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Frailty: Emergence and Consequences in Women Aged 65 and Older in the Women's Health Initiative Observational Study

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OBJECTIVES: To define frailty using simple indicators; to identify risk factors for frailty as targets for prevention; and to investigate the predictive validity of this frailty classification for death, hospitalization, hip fracture, and activity of daily living (ADL) disability.

DESIGN: Prospective study, the Women's Health Initiative Observational Study.

SETTING: Forty U.S. clinical centers.

PARTICIPANTS: Forty thousand six hundred fifty-seven women aged 65 to 79 at baseline.

MEASUREMENTS: Components of frailty included self-reported muscle weakness/impaired walking, exhaustion, low physical activity, and unintended weight loss between baseline and 3 years of follow-up. Death, hip fractures, ADL disability, and hospitalizations were ascertained during an average of 5.9 years of follow-up.

RESULTS: Baseline frailty was classified in 16.3% of participants, and incident frailty at 3-years was 14.8%. Older age, chronic conditions, smoking, and depressive symptom score were positively associated with incident frailty, whereas income, moderate alcohol use, living alone, and self-reported health were inversely associated. Being underweight, overweight, or obese all carried significantly higher risk of frailty than normal weight. Baseline frailty independently predicted risk of death (hazard ratio (HR) = 1.71, 95% confidence interval (CI) = 1.48–1.97), hip fracture (HR = 1.57, 95% CI = 1.11–2.20), ADL disability (odds ratio (OR) = 3.15, 95% CI = 2.47–4.02), and hospitalizations (OR = 1.95, 95% CI = 1.72–2.22) after adjustment for demographic characteristics, health behaviors, disability, and comorbid conditions.

CONCLUSION: These results support the robustness of the concept of frailty as a geriatric syndrome that predicts several poor outcomes in older women. Underweight, obesity, smoking, and depressive symptoms are strongly associated with the development of frailty and represent important targets for prevention. **J Am Geriatr Soc 53:1321–1330, 2005.**

Key words: frailty; activities of daily living; ethnicity; disability; postmenopausal women; Women's Health Initiative

For decades, clinicians have described older people who exhibit problems with weakness or balance as "frail," but only recently have investigators begun to define frailty clearly and operationalize it as a clinical syndrome that is causally related to, but distinct from, disability and comorbidity.[1,2] Such conceptual and operational clarification is a necessary foundation for research in this area. A cluster of indicators of frailty has been proposed that would identify study participants and patients who were at future risk of a variety of health problems.[1] These indicators operationalized the characteristics of frailty, which included shrinking/sarcopenia, weakness, poor endurance, slowness, and low activity levels. These criteria for frailty were predictive of disability in the Cardiovascular Health Study (CHS), as measured using measures of mobility and instrumental activities of daily living.[1] In addition, early reports have shown that those who met the criteria for frailty were more likely than those who had low or intermediate levels of the indicators to become hospitalized, fall, experience deterioration of functioning, and die over 3 to 7 years of follow-up.[1] Replication and extension of these findings in other populations and ethnic groups is an important step in verifying the utility of this frailty construct. In addition, some of the criteria, such as grip strength, may not be readily accessible to investigators in residential settings in which older women may live the last years of their lives.

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The ability to identify a set of readily measured indicators of frailty can serve as a foundation for further research about the mechanisms of frailty and interventions to modify it.[3] In addition, identification of a set of simply measured indicators could enable clinicians to identify those at risk in community settings and assisted living environments and to target appropriate interventions to mitigate the consequences of frailty.[4]

The purposes of this article are to:

1. define frailty in the Women's Health Initiative Observational Study (WHI-OS) using indicators from widely available instruments that operationalize the characteristics of frailty identified;[1]
2. examine associations between demographic, medical history, and behavioral risk factors, including age, income, education, smoking, alcohol use, body mass index (BMI), self-assessed health, and comorbidity, and baseline and incident frailty after 3 years of follow-up; and
3. determine associations between this frailty classification and future risk of death, hospitalizations, hip fractures, and activity of daily living (ADL) disability.

METHODS

Study Design

The WHI-OS is a prospective study of 93,676 women aged 50 to 79. This article is based on 40,657 women aged 65 to 79 at baseline who did not report a diagnosis of Parkinson's disease and were not using medications for treatment of Parkinson's disease or depression.

Women were recruited for the WHI from 1993 to 1998 from 40 clinical centers in the United States, resulting in a diverse population of women including 18% of participants from underrepresented racial/ethnic groups. Details of the design, recruitment, data collection methods, and extensive tabulations of baseline data have been published.[5–7] Women in the WHI-OS were eligible if they were postmenopausal, were unlikely to relocate or die within 3 years, and were not enrolled in another clinical trial.

Measurement of Frailty

Frailty has been operationally defined as the presence of three or more of the following criteria: muscle weakness, slow walking speed, exhaustion, low physical activity, and unintentional weight loss (Table 1). Although the WHI protocol was developed a decade before this phenotype was defined,[1] each of these components was measured, by self-report or by examination, in the WHI-OS, as described below.

