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A SIMPLE FRAILTY QUESTIONNAIRE (FRAIL) PREDICTS OUTCOMES IN MIDDLE AGED AFRICAN AMERICANS

J.E. MORLEY, **T.K. MALMSTROM**, and **D.K. MILLER**

Abstract

Objective—To validate the FRAIL scale.

Design—Longitudinal study.

Setting—Community.

Participants—Representative sample of African Americans age 49 to 65 years at onset of study.

Measurements—The 5-item FRAIL scale (Fatigue, Resistance, Ambulation, Illnesses, & Loss of Weight), at baseline and activities of daily living (ADLs), instrumental activities of daily living (IADLs), mortality, short physical performance battery (SPPB), gait speed, one-leg stand, grip strength and injurious falls at baseline and 9 years. Blood tests for CRP, SIL6R, STNFR1, STNFR2 and 25 (OH) vitamin D at baseline.

Results—Cross-sectionally the FRAIL scale correlated significantly with IADL difficulties, SPPB, grip strength and one-leg stand among participants with no baseline ADL difficulties (N=703) and those outcomes plus gait speed in those with no baseline ADL dependencies (N=883). TNFR1 was increased in pre-frail and frail subjects and CRP in some subgroups. Longitudinally (N=423 with no baseline ADL difficulties or N=528 with no baseline ADL dependencies), and adjusted for the baseline value for each outcome, being pre-frail at baseline significantly predicted future ADL difficulties, worse one-leg stand scores, and mortality in both groups, plus IADL difficulties in the dependence-excluded group. Being frail at baseline significantly predicted future ADL difficulties, IADL difficulties, and mortality in both groups, plus worse SPPB in the dependence-excluded group.

Conclusion—This study has validated the FRAIL scale in a late middle-aged African American population. This simple 5-question scale is an excellent screening test for clinicians to identify frail persons at risk of developing disability as well as decline in health functioning and mortality.

Keywords

Frailty; African Americans; disability; physical performance; mortality

Frailty can be considered a pre-disability state (1). It is a condition in which there is decreased physiological reserve and resilience (2). When frail persons are exposed to a

Corresponding Author: John E. Morley, M.B., B.Ch., Division of Geriatrics, Department of Internal Medicine, 1402 South Grand Boulevard, St. Louis, MO 63104. morley@slu.edu.

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stressor, they are at increased risk for developing disability or dying (3). Evidence is emerging that targeted therapies may decrease the negative outcomes associated with being frail (4–6). At present, the two well validated frailty scales both require face-to-face examination, i.e., the Cardiovascular Health Study (CHS) scale (7) and the Study of Osteoporotic Fractures (SOF) scale (8). The International Association of Nutrition and Aging proposed a frailty scale (FRAIL) that only requires answers to 5 simple questions (9, 10). This questionnaire contains 4 questions directed at components of the Cardiovascular Health Study Frailty Index and one (number of illnesses) at the Rockwood Scale (11, 12). A simple test that can increase the identification of frailty without a face-to-face examination could result in more efficient identification of an important medical syndrome that could be accomplished by telephone and self-administered forms and makes repeated administration to large groups of patients more feasible. These features, in turn, could lead to earlier recognition and treatment by practitioners. It also makes repeated measurement in research surveys more feasible and lower cost.

Frailty is more prevalent in African Americans than in majority whites (13). Disability and functional impairment are also more common in African Americans compared to whites (14). The African American Health (AAH) project is a longitudinal study of a representative sample of African Americans of “late middle age” (15). This population has been shown to have dysphoric symptoms and health-related quality of life below that of the national average in the United States (16, 17) as well as an excess of disability (15).

In this study we utilized the AAH population to validate the FRAIL scale. In particular we demonstrate the predictive validity of the FRAIL scale in persons who do not have basic activities of daily living (ADL) deficits (no difficulties or no dependencies) at baseline to explore the robustness of the FRAIL scale to screen adults at risk of bad outcomes. We also demonstrate that both frailty and prefrailty in this population are highly predictive of poor outcomes.

Methods

Study Sample

AAH has been described in detail previously (15). In brief, it is a population-based panel study of 998 African Americans from two socioeconomically diverse areas of St. Louis (inner-city and near northwest suburbs). Participants were born between 1936 and 1950 and were 49 to 65 years of age at the Wave 1 baseline assessment. Inclusion criteria involved community-dwelling, self-reported Black or African American race, and Mini-Mental Status Exam (MMSE) scores of 16 or greater. Recruitment proportion (participants/enumerated eligible persons) was 76%. Wave 1 was conducted at participants’ homes between September 2000 and July 2001 and averaged 2.5 hours in length. Interviewers completed 26 hours of training on study-specific interviewing and physical performance measurements. In-home assessments were repeated 9 years later after baseline during Wave 10. Of the original 998 participants, 582 were successfully re-evaluated during Wave 10. As 163 participants died between Wave 1 and Wave 10, the proportion of surviving participants who were assessed was 70%.

FRAIL Questionnaire—The FRAIL scale includes 5 components: Fatigue, Resistance, Ambulation, Illness, and Loss of weight (10). Frail scale scores range from 0–5 (i.e., 1 point for each component; 0=best to 5=worst) and represent frail (3–5), pre-frail (1–2), and robust (0) health status. For this study, AAH Wave 1 data were used to construct the FRAIL scale. Fatigue was measured by asking respondents how much time during the past 4 weeks they felt tired with responses of "all of the time" or "most of the time" scored 1 point. Resistance was assessed by asking participants if they had any difficulty walking up 10 steps alone without resting and without aids, and Ambulation by asking if they had any difficulty walking several hundred yards alone and without aids; "yes" responses were each scored as 1 point. Illness was scored 1 for respondents who reported 5 or more illnesses out of 11 total illnesses. Loss of weight was scored 1 for respondents with a weight decline of 5% or greater within the past 12 months based on self-report. A complete description of the AAH FRAIL scale items scoring criteria, and baseline prevalences are provided in Appendix 1.

