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Comparison of Two Frailty Indices in the Physicians' Health Study

Ariela R. Orkaby, MD^{a,*}, Tammy T. Hsieh, MD, MPH^a, John M. Gaziano, MD, MPH^{a,b}, Luc Djousse, MD, ScD^{a,b}, and Jane A. Driver, MD, MPH^{a,b}

^aDivision of Aging, Brigham and Women's Hospital, Harvard Medical School, 150 South Huntington St, Boston, MA 02130, USA

^bMassachusetts Veterans Epidemiology and Research Information Center (MAVERIC) and Geriatric Research (GRECC), 1620 Tremont St, Boston, MA, 02120

Abstract

Background—As the population ages it is important to identify frailty, a powerful predictor of morbidity and mortality, and often an important unmeasured confounder. We sought to develop a frailty index in the Physician's Health Study (PHS) and estimate the association with mortality.

Methods—Prospective cohort study. Annual questionnaire assessed mood, function and health status. Two frailty scores were compared – cumulative deficit frailty index (PHS FI) and modified Study of Osteoporotic Fracture (mSOF) frailty score. Endpoints committee confirmed mortality.

Results—12,180 male physicians 60 years were analyzed. Mean(SD) follow-up was 10(3) years, 2,168 deaths occurred. PHS FI identified 4,412 (36%) physicians robust, 5,305 (44%) pre-frail, and 2,463 (20%) frail, while mSOF identified 7323 (61%) robust, 3,505 (29%) pre-frail and 1,215 (10%) frail. Age-standardized rate of death was lower among subjects identified as robust using the PHS FI, 11/1000 person-years (PY) (95% Confidence Interval (CI): 9.5–11.9) compared to 14/1000PY (95% CI: 13.5–15.4) using mSOF [P-difference <0.001]. In the prefrail group, death rates were 16/1000PY in PHS FI and 21/1000PY in mSOF, [P-difference <0.001]. There was no difference in age-adjusted mortality rates in the frail group according to each definition (35 vs 33/1000PY). Survival analysis showed an increased risk of mortality in each frailty category using either definition, (log-rank $p < 0.001$).

Conclusion—The PHS FI outperformed mSOF in identifying risk of death particularly in robust and pre-frail categories. Similar indices can be created in existing datasets to identify frail individuals and where appropriate account for frailty, an often unmeasured confounder.

*Corresponding Author and Reprint Requests: Dr. Ariela Orkaby, Division of Aging, Brigham and Women's Hospital, One Brigham Circle, 1620 Tremont Street, 3rd floor, Boston, MA 02120 USA, aorkaby@partners.org, Phone: 617-525-7631; Fax: 617-525-7739.

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Keywords

Frailty; Frailty Index; Mortality; Epidemiology

1. INTRODUCTION¹

Frailty is often described as a state of depleted physiologic reserve or an accumulation of deficits.^{1, 2} Individuals identified as frail are at an increased risk for delirium, falls, functional disability, morbidity and death.^{2–5} Furthermore, frailty is an important confounder and outcome to consider in population-based studies.⁶ Models to identify frailty include Fried's frailty phenotype¹ and Rockwood's cumulative deficit model.⁷ The Fried phenotype includes five interrelated variables identifying physical frailty: unintentional weight loss, self-reported exhaustion, weakness, slow walking speed, and low physical activity. The Study of Osteoporotic fracture (SOF) validated a simplified version of Fried's phenotype using only three variables.^{5, 8} The Rockwood theory states that over time deficits accumulate in multiple health domains, such as function, cognition, and comorbidity, and these components can be used to develop a frailty index (FI) translating into a conceptually simple score.⁹ Both concepts of frailty have been shown to be highly predictive of poor clinical outcomes.²

There is no consensus, on how to best identify frailty for either clinical practice or research studies.² Currently, the most evidence-based approach to identify frailty is the resource-intensive comprehensive geriatric assessment.² In epidemiologic studies using previously collected data, the phenotype method of identifying frailty may not always be possible. Searle and colleagues have shown it is possible to utilize existing health data to create a frailty index based on the cumulative deficit theory using a standard procedure.¹⁰ Modifications made to the Fried physical phenotype model of frailty in the simplified SOF model may make this a practical tool as well.