Muscle Weakness/Slow Walking Speed

Physical performance measures (e.g., timed walk, grip strength) were not obtained in the WHI-OS, but a well-validated measure of self-reported physical function, the Rand-36 physical function scale, was administered to all participants.[8] The Physical Function Scale includes 10 items measuring whether health now limits physical function in moderate/vigorous activity (2 items); strength to lift, carry, stoop, bend, stair climb (4 items); ability to walk various

Table 1. Definitions of Frailty in the Cardiovascular Health Study (CHS)[1] and the Women's Health Initiative Observational Study (WHI-OS)

Components of Frailty	CHS[1]	WHI-OS
Slowness/weakness	Timed 15-foot walk (slowest 20%); grip strength (lowest 20%)	Rand-36 Physical Function scale (score <75)
Poor endurance/exhaustion	Two items from the Center for Epidemiologic Studies Depression Scale: *Everything I do is an effort.* *I cannot get going.* Answers >3–4 days/wk to either question were scored positive for frailty.	Rand-36 Vitality Scale (score <55) Over past 4 weeks: *Did you feel worn out?* *Did you feel tired?* *Did you have a lot of energy?* *Did you feel full of pep?*
Physical activity	Modified Minnesota Leisure Time activities: Self-report of whether a person performed any of 18 activities in the prior week. Kcal of energy expended in a week on leisure time activity was calculated. Those in the bottom quintile were deemed positive for frailty. (Men exerting <383 kcal; women exerting <270 kcal/week were scored positive for frailty.)	Detailed physical activity questionnaire assessing frequency and duration of walking and mild, moderate, and strenuous activities. Kcal of weekly energy expenditure was calculated (metabolic equivalent task hours score = kcal/wk $\times$ kg), and those in the lowest quartile were scored positive for frailty.
Unintentional weight loss	Self-reported weight loss >10 pounds in previous year at baseline and measured weight loss >5% of body weight in prior year.	No measure is available at baseline. At follow-up, measured weight loss at Year 3 clinic visit >5% and "yes" to question, "In the past two years, did you lose five or more pounds not on purpose at any time?"

distances without difficulty (3 items); and self-care (1 item). The scale is scored from 0 to 100, with higher scores indicating better physical function. In the WHI clinical trial (CT), in which timed walk and grip strength measures were available on a 25% subsample of participants aged 65 and older (n = 7,897), the correlation between Rand-36 physical function scale score and walking speed was − 0.34, and the correlation with grip strength was 0.14 (unpublished data). When both measures were dichotomized at the 25th percentile and cross-tabulated, the odds ratio for walking speed was 4.1, indicating that women with slow walking speed were four times as likely to be classified as having low physical function. The corresponding lowest quartile odds ratio for grip strength was 1.7. Thus, the Rand-36 physical function scale is a reasonable surrogate for upper and lower extremity muscle weakness.

Exhaustion

The Rand-36 vitality scale (range 0–100) includes four items pertaining to the previous 4 weeks: "Did you feel worn out?" "Did you feel tired?" "Did you have a lot of energy?" and "Did you feel full of pep?" This scale was used as an indicator of exhaustion.

Low Physical Activity

Recreational physical activity was assessed using items on the frequency and duration of four speeds of walking and activities in the prior week, classified as mild, moderate (not exhausting), or strenuous (you work up a sweat and your heart beats fast).[5,9] Kcal of energy expended in a week on leisure time activity was calculated (metabolic equivalent task hours score = kcal/wk × kg).[10]

Unintentional Weight Loss

Weight was measured at each clinic visit (baseline and Year 3 in WHI-OS) to the nearest 0.1 kg on a balance beam scale with the participant dressed in indoor clothing without shoes. At baseline, no measure of unintended weight loss was available. During follow-up, a self-reported item on whether recent weight loss was intentional was available in the WHI-OS. Thus, for the purpose of defining incident frailty during follow-up, a variable was created indicating unintentional weight loss for WHI-OS women of more than 5% of body weight in the previous 2 years. These measures are quite similar to those used in the CHS.[1]

Classification of Frailty

For each measure described above (except unintentional weight loss), a frailty component was classified as present if the participant had a score in the lowest quartile of the distribution for that component. To align the scoring with Fried's frailty measure, poor physical function was scored as 2 points because this scale measures the muscle strength and walking ability components. The number of frailty components that were present was summed, yielding a range of 0 to 5. A frailty cutpoint of 3 or more was used, as in previous studies.[1,11]

Other Variables

Data on demographic, medical history, and health behavior characteristics were obtained using self-report at baseline. Depressive symptoms were assessed using a six-item short form[12,13] of the Center for Epidemiologic Studies Depression Scale.[14] ADL disability was measured using four items asking about the amount of help (no help, some help, totally dependent) needed to eat, dress and undress, get in and out of bed, and take a bath or shower. Disability was defined as needing assistance with one or more of these ADLs.

Outcomes Ascertainment

Women in the WHI-OS completed an annual medical history update (in clinic, by mail, or via telephone interview) for reporting significant health events that occurred in the prior year. Participants indicated the occurrence of any overnight hospitalization and responded to specific queries regarding occurrence of myocardial infarction, coronary angioplasty or bypass surgery, acute chest pain, congestive heart failure, fracture, or cancer. Medical records were sought for primary and secondary outcomes in WHI (cardiovascular events, hip fracture, cancer, death) and used for adjudication, first by a local physician adjudicator and then by a panel of central adjudicators. Outcomes information is currently available through August 2003, for an average length of follow-up of 5.9 years, interquartile range 4.9 to 6.9 years. As of August 31, 2003, 94% of WHI-OS participants were still actively participating (90%) or had died (4%). This current analysis was based on 2,497 deaths, 495 hip fractures, 1,076 incident ADL disabilities (≥1 ADLs), and 18,941 self-reports of one or more overnight hospitalizations.