Outcome Measures—The associations of FRAIL scale scores categorized as frail or pre-frail (versus healthy) were examined with poor outcomes on the following measures: ADL difficulties, instrumental activities of daily living (IADL) difficulties, short physical performance battery (SPPB), gait speed, one-leg stand test, grip strength, injurious falls, laboratory tests, and mortality.

Functional Status and Body Composition—Disability was assessed using activities of daily living scales. Basic ADLs included seven items (bathing, dressing, eating, transferring bed or chair, walking across a room, getting outside, and using toilet) from the Second Longitudinal Study of Aging (LSOA-II) (18). ADL difficulties represent the number of these tasks for which respondents reported difficulty performing the task. ADL dependency was defined as positive when respondents reported difficulty on an ADL item and, also, reported a) being unable to do the task or b) receiving help from another person to do the task. IADLs included eight items (preparing meals, shopping for groceries, managing money, making phone calls, doing light housework, doing heavy housework, getting to places outside walking distance, and managing medications) from LSOA-II (18) and Lawton and Brody (19) and was scored as the number of tasks for which the respondent reported difficulty performing that task.

Physical performance was measured using the SPPB (20, 21), adapted to the AAH population (22). The SPPB is a summary measure of lower body performance based on three component tasks: standing balance, chairs stands, and usual walking speed. Each component task was scored as 0–4 (range 0 = worst to 4 = best), and a composite score was computed as the sum of scores on component tasks as 0–12 (range 0 = worst to 12 = best). Complete details on the composite SPPB score in AAH are provided by Miller and colleagues (22). Isometric grip strength was assessed using a handgrip dynamometer (Fabrication Enterprises, Inc., Irvington, NY). The mean of the last two of three maximal effort trials with the self-reported stronger hand was used in these analyses. The test was performed seated in a chair (without arm rests), with feet flat on the floor and the stronger arm held flat against the side with the elbow at 90° (23). Gait speed was assessed in respondents' homes using a standardized 3- or 4-meter course with participants instructed to walk at their usual

pace. The average walking speed (meters/second) was computed for two trials. Injurious falls were classified as the total number of falls in the past year which resulted in any of the following events: need for medical attention, inability to get up independently without help from someone else, bone fracture, or the need to cut down on usual activities due to the fall. For the one-leg stand test individuals chose their preferred leg to balance on and were required to raise the other foot at least 2 inches above the ground and hold the position for as long as possible up to 30 seconds. The Falls Efficacy Scale (FES) measures confidence in performing 10 everyday activities without falling. The response for each FES item ranges from 0 (no confidence) to 10 (complete confidence) and the FES total score ranges from 0–100 (24). Vital status was determined by proxy report as part of the annual AAH follow-up Waves 1–5 plus Waves 8 and 10 and tracing via local databases (e.g., obituaries).

Laboratory tests

Blood was drawn for laboratory analyses shortly after the baseline, in-home assessment, or at the time of further clinical examinations required for special substudies during Wave 1. Serum was stored until analysis for cytokines in 2006. Blood tests were available on 349 participants, and the characteristics of the subsample have been previously reported (25). Adiponectin was determined using a commercially available radioimmuno-assay kit (Linco Research, St. Charles, MO) with intra-assay and interassay coefficients of variation (CVs) of 5.3% and 8.1%, respectively. CRP was measured with a commercially available High-Sensitivity Enzyme Immunoassay (hsCRP ELISA) kit from MP Biomedicals (Orangeburg, NY). The intra-assay and interassay CVs were 4.5% and 4.1%, respectively. Soluble IL-6R was measured with an ELISA kit from ICN-Biomedicals (Costa Mesa, CA). The intra-assay and interassay CVs were 5.0% and 5.9%, respectively. Soluble TNFR1 and sT-NFR2 were measured using ELISA kits (BioSource, Camarillo, CA). Intra-assay and interassay CVs were 4.1% and 7.3% for sTNFR1 and 5.1% and 8.6% for sTNFR2. Measurement of serum 25(OH) Vitamin D (25OH D) was performed using a commercially available test kit (Investor, Stillwater, MN). The intra-assay and interassay coefficient of variation were 6.2% and 12.7%.

Data Analyses—Data were analyzed using IBM SPSS Statistics, version 20.0 (Somers, NY). Descriptive statistics are reported as means + standard deviations or percentages. ANOVA for continuous variables with Tukey posthoc tests and chi-square for categorical variables were used to compare population characteristics across FRAIL scale status (healthy, pre-frail, frail). Linear regression (continuous outcomes) and binary logistic regression (dichotomous outcomes) were used to investigate cross-sectional and longitudinal associations for FRAIL status groups and for each of the five individual components of the FRAIL scale. Unstandardized (b) regression coefficients and standard errors are reported for linear regression analyses, and adjusted odds ratios (AORs) and 95% confidence intervals (CIs) are reported for logistic regression analyses. Cross-sectional regression analyses were adjusted for age and gender. Longitudinal regression analyses were adjusted for age and gender for all outcomes in Models 1a & 1b, and for age, gender, and baseline values for all outcome variables in Models 2a & 2b. Analyses were performed excluding participants with 1 or more ADLs difficulties at baseline (Wave 1) and then repeated excluding participants with 1 or more ADL dependencies at baseline.

Results

In the group without ADL difficulties at baseline, 2.7% were frail and 37.4% were prefrail. At baseline, when participants with any ADL dependencies were excluded, 7.5% were judged to be frail and 42.2% were pre-frail. By Wave 10, 8.6% of continuing participants without ADL difficulty at baseline were frail and 33.8% were prefrail. Baseline characteristics of the population comparing healthy, frail, and prefrail are given in Table 1 for participants with no ADL difficulty and also those with no ADL dependence. Frail patients using either ADL exclusion criterion had worse self-rated health, a lower income, a higher BMI, poorer Falls Efficacy Scale, and lower mental status. Cross-sectional and longitudinal descriptive statistics for outcome measures for each ADL disability definition and categories by FRAIL scale classifications (healthy, pre-frail, and frail) are provided in Table 2.

Cross-sectionally (Wave 1) among those without ADL disability (difficulty or dependence definition) at baseline, both being frail and prefrail were associated with more IADL difficulties, lower SPPB scores, lower grip strength, and shorter time for one-leg stand (Table 3). Being frail or prefrail was predictive of several factors' being worse at 9 years as well, with adjustments for age and gender and for age, gender, and baseline values of outcome variables (Table 3).