Recently, large databases and clinical trials have begun to develop frailty indices based on the cumulative deficit model in an effort to define frailty in those cohorts.^{11–14} Thus, we used the Physicians' Health Study (PHS) to create a frailty index (FI) and evaluated its ability to predict mortality. Further, we sought to examine how a FI based on the cumulative deficit model compared to a phenotype definition of frailty.

¹Abbreviations:

ADL = Activities of Daily Living

FI = Frailty Index

mSOF = modified Study of Osteoporotic Fractures Frailty Index

PHS = Physicians' Health Study

PHS FI = Physicians' Health Study Frailty Index

SOF = Study of Osteoporotic Fractures

2. MATERIALS AND METHODS

2.1 Subjects

The Physicians' Health Study (PHS) was a double-blind, placebo-controlled, randomized trial that was conducted from 1982–1995 and enrolled 22 071 male physicians randomized to aspirin or placebo or beta carotene or placebo. A detailed description of PHS has been previously published.¹⁵ Briefly, the original PHS sent invitations to participate to all male physicians between 40–84 years old who lived in the United States and were registered with the American Medical Association. Physicians who did not respond, declined to participate, had a history of cardiovascular disease or cancer, or had a contraindication to taking aspirin or beta carotene were excluded.¹⁶ All participants provided written informed consent and the Institutional Review Board at Brigham and Women's Hospital approved the study.

At the completion of the trial, participants were invited to participate in an ongoing epidemiologic study with annual questionnaires. Questions regarding functional status, health status, and mood were included in the 1998 annual questionnaire. All participants 60 years at this questionnaire (n=14,435) were eligible for this current study. Participants who had left out the entire function or emotion sections were excluded as missing data could not be imputed.

2.2 PHS Frailty Index Score: Cumulative Deficit Model

Candidate variables were chosen based on the criteria defined by Searle et al.¹⁰ A variable was excluded if >10% of data was missing. Comorbidities covered a broad range of systems, including cardiovascular, endocrine, pulmonary, renal, vision and dental health. Mood was assessed using the Short Form Health Survey-36 (SF-36) with "feelings about life" questions, such as, "In the past 4 weeks... have you felt calm and peaceful?" General health status was assessed by the question "How is your health compared to your peers?" Social isolation was assessed with the question asking participants whether they had "someone to share confidences with." Change in weight was calculated by subtracting reported weight in 1998 from the year prior. Weight loss of >10 pounds was considered a deficit as recommended by Searle and colleagues.¹⁰ Regarding functional status, those who answered "no limitations" for vigorous activity ("running, lifting heavy objects, or participating in strenuous sports") but did not answer any other function questions were considered as "not impaired" for all function questions. Likewise, missing responses were imputed logically. For example, those who reported being able to walk a mile, but left responses regarding ability to walk a block or several blocks empty, were assumed to be unimpaired in those categories. After imputing using this logical approach, less than 3% of the cohort had missing data. As a result we chose to omit these participants.

Thirty-three variables, including domains of comorbidity, functional status and mood, were chosen for inclusion in the PHS FI. (Appendix A) To create the PHS FI score, each of the 33 variables was recoded to a maximum of one point. Binary variables were coded as 0 and 1 to indicate absence or presence. Variables with three responses were graded as 0, 0.5, and 1, with higher values indicating increased frailty. For the SF-36 questions assessing emotional well-being, responses were trichotomized to 0, 0.5, or 1 with higher values indicating poorer

mood.^{10,17} For the question on general health status the 5 responses were graded as 0, 0.25, 0.5, 0.75 and 1, with higher values indicating poorer rating of health.¹⁰ A frailty score was calculated for each individual in the dataset by dividing the numbers of accumulated deficits by the total number of possible deficits (33), resulting in a value between 0 and 1.¹⁸ Scores were categorized as robust ($0 < 0.1$), pre-frail ($0.1 < 0.21$) and frail (> 0.21) based on previously published cut-points.^{14, 19, 20}