Statistical Analysis

Baseline demographic, medical history, and health behavior characteristics were compared for women classified as frail (frailty score ≥3), intermediate (frailty score = 1 or 2), or nonfrail (frailty score = 0) at baseline. Corresponding *P*-values are based on chi-square tests for heterogeneity.

Frailty at the third annual follow-up, for participants not classified as frail at baseline, was predicted by fitting a nominal multinomial logistic regression model. The response variable was coded as not frail (referent category), intermediate frailty, and frail. The predictor variables were age, income, education, ethnicity, health-risk variables (body mass index (BMI), smoking, alcohol consumption, hormone therapy use, self-reported health), disability (≥1 ADLs affected), whether the participant lived alone, and comorbid conditions (treatment for diabetes mellitus; treatment for hypertension or elevated blood pressure (systolic ≥140 mmHg, diastolic ≥90 mmHg); depressive symptoms; and history of hip fracture, falling within the last year, arthritis, cancer, chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), congestive heart failure (CHF), and stroke). For the multivariate analysis, a complete case analysis is presented in this article in which women with missing data on the frailty outcome or any of the covariates were excluded from the multivariate model. Of the women free of frailty at baseline, 28,181 provided frailty information at Year 3, and of these, 20,767 had information on all of the covariates in the multivariate

model. Sensitivity analyses using multiple imputation techniques to account for missing data did not importantly change any of the results.

Cox proportional hazards models were used to assess the independent contribution of baseline frailty in predicting incident hip fracture and death. For this analysis, baseline frailty was again coded as three levels (not frail, intermediate, and frail). The time to event was calculated from the date of enrollment to the date of first hip fracture or the date of death. Partially adjusted (age, ethnicity, income, and education) and fully adjusted (ethnicity, income, education, baseline health risk factors, disability, and comorbid conditions) models were fit for these outcomes. Cox models were stratified by age.

Logistic regression models were used to assess the independent contribution of baseline frailty in predicting ADL disability at Year 3 ($\geq$1 ADLs) and average number of hospitalizations during follow-up. Year 3 disability was coded as a binary response variable (1 for $\geq$1 ADLs, 0 for none); participants reporting one or more ADLs affected at baseline were excluded from this portion of the analysis. Average number of hospitalizations during follow-up was calculated by dividing the total number of self-reported overnight hospitalizations during follow-up by total follow-up time and then categorizing participants into three levels (no hospitalizations, 0 to $<$0.5 hospitalizations per year, 0.5 hospitalizations per year). Partially adjusted (age, ethnicity, income, and education) and fully adjusted (ethnicity, income, education, baseline risk factors, disability, and comorbid conditions) models were also fit for these outcomes.

RESULTS

A total of 6,619 women (16.3% of OS participants aged $\geq$65) were classified as frail at baseline, and 11,517 (28.3%) had intermediate frailty scores. Those classified as frail at baseline were more likely than the nonfrail to be older, have lower family income, and have lower educational attainment (Table 2). African-American and Hispanic women were more likely to be classified as frail than white or Asian/Pacific Islander women. BMI was a strong correlate of frailty at baseline, with obese women (BMI

Table 2. Baseline Characteristics of Women's Health Initiative Observational Study Participants According to Baseline Frailty Classification (N = 40,657 Women Aged 65–79)

Characteristic	Frailty Status at Baseline*			*P*-value
	Not Frail	Intermediate	Frail	
	n (%)			
Age at screening				$<$.001
65–69	11,390 (50.6)	5,441 (47.2)	2,539 (38.4)	
70–79	11,131 (49.4)	6,076 (52.8)	4,080 (61.6)	
Family income, $				$<$.001
$<$20,000	3,313 (16.1)	2,525 (24.1)	2,104 (35.0)	
20,000–34,999	5,801 (28.1)	3,169 (30.3)	1,941 (32.3)	
35,000–49,999	4,531 (22.0)	2,148 (20.5)	1,013 (16.9)	
50,000–74,999	3,824 (18.5)	1,563 (14.9)	579 (9.6)	
$\geq$75,000	3,153 (15.3)	1,066 (10.2)	367 (6.1)	
Education				$<$.001
$\leq$High school/general equivalency degree	4,395 (19.7)	3,184 (27.8)	2,239 (34.1)	
School after high school	8,240 (36.9)	4,348 (38.0)	2,541 (38.7)	
$\geq$College degree	9,716 (43.5)	3,904 (34.1)	1,786 (27.2)	
Race/ethnicity				$<$.001
White	19,931 (88.5)	9,691 (84.1)	5,370 (81.1)	
Black	1,001 (4.4)	905 (7.9)	755 (11.4)	
Hispanic	488 (2.2)	332 (2.9)	200 (3.0)	
American Indian	58 (0.3)	37 (0.3)	46 (0.7)	
Asian/Pacific Islander	729 (3.2)	363 (3.2)	141 (2.1)	
Unknown	314 (1.4)	189 (1.6)	107 (1.6)	
Body mass index, kg/m^2				$<$.001
$<$18.5	325 (1.5)	158 (1.4)	72 (1.1)	
18.5–24.9	10,776 (48.4)	4,019 (35.3)	1,444 (22.1)	
25.0–29.9	7,914 (35.5)	4,173 (36.7)	2,138 (32.7)	
$\geq$30.0	3,267 (14.7)	3,033 (26.6)	2,877 (44.1)	
Smoking				$<$.001
Never smoked	11,797 (53.3)	6,147 (54.3)	3,352 (51.4)	
Past smoker	9,483 (42.9)	4,539 (40.1)	2,755 (42.3)	
Current smoker	845 (3.8)	625 (5.5)	411 (6.3)	