Notably, both being frail and being prefrail were associated with mortality over the 9 year period (Table 3), with estimated ORs about 4 for frailty and 1.7 for pre-frailty. Persons with no ADL difficulty, or no ADL dependence, who were frail or prefrail at baseline (Wave 1) were more likely to have deficits in ADLs after 9 years than those who were healthy at baseline. A separate analysis of the FRAIL components' ability to predict ADLs and mortality at Wave 10 is given in Table 5. As can be seen, mortality and SPPB were predicted by resistance and ambulation, while ADL decline was predicted by fatigue, resistance, ambulation, and by illnesses in the dependence-excluded group. IADL difficulties, gait speed, one-leg stand, and grip strength were predicted by resistance in Models 1a and 1b, while only IADL difficulties showed a statistically significant relationship with resistance in Models 2a and 2b. Similar associations were seen in cross-sectional comparisons (Table 4).

Table 6 compares the cytokine receptor, C-reactive protein, adiponectin and leptin levels in healthy, prefrail and frail groups. Table 7 provides the age- and sex-adjusted associations of cytokine receptors, leptin, and adiponectin with frailty and prefrailty at baseline (Wave 1). Among those with no ADL difficulty or no ADL dependence at baseline, higher sTNFR1 (log 10) levels were seen in both prefrail and frail, whereas an increased CRP (log 10) was present in frail subjects only for those with no ADL difficulties.

There was no association of 25(OH) vitamin D with either frailty or prefrailty among participants with no ADL difficulty or no ADL dependence at baseline (Tables 6 and 7) or in the total sample (data available on request).

Discussion

The FRAIL scale showed strong convergent and predictive validity in this population of late middle-aged African Americans. Cross-sectional analyses demonstrated that the FRAIL questionnaire correlates significantly with a series of markers, viz IADL's, SPPB, gait speed, grip strength, and one-leg stand, that are classically associated with frailty. Most notably, we showed that being frail or prefrail significantly predicts mortality and increased ADL and IADL disability levels over 9 years of follow-up. One strength of this study is that the FRAIL scale was predictive of these changes in outcomes even when persons who had ADL disability (difficulty or dependence criterion) at baseline were excluded. A useful frailty scale should be able to predict future disability before the person becomes disabled (9).

The two most commonly used frailty scales, viz, the CHS and the Study of Osteoporotic Fractures (SOF), require physical examination techniques not commonly performed by practicing physicians (7, 8). The FRAIL scale is a simple questionnaire that can be rapidly administered by the physician, healthcare professional or even by the patient or a relative. It is also easy to perform by telephone or self-administered questionnaires and can be performed at frequent intervals quite economically, as opposed to the CHS and SOF scales. Another study found that the components of the FRAIL scale predicted both mortality and disability after four to eight years of follow-up in males aged 65 years and older (26).

Another frail scale which has been validated is the scale of Rockwood et al (27). This scale depends on the addition of the number of deficits resulting in an accumulated deficit score. Its utility as a true frailty scale as opposed to a disease/disability index can be questioned. The inclusion of the illness category in the FRAIL scale allows this component to be captured, but not at the expense of the other potentially predictive factors.

A simple FRAIL score that can be repeated frequently allows the physician to identify frailty at an early stage. In theory, this should allow early intervention in an attempt to slow the rate of the development of disabilities. There is evidence that exercise therapy (aerobic, resistance and balance) can slow the progression of the frailty syndrome (4, 28). In addition, replacement of 25(OH) vitamin D and testosterone may reverse some of the sarcopenic features of frailty (5). There is also evidence that a leucine enriched essential amino acid supplement may improve mobility (5). Testosterone may also decrease frailty (6, 29).

Chronic inflammation has been shown to be associated with frailty (30). In this population, we have previously demonstrated that inflammatory markers are associated with functional limitations and disability (25). Here we extended that finding to show that soluble cytokine receptors as well as CRP are related to frailty. These findings are in concert with the fact that elevated cytokines are associated with poorer physical performance, muscle strength and weight loss (31–33).

A surprising finding was the failure to find an association of 25(OH) vitamin D levels with frailty. 25(OH) vitamin D levels have been associated with loss of muscle strength, function and mortality in older populations (34). Some studies have previously suggested an association of 25(OH) vitamin D with frailty (35, 36). The very low levels of 25(OH)

vitamin D in this African American population (both healthy and frail) may explain the lack of association in this study.

A limitation of this study is that there is low power for the longitudinal analyses that involve participants classified as frail on the FRAIL scale due to significant excess mortality for people with frailty and with ADL difficulties. Power is also reduced in cross-sectional analyses for the frail group when those with ADL problems were removed because approximately 25% of AAH participants were excluded due to pre-existing ADL difficulty at baseline. Another limitation is that the AAH cohort includes late middle-aged adults at baseline, so it is expected that the prevalence of frailty among African Americans would be higher in an older cohort. Finally, these results in an African American population may not generalize to other populations.

In summary, we have provided an extensive validation for the FRAIL scale in a late middle-aged African-American population. We suggest that this questionnaire would be an excellent screening test for clinicians to identify persons at risk of developing disability. This would allow the institution of an aggressive management program to prevent disability. In addition, we have confirmed the association between frailty and chronic inflammation. Studies examining the cross-sectional and longitudinal validity of the FRAIL scale in other populations are needed.

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Appendix 1. FRAIL scale items in AAH

Fatigue: “How much of the time during the past 4 weeks did you feel tired?” 1 = All of the time, 2 = Most of the time, 3 = Some of the time, 4 = A little of the time, 5 = None of the time. Responses of “1” or “2” are scored as 1 and all others as 0. Baseline prevalence = 20.1%.

Resistance: “By yourself and not using aids, do you have any difficulty walking up 10 steps without resting?” 1 = Yes, 0 = No. Baseline prevalence = 25.5%.

Ambulation: By yourself and not using aids, do you have any difficulty walking several hundred yards?” 1 = Yes, 0 = No. Baseline prevalence = 27.7%.

