body mass index (BMI) quartiles:

Men	*Cutoff for grip strength (Kg) criterion for frailty*
BMI $\leq$ 24	$\leq$29
BMI 24.1–26	$\leq$30
BMI 26.1–28	$\leq$30
BMI > 28	$\leq$32
Women	
BMI $\leq$ 23	$\leq$17
BMI 23.1–26	$\leq$17.3
BMI 26.1–29	$\leq$18
BMI > 29	$\leq$21