(*Continued*)

Table 2. (Contd.)

Characteristic	Frailty Status at Baseline*			*P*-value
	Not Frail	Intermediate	Frail	
	n (%)			
Alcohol intake, drinks/wk				<.001
0/past drinker	5,737 (25.7)	4,070 (35.7)	3,105 (47.3)	
<1	6,668 (29.8)	3,552 (31.1)	1,928 (29.3)	
1–14	8,846 (39.6)	3,333 (29.2)	1,341 (20.4)	
≥14	1,096 (4.9)	457 (4.0)	197 (3.0)	
Hormone use				<.001
Never	10,608 (47.2)	5,582 (48.5)	3,325 (50.3)	
Past	3,735 (16.6)	2,044 (17.8)	1,272 (19.2)	
Current	8,152 (36.2)	3,879 (33.7)	2,018 (30.5)	
Current healthcare provider	21,452 (96.2)	10,891 (95.6)	6,312 (96.5)	.01
In general, health is				<.001
Excellent	4,971 (22.3)	941 (8.2)	113 (1.7)	
Very good	11,101 (49.8)	4,242 (37.2)	1,079 (16.3)	
Good	5,726 (25.7)	5,110 (44.8)	3,138 (47.4)	
Fair/Poor	484 (2.2)	1,120 (9.8)	2,284 (34.5)	
Depressed mood (6-item Center for Epidemiologic Studies Depression Scale score)				<.001
0	7,249 (32.9)	2,444 (21.7)	951 (14.7)	
1–2	8,892 (40.3)	4,142 (36.8)	2,118 (32.7)	
3–4	4,190 (19.0)	2,633 (23.4)	1,682 (25.9)	
≥5	1,716 (7.8)	2,042 (18.1)	1,732 (26.7)	
Living alone	7,295 (32.7)	3,759 (32.9)	2,342 (35.6)	<.001
Activity of daily living disability	155 (0.7)	213 (1.9)	378 (5.9)	<.001
History of coronary heart disease	1,275 (5.8)	1,027 (9.1)	1,111 (17.2)	<.001
History of congestive heart failure	132 (0.6)	145 (1.3)	232 (3.5)	<.001
History of stroke	250 (1.1)	284 (2.5)	290 (4.4)	<.001
Treated diabetes mellitus (pills or injections)	577 (2.6)	613 (5.3)	651 (9.9)	<.001
Hypertensive (on medications or high blood pressure)	9,630 (43.4)	5,732 (50.4)	3,972 (60.8)	<.001
History of arthritis	10,730 (48.1)	6,837 (59.9)	5,128 (78.2)	<.001
History of cancer	3,140 (14.1)	1,808 (15.8)	1,183 (18.1)	<.001
Chronic obstructive pulmonary disease	558 (2.5)	533 (4.7)	635 (9.8)	<.001
History of hip fracture at age ≥55	160 (0.8)	141 (1.4)	120 (2.0)	<.001
Number of falls in previous 12 months				<.001
None	15,648 (70.5)	7,660 (67.3)	4,109 (62.7)	
1	4,409 (19.9)	2,342 (20.6)	1,343 (20.5)	
2	1,562 (7.0)	936 (8.2)	667 (10.2)	
≥3	576 (2.6)	436 (3.8)	432 (6.6)	
Number of chronic diseases				<.001
0	4,086 (18.1)	1,316 (11.4)	250 (3.8)	
1	7,766 (34.5)	3,319 (28.8)	1,221 (18.4)	
2	6,216 (27.6)	3,455 (30)	2,023 (30.6)	
3	2,884 (12.8)	2,000 (17.4)	1,542 (23.3)	
4	1,103 (4.9)	908 (7.9)	859 (13.0)	
≥5	466 (2.1)	519 (4.5)	724 (10.9)	

*Frailty score (range 0–5) was defined as the sum of poor self-reported physical function (2 points), exhaustion (1 point), low physical activity (1 point), and unintentional weight loss (1 point, measured at follow-up only). Scores ≥3 were classified as "frailty"; scores of 1–2 were classified as "intermediate frailty."