Illnesse: For 11 illnesses, participants are asked, “Did a doctor ever tell you that you have [illness]?” 1 = Yes, 0 = No. The total illnesses (0–11) are recoded as 0–4 = 0 and 5–11 = 1. The illnesses include hypertension, diabetes, cancer (other than a minor skin cancer), chronic lung disease, heart attack, congestive heart failure, angina, asthma, arthritis, stroke, and kidney disease. Baseline prevalence = 2.1%.

Loss of weight: “How much do you weigh with your clothes on but without shoes? [current weight]” “One year ago in (MO, YR), how much did you weigh without your shoes and with your clothes on? [weight 1 year ago]” Percent weight change is computed as: [[weight 1 year ago - current weight]/weight 1 year ago]] * 100. Percent change > 5 (representing a 5% loss of weight) is scored as 1 and < 5 as 0. Baseline prevalence = 21.0%.

Table 1

Baseline characteristics for AAH participants with no ADL difficulty or no ADL dependence

	No ADL difficulty at Baseline (N=703)			
	Healthy (n=421)	**Prefrail (n=263)**	**Frail (n=19)**	**P-Value***
Age, y	56.10 + 4.5	56.10 + 4.4	57.79 + 3.9	.263
Male	46.1%	29.7%	21.1%	<.001
Education, y	12.93 + 3.0	12.34 + 2.9	12.00 + 2.4	.024[a]
Marital Status				.029
Married	36.1%	36.3%	31.6%	
Divorced/Separated	40.7%	30.2%	52.6%	
Widowed	9.6%	14.5%	10.5%	
Single	13.6%	19.1%	5.3%	
Self-Rated Health Fair or Poor	18.8%	43.0%	84.2%	<.001
Had any health Insurance	85.0%	83.2%	78.9%	.667
Ever Received Medicaid Insurance	11.9%	25.2%	26.3%	<.001
Income (below 20k)	26.6%	34.2%	52.6%	.010
MMSE	28.30 + 2.4	27.81 + 2.7	27.53 + 2.8	.031a
Animal Naming	19.89 + 6.1	18.27 + 6.2	17.11 + 6.1	.002a
BMI	28.63 + 5.6	30.44 + 6.6	32.08 + 7.2	<.001[a,b]
Smoking Status				.316
Non-Smoker	34.9%	32.7%	21.1%	
Past Smoker	34.0%	29.7%	42.1%	
Current Smoker	31.1%	37.6%	36.8%	
Falls Efficacy Scale	98.72 + 5.2	95.97 + 8.3	92.95 + 7.6	<.001[a,b]

	No ADL Dependence at Baseline (N=883)			
	Healthy (n=444)	**Prefrail (n=373)**	**Frail (n=66)**	**P-Value***
Age, y	56.15 + 4.5	56.37 + 4.4	56.71 + 4.0	.555
Male	46.2%	30.3%	27.3%	<.001
Education, y	12.89 + 3.0	12.29 + 2.9	11.15 + 2.8	<.001[a–c]
Marital Status				.003
Married	37.0%	32.2%	22.7%	
Divorced/Separated	39.5%	31.9%	47.0%	
Widowed	10.4%	17.3%	15.2%	
Single	13.2%	18.6%	15.2%	
Self-Rated Health Fair or Poor	20.0%	47.5%	89.4%	<.001
Had any health Insurance	85.1%	83.1%	71.9%	.029
Ever Received Medicaid Insurance	11.9%	30.6%	39.1%	<.001
Income (below 20k)	27.0%	40.5%	53.0%	<.001
MMSE	28.30 + 2.4	27.79 + 2.7	26.68 + 3.4	<.001[a–c]
Animal Naming	19.85 + 6.0	18.26 + 6.0	17.19 + 5.8	<.001[a,b]

No ADL Dependence at Baseline (N=883)

	Healthy (n=444)	Prefrail (n=373)	Frail (n=66)	P-Value*
BMI	28.66 + 5.8	31.12 + 7.0	33.50 + 9.7	<.001[a–c]
Smoking Status				.556
Non-Smoker	34.5%	32.2%	28.8%	
Past Smoker	34.2%	31.4%	34.8%	
Current Smoker	31.3%	34.8%	36.4%	
Falls Efficacy Scale	98.70 + 5.2	93.25 + 11.5	80.94 + 20.0	<.001[a–c]

*ANOVA for continuous outcomes and chi-square for categorical outcomes;

[a]Pre-frail versus healthy p<.05 by Tukey posthoc analysis for ANOVA;

[b]Frail versus healthy p<.05 by Tukey posthoc analysis for ANOVA;

[c]Frail versus pre-frail p<.05 by Tukey posthoc analysis for ANOVA.

Table 2

Baseline descriptive statistics for outcome measures among AAH participants with no ADL difficulty or no ADL dependence

	No ADL difficulty at Baseline		
Baseline (N max=703)	**Healthy (n=421)**	**Prefrail (n=263)**	**Frail (n=19)**
IADL difficulties (0–8); n=701	0.08 + 0.3	0.49 + 0.9	1.47 + 1.4
SPPB (0–12); n=650	9.26 + 2.3	8.30 + 3.0	6.75 + 2.8
Gait Speed (meters/second); n=368	0.84 + 0.2	0.79 + 0.2	0.74 + 0.2
Injurious Fall Past Year; n=703	3.6%	3.0%	5.3%
One-Leg Stand (0–30 seconds); n=612	22.17 + 10.3	18.62 + 11.8	12.25 + 11.9
Grip Strength (kg); n=659	38.98 + 13.3	32.98 + 10.8	28.67 + 10.8
9-Year Follow-Up (N max=423)	**Healthy (n=263)**	**Prefrail (n=153)**	**Frail (n=7)**
ADL difficulties (0–7); n=423	0.32 + 1.1	0.59 + 1.5	2.29 + 2.29
IADL difficulties (0–8); n=415	0.50 + 1.4	0.99 + 1.8	2.00 + 2.2
SPPB (0–12); n=349	8.83 + 2.4	8.08 + 2.8	5.83 + 3.2
Gait Speed (meters/second); n=334	0.84 + 0.3	0.81 + 0.3	0.73 + 0.2
Injurious Fall Past Year; n=423	4.6%	3.3%	14.3%
One-Leg Stand (0–30 seconds); n=328	18.21 + 11.1	13.38 + 11.8	15.60 + 15.1
Grip Strength (kg); n=364	34.69 + 11.9	29.90 + 11.6	23.33 + 8.8