2.3 Modified SOF Frailty Score: Phenotype Model

The SOF index includes three components: intentional or unintentional weight loss of $>5\%$ over the past year, inability to get up from a chair without using arms, and self-reported reduced energy level.⁵ Individuals are robust if none of the criteria are met, pre-frail if one criterion is present, and frail if two or more criteria are satisfied. Using data available in PHS, we created a modified version of the SOF (mSOF) frailty score. For weight loss we calculated the change in reported weight on annual questionnaires. The question “do you have difficulty with bending, kneeling, or stooping” was used as a proxy for difficulty with chair stands. Energy level was assessed by the question: “In the last year, have you experienced fatigue?”

2.4 Outcome

All-cause mortality was confirmed by an endpoints committee after review of medical records, death certificates and family/next of kin report. Details on mortality endpoint validation in the PHS have been published previously.^{21, 22} Follow-up for mortality continued through the end of 2012.

2.5 Statistical Analysis

To estimate internal consistency of the PHS FI, we analyzed responses to determine Cronbach’s alpha. We completed survival analysis and generated Kaplan Meier curves with hazard ratios based on each category of the PHS FI score.

Modified SOF scores were calculated, with individuals identified as robust, pre-frail, or frail. The ability of each index to identify robust, pre-frail, and frail individuals was examined using a weighted kappa. The ability of each index to predict mortality within each frailty group was evaluated using Kaplan Meier curves. We compared age-adjusted rates of death between robust, pre-frail, and frail subjects identified by PHS FI vs. mSOF method using direct standardization technique (where the entire PHS population served as standard and provided age distribution).

Using the trichotomized PHS FI score (robust, pre-frail, and frail) as the independent variable, we ran Cox proportional hazards regression on the average PHS FI score by age group category, i.e. 60–69, 70–79, 80 years. Results were adjusted for potential confounders, including age, smoking, alcohol consumption, current employment and marital status.

All analyses were performed using SAS, version 9.3 (SAS Institute, North Carolina). Significance level was set at $\alpha = 0.05$, p-values were two-tailed.

3. RESULTS

Data were available for 12,180 physicians to create the PHS FI. Standardized Cronbach's alpha for the PHS FI was 0.78, suggesting strong internal consistency of the index. The median PHS FI score was 0.13 (range 0.00–0.67), similar to that reported by other frailty indices.²³ The distribution of PHS FI scores is shown in Figure 1.

Complete data was available for 12,043 participants to calculate the mSOF frailty score. The PHS FI score identified 4412 (36.2%) physicians as robust, 5,305 (43.6%) as pre-frail, and 2,463 (20.2%) as frail, while the mSOF frailty score identified 7,323 (60.8%) physicians as robust, 3,505 (29.1%) as pre-frail, and 1,215 (10.1%) as frail.

Modifications to the phenotype definition can change the distribution of participants who are identified as frail.²⁴ We compared the proportion of individuals with deficits according to mSOF in PHS and the original SOF criteria.⁵ In SOF, 15% reported unintentional weight loss, inability to rise from chair was reported in 12% and 43% reported fatigue. In PHS the distribution for weight loss was 7.4%, difficulty with bending 25.6% and fatigue 17.2%.

Median age at baseline was 69.4 (range 60–101) years old. Participants who were categorized as frail were older, more likely to be retired, current or former smokers, and divorced or widowed. Robust participants were more likely to consume alcohol more frequently. Baseline characteristics for participants stratified by PHS FI category and mSOF frail score are shown in Table 1. During the mean (SD) follow-up of 9.7 (± 3.0) years, 2,168 deaths occurred.