≥30 kg/m^2) representing 44.1% of frail women, compared with 14.7% of nonfrail women (Table 2). Each of the diseases examined at baseline (CHD, CHF, stroke, diabetes mellitus, hypertension, hip fracture, COPD, arthritis, cancer) was significantly associated with baseline frailty, as were depressive symptom score and history of falling. ADL disability at baseline was low in WHI-OS women and, not surprisingly, was more common in women classified as frail (5.9%) than nonfrail (0.7%). The majority (78%) of women classified as frail reported at least two of the comorbid disease conditions studied. Of the women reporting comorbidity (≥2 diseases) at baseline (n = 22,687), 22.7%

Table 3. Odds Ratios Relating Baseline Characteristics to Incident Frailty at Year 3: 28,181 Women's Health Initiative Observational Study Participants Aged 65 to 79 and Free of Frailty at Baseline

Frailty Classification at Year 3	Not Frail (n = 15,537, 55.1%) n (%)	Intermediate (n = 8,486, 30.1%) n (%)	Intermediate OR (95% CI)	Frail (n = 4,158, 14.8%) n (%)	Frail OR (95% CI)	*P*-value
Age at screening						<.001
65–69	8,439 (54.3)	4,139 (48.8)	ref	1,736 (41.8)	ref	
70–79	7,098 (45.7)	4,347 (51.2)	1.28 (1.20–1.37)	2,422 (58.2)	1.70 (1.56–1.86)	
Family income, $						<.001
<20,000	1,997 (13.9)	1,466 (19.0)	1.29 (1.13–1.47)	967 (25.3)	1.95 (1.62–2.36)	
20,000–34,999	3,884 (27.1)	2,334 (30.2)	1.18 (1.06–1.32)	1,246 (32.6)	1.60 (1.35–1.89)	
35,000–49,999	3,193 (22.3)	1,712 (22.1)	1.10 (0.98–1.23)	755 (19.7)	1.38 (1.17–1.64)	
50,000–74,999	2,863 (20.0)	1,264 (16.3)	0.98 (0.87–1.10)	544 (14.2)	1.22 (1.02–1.46)	
≥75,000	2,406 (16.8)	956 (12.4)	ref	313 (8.2)	ref	
Education						.003
<High school/general equivalency degree	2,798 (18.1)	2,052 (24.3)	1.20 (1.10–1.32)	1,099 (26.6)	1.12 (0.98–1.27)	
School after high school	5,549 (35.9)	3,168 (37.6)	1.09 (1.01–1.17)	1,645 (39.8)	1.06 (0.95–1.18)	
≥College degree	7,089 (45.9)	3,210 (38.1)	ref	1,390 (33.6)	ref	
Race/ethnicity						.002
White	13,905 (89.5)	7,447 (87.8)	ref	3,622 (87.1)	ref	
Black	588 (3.8)	423 (5.0)	0.91 (0.77–1.07)	260 (6.3)	0.71 (0.57–0.88)	
Hispanic	251 (1.6)	211 (2.5)	1.32 (1.05–1.66)	98 (2.4)	1.06 (0.78–1.45)	
American Indian	32 (0.2)	24 (0.3)	1.04 (0.55–1.98)	10 (0.2)	0.65 (0.26–1.63)	
Asian/Pacific Islander	556 (3.6)	258 (3.0)	0.81 (0.68–0.97)	104 (2.5)	0.68 (0.52–0.88)	
Unknown	205 (1.3)	123 (1.4)	1.14 (0.87–1.51)	64 (1.5)	1.03 (0.70–1.50)	
Body mass index, kg/m^2						<.001
<18.5	216 (1.4)	123 (1.5)	1.36 (1.03–1.81)	56 (1.4)	1.65 (1.11–2.45)	
18.5–24.9	7,989 (51.9)	3,356 (39.9)	ref	1,154 (28.1)	ref	
25.0–29.9	5,307 (34.5)	3,154 (37.5)	1.36 (1.26–1.46)	1,567 (38.1)	1.92 (1.73–2.13)	
≥30.0	1,882 (12.2)	1,781 (21.2)	2.04 (1.85–2.24)	1,337 (32.5)	3.95 (3.50–4.47)	
Current health care provider	14,812 (96.2)	8,113 (96.4)	0.90 (0.75–1.07)	3,983 (96.6)	0.88 (0.69–1.13)	.38
Smoking						<.001
Never	8,282 (54.0)	4,672 (55.9)	ref	2,103 (51.6)	ref	
Past	6,573 (42.9)	3,306 (39.6)	0.95 (0.89–1.02)	1,716 (42.1)	1.12 (1.02–1.23)	
Current	472 (3.1)	381 (4.6)	1.76 (1.49–2.09)	257 (6.3)	2.90 (2.35–3.57)	
Alcohol intake, drinks/wk						<.001
0/past drinker	3,710 (24.0)	2,552 (30.3)	ref	1,451 (35.2)	ref	
<1	4,564 (29.5)	2,633 (31.3)	0.89 (0.82–0.97)	1,339 (32.4)	0.87 (0.77–0.97)	
1–14	6,413 (41.5)	2,854 (33.9)	0.77 (0.70–0.84)	1,155 (28.0)	0.69 (0.61–0.77)	
>14	764 (4.9)	385 (4.6)	0.89 (0.75–1.05)	183 (4.4)	0.93 (0.74–1.16)	
Hormone use						<.001
Never	7,182 (46.3)	3,970 (46.8)	ref	1,931 (46.4)	ref	
Past	2,511 (16.2)	1,477 (17.4)	1.03 (0.94–1.13)	767 (18.4)	1.15 (1.02–1.30)	
Current	5,824 (37.5)	3,031 (35.8)	1.10 (1.03–1.19)	1,460 (35.1)	1.29 (1.16–1.42)	
Living alone						<.001
No	10,478 (68.0)	5,836 (69.3)	ref	2,731 (66.4)	ref	
Yes	4,942 (32.0)	2,591 (30.7)	0.81 (0.75–0.87)	1,384 (33.6)	0.80 (0.72–0.88)	
In general, health is						<.001
Excellent	3,848 (24.9)	1,049 (12.5)	ref	249 (6.1)	ref	
Very good	7,787 (50.4)	3,845 (45.7)	1.52 (1.38–1.66)	1,410 (34.4)	2.13 (1.80–2.52)	
Good	3,556 (23.0)	3,111 (36.9)	2.30 (2.07–2.55)	2,001 (48.8)	4.97 (4.18–5.91)	
Fair/poor	253 (1.6)	417 (5.0)	3.77 (3.05–4.66)	437 (10.7)	11.51 (8.88–14.91)	
History of congestive heart failure	68 (0.4)	70 (0.8)	1.32 (0.88–1.98)	57 (1.4)	1.26 (0.79–2.03)	.39
History of coronary heart disease	736 (4.8)	582 (7.0)	1.17 (1.02–1.34)	474 (11.6)	1.47 (1.25–1.73)	<.001
History of stroke	156 (1.0)	102 (1.2)	0.90 (0.66–1.23)	120 (2.9)	1.71 (1.24–2.36)	<.001
	297 (1.9)	277 (3.3)	1.18 (0.96–1.44)	249 (6.0)	1.40 (1.11–1.76)	.02