	No ADL Dependence at Baseline		
Baseline (N max=883)	**Healthy (n=444)**	**Prefrail (n=373)**	**Frail (n=66)**
ADL difficulties (0–7); n=883	0.05 + 0.2	0.65 + 1.3	2.11 + 2.1
IADL difficulties (0–8); n=881	0.09 + 0.4	0.85 + 1.3	2.17 + 1.6
SPPB (0–12); n=805	9.25 + 2.2	7.70 + 3.2	5.32 + 3.3
Gait Speed (meters/second); n=449	0.84 + 0.2	0.77 + 0.2	0.69 + 0.2
Injurious Fall Past Year; n=883	3.6%	4.6%	9.1%
One-Leg Stand (0–30 seconds); n=732	22.22 + 10.3	17.93 + 11.7	13.09 + 11.8
Grip Strength (kg); n=814	38.76 + 13.2	32.43 + 11.2	31.90 + 13.9
9-Year Follow-Up (N max=528)	**Healthy (n=276)**	**Prefrail (n=225)**	**Frail (n=27)**
ADL difficulties (0–7); n=528	0.32 + 1.1	0.84 + 1.7	2.59 + 2.5
IADL difficulties (0–8); n=516	0.51 + 1.3	1.25 + 2.0	2.36 + 2.4
SPPB (0–12); n=431	8.77 + 2.4	7.6 + 3.1	4.14 + 3.6
Gait Speed (meters/second); n=406	0.83 + 0.3	0.78 + 0.3	0.63 + 0.2
Injurious Fall Past Year; n=528	4.4%	5.3%	3.7%
One-Leg Stand (0–30 seconds); n=391	18.07 + 11.1	13.05 + 11.6	15.49 + 11.2
Grip Strength (kg); n=448	34.30 + 11.9	29.80 + 11.1	27.28 + 8.8

Table 3

Cross-sectional and longitudinal associations for baseline prefrail and frail status with outcome measures among AAH participants

Cross-sectional Outcomes	Activities of Daily Living Status at Baseline			
	No ADL Difficulty (n=703)* Ordinary Least Squares Regression		No ADL Dependence (n=883)* Ordinary Least Squares Regression	
	Unstandardized Coefficients B (SE)	P-Value	Unstandardized Coefficients B (SE)	P-Value
IADLs				
Pre-Frail	0.42 (0.05)	<.001	0.77 (0.07)	<.001
Frail	1.38 (0.16)	<.001	2.08 (0.13)	<.001
SPPB				
Pre-Frail	−0.93 (0.21)	<.001	−1.54 (0.20)	<.001
Frail	−2.37 (0.64)	<.001	−3.89 (0.40)	<.001
Gait Speed				
Pre-Frail	−0.04 (0.03)	.11	−0.07 (0.02)	.003
Frail	−0.09 (0.07)	.21	−0.14 (0.05)	.002
1-Leg Stand				
Pre-Frail	−3.23 (0.89)	<.001	−3.97 (0.82)	<.001
Frail	−8.82 (2.73)	.001	−8.47 (1.79)	<.001
Grip Strength				
Pre-Frail	−3.11 (0.82)	<.001	−3.58 (0.74)	<.001
Frail	−6.28 (2.39)	.009	−4.13 (1.46)	.005
	Binary Logistic Regression		Binary Logistic Regression	
	Odds Ratio (95% CI)	P-Value	Odds Ratio (95% CI)	P-Value
Injurious Falls				
Pre-Frail	0.72 (0.30–1.73)	.834	1.14 (0.56–2.30)	.720
Frail	1.25 (0.15–10.19)	.732	2.35 (0.88–6.30)	.089

Longitudinal Outcomes (9-Years)	Activities of Daily Living Status at Baseline							
	No ADL Difficulty (N=423)				No ADL Dependence (N=528)			
	Ordinary Least Squares Regression Model 1a*		Ordinary Least Squares Regression Model 2a**		Ordinary Least Squares Regression Model 1b*		Ordinary Least Squares Regression Model 2b**	
	Unstandardized Coefficients B (SE)	P-Value	Unstandardized Coefficients B (SE)	P-Value	Unstandardized Coefficients B (SE)	P-Value	Unstandardized Coefficients B (SE)	P-Value
ADLs								
Pre-Frail	0.27 (0.13)	.041	-----	-----	0.53 (0.14)	<.001	0.36 (0.14)	.012
Frail	1.96 (0.50)	<.001			2.28 (0.30)	<.001	1.82 (0.32)	<.001
IADLs								
Pre-Frail	0.48 (0.16)	.003	0.23 (0.16)	.151	0.74 (0.16)	<.001	0.35 (0.16)	.029
Frail	1.46 (0.60)	.015	0.40 (0.60)	.508	1.84 (0.36)	<.001	0.99 (0.36)	.006
SPPB								
Pre-Frail	−0.72 (0.29)	.013	−0.47 (0.27)	.088	−1.09 (0.27)	<.001	−0.45 (0.26)	.089
Frail	−2.72 (1.04)	.009	−1.40 (0.97)	.151	−4.60 (0.60)	<.001	−2.66 (0.60)	<.001
Gait Speed								
Pre-Frail	−0.02 (0.03)	.449	0.04 (0.04)	.385	−0.05 (0.03)	.094	0.03 (0.04)	.506
Frail	−0.09 (0.12)	.439	−0.07 (0.13)	.606	−0.20 (0.07)	.004	−0.11 (0.11)	.297
1-Leg Stand								
Pre-Frail	−4.17 (1.30)	.001	−3.20 (1.20)	.008	−4.09 (1.15)	<.001	−3.27 (1.11)	.004
Frail	−0.75 (4.93)	.879	2.74 (4.42)	.536	−1.64 (3.36)	.626	0.58 (3.24)	.857
Grip Strength								
Pre-Frail	−2.21 (0.98)	.025	−0.65 (0.95)	.499	−1.63 (0.87)	.063	−0.21 (0.86)	.810
Frail	−6.25 (3.62)	.085	−3.67 (3.38)	.278	−3.61 (2.05)	.079	−1.55 (2.08)	.458
	Binary Logistic Regression		Binary Logistic Regression		Binary Logistic Regression		Binary Logistic Regression	
	Odds Ratio (95% CI)	P-Value	Odds Ratio (95% CI)	P-Value	Odds Ratio (95% CI)		Odds Ratio (95% CI)	P-Value
Injurious Falls								
Pre-Frail	0.60 (0.21–1.77)	.357	0.59 (0.20–1.75)	.344	1.10 (0.48–2.52)	.827	1.06 (0.46–2.45)	.894
Frail	3.31 (0.36–30.8)	.293	3.62 (0.39–34)	.260	0.72 (0.09–5.80)	.437	0.72 (0.09–5.84)	.758
Mortality								
Pre-Frail	1.69 (1.07–2.67)	.025	-----	-----	1.61 (1.06–2.44)	.027	-----	-----
Frail	3.64 (1.12–11.8)	.032			4.19 (2.10–8.35)	<.001		

*Models adjusted for age and sex;

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*** Models adjusted for age, sex, and baseline value of the outcome variable being examined.

Table 4

Individual components associations with cross-sectional outcomes among AAH participants with no ADL disability (difficulty or dependence criterion) at baseline

	No ADL Difficulty (N=703) Model 1a*		No ADL Dependence (n=883) Model 1b*	
Ordinary Least Squares Regression	**Unstandardized Coefficients B (SE)**	**P-Value**	**Unstandardized Coefficients B (SE)**	**P-Value**
IADL difficulties				
Fatigue	0.35 (0.08)	<.001	0.75 (0.10)	<.001
Resistance	0.93 (0.08)	<.001	1.35 (0.09)	<.001
Ambulation	1.18 (0.07)	<.001	1.65 (0.08)	<.001
Illnesses	0.33 (0.42)	.428	1.48 (0.35)	<.001
Weight Loss	−0.00 (0.07)	.996	−0.07 (0.10)	.481
SPPB				
Fatigue	−0.34 (0.30)	.261	−1.03 (0.28)	<.001
Resistance	−2.52 (0.30)	<.001	−3.11 (0.24)	<.001
Ambulation	−2.71 (0.30)	<.001	−3.22 (0.23)	<.001
Illnesses	0.02 (1.82)	.991	−4.35 (1.02)	<.001
Weight Loss	0.18 (0.26)	.503	0.12 (0.26)	.646
Gait Speed				
Fatigue	0.01 (0.04)	.696	−0.01 (0.03)	.690
Resistance	−0.13 (0.04)	.001	−0.14 (0.03)	<.001
Ambulation	−0.13 (0.04)	.002	−0.14 (0.03)	<.001
Illnesses	0.01 (0.17)	.953	−0.13 (0.12)	.250
Weight Loss	−0.01 (0.03)	.777	−0.01 (0.03)	.781
One-Leg Stand				
Fatigue	−1.09 (1.26)	.388	−1.83 (1.09)	.094
Resistance	−7.54 (1.43)	<.001	−7.10 (1.09)	<.001
Ambulation	−8.13 (1.44)	<.001	−7.30 (1.05)	<.001
Illnesses	0.95 (7.44)	.898	−0.22 (5.40)	.967
Weight Loss	−0.79 (1.09)	.471	−0.33 (1.01)	.742
Grip Strength				
Fatigue	−2.50 (1.15)	.030	−1.91 (0.96)	.048
Resistance	−4.30 (1.19)	<.001	−4.21 (0.90)	<.001
Ambulation	−3.23 (1.23)	.009	−2.50 (0.89)	.005
Illnesses	−6.92 (5.80)	.233	−9.17 (3.60)	.011
Weight Loss	−1.43 (1.01)	.156	−1.78 (0.90)	.049
Binary Logistic Regression	**Odds Ratio (95% CI)**	**P-Value**	**Odds Ratio (95% CI)**	**P-Value**
Injurious Falls				
Fatigue**	---	---	0.17 (0.02–1.29)	.086
Resistance	1.81 (0.65–5.05)	.257	2.40 (1.22–4.72)	.011
Ambulation	0.66 (0.15–2.87)	.574	1.84 (0.92–3.68)	.083
Illnesses**	---	---	4.82 (0.98–23.65)	.052

	No ADL Difficulty (N=703) Model 1a*		No ADL Dependence (n=883) Model 1b*	
Ordinary Least Squares Regression	**Unstandardized Coefficients B (SE)**	**P-Value**	**Unstandardized Coefficients B (SE)**	**P-Value**
Weight Loss	0.95 (0.34–2.61)	.914	0.89 (0.40–1.98)	.768

* Models adjusted for age and sex;

** The were no participants who had zero ADL difficulties and were positive for fatigue or illnesses on the FRAIL scale.

Table 5

Longitudinal association of FRAIL scale items with outcomes among AAH participants with no ADL disability at baseline or no ADL dependence at baseline