(*Continued*)

Table 3. (Contd.)

Frailty Classification at Year 3	Not Frail (n = 15,537, 55.1%) n (%)	Intermediate (n = 8,486, 30.1%) n (%)	Intermediate OR (95% CI)	Frail (n = 4,158, 14.8%) n (%)	Frail OR (95% CI)	*P*-value
Treated diabetes (pills or shots)						
Hypertensive (on medication or high blood pressure)	6,175 (40.2)	3,969 (47.3)	1.06 (1.00–1.14)	2,272 (55.4)	1.18 (1.08–1.29)	.001
History of hip fracture at age ≥55	114 (0.8)	68 (0.9)	1.29 (0.91–1.82)	53 (1.5)	1.89 (1.25–2.86)	.006
Chronic obstructive pulmonary disease	328 (2.2)	292 (3.5)	1.50 (1.24–1.82)	241 (5.9)	2.01 (1.61–2.52)	<.001
Number of falls in previous 12 months						<.001
0	10,952 (71.3)	5,691 (67.9)	ref	2,699 (65.9)	ref	
1	3,014 (19.6)	1,765 (21.1)	1.09 (1.01–1.19)	864 (21.1)	1.05 (0.94–1.18)	
2	1,011 (6.6)	657 (7.8)	1.25 (1.10–1.42)	361 (8.8)	1.36 (1.15–1.60)	
≥3	384 (2.5)	264 (3.2)	1.26 (1.03–1.53)	170 (4.2)	1.66 (1.30–2.12)	
≥1 activity of daily living disability (baseline)	120 (0.8)	86 (1.0)	1.04 (0.75–1.46)	89 (2.2)	1.84 (1.28–2.65)	.002
Depressed mood (6-item Center for Epidemiologic Studies Depression Scale score)						<.001
0	5,209 (34.0)	2,188 (26.2)	ref	820 (20.2)	ref	
1–2	1,193 (7.8)	1,110 (13.3)	1.16 (1.07–1.26)	624 (15.3)	1.46 (1.30–1.63)	
3–4	6,169 (40.3)	3,259 (39.1)	1.36 (1.24–1.49)	1,641 (40.4)	1.75 (1.54–2.00)	
≥5	2,739 (17.9)	1,781 (21.4)	1.80 (1.60–2.02)	981 (24.1)	2.20 (1.88–2.57)	
History of arthritis	7,046 (45.7)	4,665 (55.4)	1.28 (1.20–1.37)	2,826 (68.6)	1.89 (1.72–2.07)	<.001
History of cancer	2,070 (13.4)	1,279 (15.2)	1.04 (0.94–1.14)	675 (16.4)	1.05 (0.93–1.19)	.63

* Frailty score (range 0–5) was defined as the sum of poor self-reported physical function (2 points), exhaustion (1 point), low physical activity (1 point), and unintentional weight loss (1 point, measured at follow-up only). Scores ≥3 were classified as "frailty"; scores of 1–2 were classified as "intermediate frailty."
OR = odds ratio; CI = confidence interval; ref = reference.

were classified as frail, whereas only 2.5% had ADL disability.

Of the 28,181 women who were free of frailty at baseline and who provided frailty information at follow-up, 14.8% were classified as frail at Year 3. A primary concern of these analyses was predicting incident frailty from measures obtained from the WHI-OS cohort at baseline. As seen in Table 3, age, education, income, BMI, smoking, moderate alcohol intake, hormone use, history of CHD, stroke, hip fracture, COPD, treated diabetes mellitus, and arthritis were all significantly related to incident frailty. Women who became frail were older, had lower education and family incomes, were more likely to be current smokers, and were more likely to be current hormone therapy users. African-American women were less likely to develop incident frailty after accounting for other covariates. Underweight participants (BMI <18.5) were at higher risk of frailty than normal weight participants (OR = 1.65, 95% CI = 1.11–2.45), similar to the risk for overweight women with a BMI of 25.0 to 29.9. The risk of frailty for obese women with a BMI of 30 or greater was even greater (OR = 3.95, 95% CI = 3.50–4.47).

In addition, frail women were less likely to be living alone and more likely to rate their health as fair or poor. Women who developed frailty were more likely to have fallen at least twice in the 12 months before baseline and had higher scores on the depressive symptom scale.

Baseline frailty was strongly and significantly associated with ADL disability at Year 3, higher mean number of hospitalizations, hip fracture, and death (Tables 4 and 5). Odds ratios adjusted for age, ethnicity, education, and income showed that baseline frailty increased the risk of these outcomes by about two to five times. Multivariate adjustment diminished the magnitude of the associations between baseline frailty and each outcome, but in every case the odds ratios or hazard ratios remained importantly and significantly elevated. Moreover, intermediate frailty was a statistically significant, although more modest, predictor of all four health outcomes.

DISCUSSION

In this study of 40,657 women aged 65 to 79 in the WHI-OS, a multicomponent measure of frailty was found to be strongly and independently associated with risk of death, hip fracture, disability, and hospitalization during an average of 5.9 years of follow-up after adjusting for demographic variables, health risk factors, ADL disability, and

comorbid conditions. These results are consistent with the pioneering study on frailty conducted in older men and women in the CHS, which showed similar associations.[1] The magnitude of the hazard ratios was similar in both studies; for example, the adjusted hazard ratios for death were 1.7 in the WHI women over an average 5.9 years and 1.6 in the CHS of men and women over 7 years of follow-up. Thus, this large prospective study of older women supports the robustness of the concept of frailty as a distinct clinical entity that is associated with poor prognosis overall and greater risk of numerous acute health events. Because the concept of frailty was so recently defined, the ability to replicate the initial findings of its creators in a different cohort of older women, using similar but not identical measures to define frailty, is an important contribution of this research.

At baseline, frailty was strongly associated with older age, lower family income, less education, and being African American. Frail women at baseline were also more likely to report a prior diagnosis of CHD, stroke, diabetes mellitus, hypertension, arthritis, cancer, and COPD. These cross-sectional associations are similar to prior reports.[1,11,15,16] This study has expanded on prior work by examining the independent contribution of several baseline demographic characteristics, health risk factors, and comorbid conditions for development of frailty at 3 years of follow-up in women without frailty at baseline. Several of the associations found in the cross-sectional analysis were not significant in the multivariable models. Most notable, educational attainment and race/ethnicity were only weakly associated with frailty after multivariate adjustment, suggesting that differences in health status and risk-factor levels may explain differences in frailty by education level or race/ethnicity. Living alone was associated with a lower risk of becoming frail, presumably because the most disabled women lose the capability to live independently.

Many chronic conditions at baseline were independently associated with baseline and incident frailty. Cancer was not associated with becoming frail in the WHI-OS and was the only disease state not related to frailty cross-sectionally in the CHS.[1,16] A history of frequent falling, number of comorbid conditions, and presence of an ADL disability or of intermediate frailty at baseline were all associated with greater risk of becoming frail. Health behaviors also appeared to independently influence risk of frailty, with smokers being 2.9 times as likely to become frail as nonsmokers and moderate alcohol drinkers having a 13% to 31% lower risk than nondrinkers. The latter finding persisted even after adjustment for many of the chronic diseases that have been similarly associated with moderate alcohol consumption.[17] A strong relationship between depressive symptoms and incident frailty was observed, suggesting a possible psychosocial or psychobiological component of the frailty syndrome.

Underweight and overweight women had a greater risk of baseline and incident frailty, suggesting a U-shaped relationship between BMI and the frailty syndrome, which has not been reported before. In the CHS, significantly higher BMI was reported in frail men and women studied cross-sectionally, and the paradox of this finding with low body weight and weight loss as a component for defining frailty was noted.[16] A quadratic relationship between body fat and strength in people aged 70 to 79 has been reported in which high and low extremes of body fat were associated with lower muscle strength in the arms and legs.[18] Moreover, higher fat mass, rather than low skeletal muscle mass, has been shown to be related to worse functional performance and disability in older men and women.[19–21] A prospective study showed loss of muscle mass (sarcopenia) in older men and women over time that stable weight or weight gain masked, leading the authors to speculate that sarcopenic obesity may be common in older women who are significantly overweight.[22] Frailty has been conceptualized as a wasting syndrome involving loss of muscle strength and weight loss, yet the increased risk of frailty in the obese suggests that higher levels of body weight do not protect older people from this syndrome and instead convey risk, particularly in those who are less physically active.[23] These findings support the need for carefully controlled trials to test weight loss interventions as a means for improving muscle strength and reducing risk of frailty in obese older adults.[24,25]

Strengths of this study include the large number and diversity of the women studied, the prospective design, the ability to examine numerous reported chronic conditions and health behaviors as risk factors for future frailty, and the availability of follow-up information on several important health outcomes. Lack of information on physical performance tests and unintentional weight loss (at baseline only) are unavoidable limitations of this analysis. The study