Longitudinal Outcomes (9-Years)	Activities of Daily Living Status at Baseline							
	No ADL Difficulty (N=423)				No ADL Dependence (N=528)			
	Ordinary Least Squares Regression Model 1a*		Ordinary Least Squares Regression Model 2a**		Ordinary Least Squares Regression Model 1b*		Ordinary Least Squares Regression Model 2b**	
	Unstandardized Coefficients B (SE)	P-Value	Unstandardized Coefficients B (SE)	P-Value	Unstandardized Coefficients B (SE)	P-Value	Unstandardized Coefficients B (SE)	P-Value
ADLs								
Fatigue	0.48 (0.19)	.012			0.59 (0.19)	.002	0.44 (0.18)	.016
Resistance	1.01 (0.22)	<.001			1.39 (0.17)	<.001	1.09 (0.19)	<.001
Ambulation	0.91 (0.22)	<.001	-----	-----	1.27 (0.17)	<.001	0.93 (0.20)	<.001
Illnesses	-----	-----			3.65 (0.90)	<.001	3.18 (0.87)	<.001
Weight Loss	−0.22 (0.17)	.183			−0.08 (0.17)	.664	−0.09 (0.17)	.608
IADLs								
Fatigue	0.50 (0.23)	.031	0.26 (0.22)	.249	0.56 (0.21)	.009	0.21 (0.20)	.292
Resistance	1.21 (0.26)	<.001	0.65 (0.27)	.016	1.40 (0.20)	<.001	0.78 (0.21)	<.001
Ambulation	1.35 (0.27)	<.001	0.57 (0.30)	.059	1.43 (0.19)	<.001	0.70 (0.22)	.002
Illnesses	-----	-----	-----	-----	4.69 (1.00)	<.001	3.91 (0.94)	<.001
Weight Loss	−0.15 (0.20)	.463	−0.16 (0.19)	.392	−0.05 (0.20)	.814	0.05 (0.18)	.772
SPPB								
Fatigue	−0.33 (0.42)	.435	−0.31 (0.39)	.432	−1.06 (0.39)	.008	−0.65 (0.36)	.071
Resistance	−3.03 (0.46)	<.001	−1.96 (0.46)	<.001	−3.39 (0.35)	<.001	−1.96 (0.36)	<.001
Ambulation	−2.24 (0.47)	<.001	−1.11 (0.48)	.021	−2.76 (0.33)	<.001	−1.35 (0.35)	<.001
Illnesses	-----	-----	-----	-----	−7.51 (2.03)	<.001	−2.66 (2.53)	.294
Weight Loss	0.21 (0.36)	.547	0.09 (0.33)	.796	0.19 (0.35)	.595	0.15 (0.31)	.623
Gait Speed								
Fatigue	−0.00 (0.05)	.959	−0.04 (0.06)	.517	−0.07 (0.04)	.079	−0.03 (0.05)	.624
Resistance	−0.17 (0.05)	.002	−0.13 (0.07)	.079	−0.15 (0.04)	<.001	−0.07 (0.06)	.241
Ambulation	−0.11 (0.05)	.042	−0.08 (0.08)	.311	−0.11 (0.04)	.002	−0.04 (0.05)	.473
Illnesses	-----	-----	-----	-----	−0.66 (0.26)	.013	-----	-----

Longitudinal Outcomes (9-Years)	Activities of Daily Living Status at Baseline							
	No ADL Difficulty (N=423)				No ADL Dependence (N=528)			
	Ordinary Least Squares Regression Model 1a*		Ordinary Least Squares Regression Model 2a**		Ordinary Least Squares Regression Model 1b*		Ordinary Least Squares Regression Model 2b**	
	Unstandardized Coefficients B (SE)	P-Value	Unstandardized Coefficients B (SE)	P-Value	Unstandardized Coefficients B (SE)	P-Value	Unstandardized Coefficients B (SE)	P-Value
Weight Loss	0.03 (0.04)	.377	0.07 (0.05)	.184	0.02 (0.03)	.486	0.06 (0.05)	.209
One-Leg Stand								
Fatigue	−1.83 (1.87)	.329	−1.39 (1.69)	.413	−2.78 (1.62)	.086	−1.83 (1.54)	.236
Resistance	−7.21 (2.33)	.002	−3.53 (2.25)	.118	−4.39 (1.73)	.012	−1.18 (1.72)	.492
Ambulation	−5.67 (2.29)	.014	−1.81 (2.23)	.419	−4.02 (1.54)	.009	−2.03 (1.57)	.197
Illnesses	-----	-----	-----	-----	-----	-----	-----	-----
Weight Loss	−2.06 (1.57)	.191	−2.48 (1.43)	.083	−1.63 (1.41)	.249	−2.36 (1.35)	.081
Grip Strength								
Fatigue	−1.70 (1.38)	.219	−0.43 (1.31)	.741	−1.29 (1.17)	.272	−0.25 (1.15)	.831
Resistance	−5.07 (1.63)	.002	−2.84 (1.58)	.074	−3.27 (1.14)	.004	−1.05 (1.16)	.363
Ambulation	−2.50 (1.68)	.138	−0.69 (1.62)	.671	−0.99 (1.09)	.361	0.20 (1.08)	.857
Illnesses	-----	-----	-----	-----	−7.24 (6.23)	.246	−14.85 (8.19)	.071
Weight Loss	−1.29 (1.21)	.286	−0.44 (1.13)	.696	−0.79 (1.06)	.460	0.42 (1.02)	.813
	Binary Logistic Regression Model 1a*		Binary Logistic Regression Model 2a**		Binary Logistic Regression Model 1b*		Binary Logistic Regression Model 2b**	
	Odds Ratio (95% CI)	P-Value	Odds Ratio (95% CI)	P-Value	Odds Ratio (95% CI)	P-Value	Odds Ratio (95% CI)	P-Value
Injurious Falls								
Fatigue	-----	-----	-----	-----	0.17 (0.02–1.29)	.086	0.18 (0.02–1.35)	.095
Resistance	1.17 (0.25–5.40)	.839	0.95 (0.22–4.98)	.952	1.11 (0.41–3.11)	.825	1.01 (0.36–2.85)	.992
Ambulation	3.10 (0.94–10.2)	.063	3.01 (0.90–10.0)	.072	2.03 (0.84–4.88)	.116	1.98 (0.81–4.79)	.132
Illnesses	-----	-----	-----	-----	-----	-----	-----	-----
Weight Loss	1.04 (0.33–3.29)	.952	1.04 (0.33–3.34)	.856	1.11 (0.43–2.89)	.827	1.11 (0.42–2.92)	.829
Mortality								
Fatigue	1.28 (0.68–2.41)	.449			1.41 (0.85–2.34)	.187		
Resistance	2.72 (1.53–4.85)	<.001	-----	-----	2.41 (1.56–3.74)	<.001	-----	-----
Ambulation	2.51 (1.39–4.56)	.002			2.11 (1.38–3.23)	<.001		