Table 4. Odds Ratios (ORs) Relating Frailty at Baseline to Activity of Daily Living (ADL) Disability and Number of Hospitalizations During Follow-Up, Through August 31, 2003: Women's Health Initiative Observational Study Participants Aged 65 to 79 at Baseline

	Intermediate	Frail
Outcome	OR (95% Confidence Interval)	
ADL disability at Year 3		
Partially adjusted*	2.16 (1.79–2.60)	5.44 (4.54–6.52)
Fully adjusted†	1.64 (1.31–2.04)	3.15 (2.47–4.02)
Average number of hospitalizations per year during follow-up (reference = no hospitalizations)		
Partially adjusted*		
<0.5	1.32 (1.26–1.39)	1.98 (1.85–2.11)
≥0.5	1.77 (1.62–1.93)	4.21 (3.84–4.63)
Fully adjusted†		
<0.5	1.17 (1.10–1.25)	1.42 (1.30–1.55)
≥0.5	1.30 (1.17–1.45)	1.95 (1.72–2.22)

* Adjusted for age, ethnicity, education, and income.

† Adjusted for age; income; education; ethnicity; health risk variables (body mass index; smoking; alcohol consumption; history of hormone use; self-reported health; current healthcare provider); disability (>1 ADL affected; whether the participant lives alone); comorbid conditions (treatment for diabetes mellitus; treatment for hypertension or elevated blood pressure (systolic ≥140 mmHg; diastolic ≥90 mmHg); depressed mood; and history of hip fracture, falling within the previous year, arthritis, cancer, chronic obstructive pulmonary disease, coronary heart disease, congestive heart failure, and stroke. Cox regression models stratify on age.

Table 5. Hazard Ratios (HRs) Relating Frailty at Baseline to Hip Fracture and Death During Follow-Up, Through August 31, 2003: Women's Health Initiative Observational Study Participants Aged 65 to 79 at Baseline

Outcome	HR (95% Confidence Interval)	
Hip fracture		
Partially adjusted*	1.43 (1.15–1.77)	1.74 (1.37–2.22)
Fully adjusted†	1.31 (1.00–1.71)	1.57 (1.11–2.20)
Death		
Partially adjusted*	1.38 (1.25–1.52)	2.45 (2.21–2.72)
Fully adjusted†	1.25 (1.11–1.41)	1.71 (1.48–1.97)

* Adjusted for age, ethnicity, education, and income.

† Adjusted for age; income; education; ethnicity; health risk variables (body mass index; smoking; alcohol consumption; history of hormone use; self-reported health; current healthcare provider); disability (>1 ADL affected; whether the participant lives alone); comorbid conditions (treatment for diabetes mellitus; treatment for hypertension or elevated blood pressure (systolic ≥140 mmHg; diastolic ≥90 mmHg); depressed mood; and history of hip fracture, falling within the previous year, arthritis, cancer, chronic obstructive pulmonary disease, coronary heart disease, congestive heart failure, and stroke. Cox regression models stratify on age.

population was restricted to older women; the extent to which these findings can be generalized to men is not known. Impaired cognition is an unmeasured potential confounder in these analyses, although in the WHI hormone trials, in which cognitive impairment was assessed at baseline, few women had low cognitive scores at enrollment.

The main difference between the measure of frailty used in this report and that defined previously[1] is the use in the current study of a self-reported measure of physical function, the Rand-36 physical function scale, as a surrogate for the grip strength and timed walk measures. The physical function scale dichotomized at the 25th percentile showed a strong association with poor walking speed and a moderate association with poor grip strength in the WHI-CT subgroup of women aged 65 and older who completed the physical performance tests. Nonetheless, the WHI-OS frailty definition predicted outcomes as well as the original definition. Ideally, a measure of frailty would identify women at risk of these serious outcomes who were not already overtly disabled. In the CHS, 27% of women classified as frail reported ADL disability, whereas in this study only 6% of women classified as frail also reported ADL disability. These findings demonstrate that it is possible to identify a larger group of frail women, 94% of whom have no ADL disability, and yet this frail group is still at substantially greater risk of death, hospitalization, hip fracture, and future ADL disability.

The strong, orderly relationships between the absent, intermediate, and frail categories in this study and the initial report[1] argue for studying frailty scores across their full distribution to discern increasing risk levels. As the study of frailty moves forward, it will be important to continue to refine how best to measure and aggregate the individual components. The present findings support further exploration of self-reported indicators of physical function for the muscle weakness components, especially in populations at risk for frailty for whom standardized performance examinations could be impractical, such as those in retirement homes, assisted living, and other long-term care environments. Moreover, these indicators may have utility for predicting the need for higher levels of service or indicated preventive interventions to reduce outcomes such as falls.

Taken together, these findings support further research on multiple pathways that may lead to frailty, among them a pathway related to depressed mood and another pathway related to obesity and high fat mass. This approach is consistent with the caution that no single altered system defines this state and that multiple systems are involved.[1,2] Such a multicausal model of frailty could also form the basis for understanding the development of different types of disability is later life related to pain, mobility and balance problems, weakness, and poor endurance.[26]

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