Longitudinal Outcomes (9-Years)	Activities of Daily Living Status at Baseline							
	No ADL Difficulty (N=423)				No ADL Dependence (N=528)			
	Ordinary Least Squares Regression Model 1a*		Ordinary Least Squares Regression Model 2a**		Ordinary Least Squares Regression Model 1b*		Ordinary Least Squares Regression Model 2b**	
	Unstandardized Coefficients B (SE)	P-Value	Unstandardized Coefficients B (SE)	P-Value	Unstandardized Coefficients B (SE)	P-Value	Unstandardized Coefficients B (SE)	P-Value
Illnesses	-----	-----			5.98 (1.30–27.6)	.022		
Weight Loss	1.04 (0.59–1.86)	.889			1.20 (0.73–1.96)	.481		

*Model adjusted for age and sex;

**Models adjusted for age, sex, and baseline value of the outcome variable being examined;

***The 9-year follow-up group did not have any continuing participants who had zero ADL difficulties and 5 or more illnesses at baseline; and there were no continuing participants who had zero ADL dependencies and 5 or more illness at baseline for gait speed (model 2b only), one-leg stand, and injurious falls.

Table 6

Descriptive statistics for hormones, cytokines, & vitamin D according to baseline FRAIL scale categorization among AAH participants with no ADL disability (difficulty or dependency criterion) at baseline

	No ADL Difficulty			
Baseline (N=239)	**Healthy (n=136)**	**Prefrail (n=95)**	**Frail (n=8)**	**P-Value**
sIL-6R (ng/mL)	61.55 + 24.23	59.72 + 22.12	48.63 + 11.26	.295
sIL (log10)	1.75 + 0.19	1.74 + 0.17	1.68 + 0.11	.498
sTNFR1 (ng/mL)	2.81 + 3.94	3.60 + 5.03	4.10 + 2.27	.323
sTNFR1 (log10)	0.38 + 0.18	0.46 + 0.23	0.56 + 0.22	<.001[a,b]
sTNFR2 (ng/mL)	7.13 + 9.51	8.76 + 14.12	6.96 + 1.93	.592
sTNFR2 (log 10)	0.78 + 0.20	0.83 + 0.24	0.82 + 0.12	.303
CRP (mg/L)	6.27 + 7.77	6.54 + 5.94	13.35 + 12.04	.026[b]
CRP (log10)	0.49 + 0.55	0.61 + 0.48	0.94 + 0.45	.022[b,c]
Adiponectin (ug/L)	8.00 + 5.39	7.85 + 5.33	6.24 + 2.45	.650
Adiponectin (log10)	0.81 + 0.29	0.82 + 0.26	0.77 + 0.17	.887
25(OH) vitamin D (ng/mL)	11.87 + 5.74	11.20 + 5.04	11.13 + 5.89	.647
25(OH) vitamin D (log10)	1.03 + 0.21	1.01 + 0.19	0.99 + 0.23	.741

	No ADL Dependence			
Baseline (N=317)	**Healthy (n=147)**	**Prefrail (n=142)**	**Frail (n=28)**	**P-Value**
sIL-6R (ng/mL)	61.86 + 23.83	60.17 + 23.51	53.39 + 20.12	.215
sIL (log10)	1.76 + 0.18	1.74 + 0.18	1.70 + 0.15	.327
sTNFR1 (ng/mL)	2.78 + 3.76	3.76 + 5.58	3.47 + 1.64	.189
sTNFR1 (log10)	0.38 + 0.18	0.46 + 0.22	0.50 + 0.18	<.001[a,b]
sTNFR2 (ng/mL)	7.20 + 9.13	8.95 + 13.63	7.78 + 5.49	.413
sTNFR2 (log 10)	0.79 + 0.20	0.84 + 0.24	0.83 + 0.20	.151
CRP (mg/L)	5.97 + 7.45	7.13 + 6.19	9.14 + 10.17	.078
CRP (log10)	0.49 + 0.54	0.67 + 0.46	0.69 + 0.54	.005[b]
Adiponectin (ug/L)	8.08 + 5.32	8.32 + 5.43	7.21 + 2.79	.590
Adiponectin (log10)	0.82 + 0.29	0.84 + 0.26	0.83 + 0.17	.750
25(OH) vitamin D (ng/mL)	12.12 + 6.17	11.56 + 5.36	12.07 + 5.66	.703
25(OH) vitamin D (log10)	1.03 + 0.21	1.02 + 0.20	1.03 + 0.21	.850

[a] Pre-frail versus healthy p<.05 by Tukey posthoc analysis for ANOVA;

[b] Frail versus healthy p<.05 by Tukey posthoc analysis for ANOVA;

[c] Frail versus pre-frail p<.05 by Tukey posthoc analysis for ANOVA;

Table 7

Cross-sectional associations for baseline prefrail and frail status with labs among AAH participants with no ADL disability at baseline or No ADL dependence at baseline

	No ADL Difficulty (N=239)		No ADL Dependence (N=317)	
Ordinary Least Squares Regression*	**Unstandardized Coefficients B (SE)**	**P-Value**	**Unstandardized Coefficients B (SE)**	**P-Value**
sIL-6R (log10)				
Pre-Frail	0.02 (0.02)	.337	0.02 (0.02)	.234
Frail	−0.02 (0.06)	.713	0.01 (0.03)	.772
sTNFR1 (log10)				
Pre-Frail	0.08 (0.03)	.003	0.08 (0.02)	<.001
Frail	0.16 (0.07)	.023	0.12 (0.04)	.005
sTNFR2 (log10)				
Pre-Frail	0.06 (0.03)	.029	0.07 (0.03)	.009
Frail	0.06 (0.08)	.444	0.08 (0.05)	.082
CRP (log10)				
Pre-Frail	0.08 (0.07)	.242	0.13 (0.06)	.024
Frail	0.39 (0.19)	.041	0.12 (0.10)	.244
Adiponectin (log10)				
Pre-Frail	−0.02 (0.04)	.573	0.00 (0.03)	.905
Frail	−0.10 (0.10)	.284	−0.04 (0.05)	.433
25(OH) vitamin D (log10)				
Pre-Frail	−0.01 (0.03)	.744	0.00 (0.02)	.959
Frail	−0.02 (0.07)	.741	0.02 (0.04)	.623

*All models adjusted for age and sex.