There was poor agreement between the PHS FI score and mSOF frailty score, with a weighted Kappa of 0.34.

The age-standardized rate of death was lower among subjects identified as robust using the PHS FI score: 11 deaths per 1000 person-years (PY) (95% Confidence Interval (CI): 9.5–11.9) compared to 14 deaths per 1000PY (95% CI: 13.5–15.4) in participants identified as robust using the mSOF frailty score (P-for-difference < 0.001), Figure 2. Corresponding rates were 16 (95% CI: 15.1–17.2) and 21 (95% CI: 19.6–22.6) for subjects identified as pre-frail by PHS and mSOF, respectively (P-for-difference < 0.001). There was no difference in age-standardized death rates among frail subjects when both methods were contrasted (Figure 2). We compared the PHS FI score and mSOF frailty score in specific age categories and obtained rate ratios for mortality stratified by age group (Table 2).

Kaplan Meier survival curves showed a significantly increased risk of mortality by frailty category using either definition of frailty (Figure 3), and remained significant for both scores after adjusting for age categories, (log-rank $p < 0.001$) (not shown). There was virtually no overlap between the survival curves for the three frailty categories in either the unadjusted or adjusted curves suggesting heterogeneity between each category.

Crude Cox Proportional Hazards model for the PHS FI score showed that participants categorized as pre-frail had an increased relative risk of mortality, with a hazard ratio (HR) of 1.98 (95% CI: 1.76–2.23), while those categorized as frail had a HR of 5.71 (95% CI:

5.07–6.43), compared to robust participants. Similarly, using the mSOF frailty score those identified as pre-frail had an increased relative risk of mortality, HR 1.80 (95% CI: 1.64–1.98), while those categorized as frail had a HR of 3.63 (95% CI: 3.24–4.07). Multivariable models adjusting for age, smoking, alcohol intake, and employment attenuated the results for all-cause mortality, although they remained statistically significant. Using the PHS FI score, HR for mortality in the pre-frail group was 1.48 (95% CI: 1.31–1.67) and frail was 3.15 (95% CI: 2.77–3.57), while using the mSOF score HR for mortality in the pre-frail group was 1.45 (95% CI: 1.31–1.60) and frail was 2.30 (95% CI: 2.04–2.60).

4. DISCUSSION

We identified frail and pre-frail individuals in the existing PHS dataset, using established approaches derived from two different theories of frailty. The PHS FI score, based on the cumulative deficit theory, was better able to discriminate those at risk of death compared to the phenotype-based mSOF frailty score. This was particularly evident in the ability to identify mortality among robust and pre-frail participants.

Our data suggests that while both the PHS FI score and mSOF frailty score were able to identify broad groups of robust, pre-frail, and frail individuals, each method identified different groups of people, indicated by the low kappa. Although both scores identified individuals at risk of death, compared to the PHS FI, the mSOF appeared to misclassify more individuals as robust and pre-frail, across all age groups. This may have been due to constraints within the available data; for example, we could not directly measure strength in our pre-collected dataset and relied on a proxy instead. This is also reflected in the different proportions of individuals with mSOF deficits compared to the original SOF frailty definition. SOF was first derived in a cohort of 6701 women while PHS included only male physicians. In a cohort of 765 community dwelling individuals⁸ of which 36% were male, the distribution of SOF deficits was closer to that of PHS, with 7.4% of participants reporting unintentional weight loss, 11.4% an inability to rise from a chair, and 8.8% reduced energy.

Differences in the ability of the cumulative deficit and phenotypic score to identify frailty have been noted previously by other investigators.^{23, 25, 26} It has also been shown that the cumulative deficit model of determining frailty performs better in predicting outcomes such as mortality compared to the 5 items suggested in the Fried phenotype model.^{13, 27} In our study this is particularly evident in the robust and pre-frail categories where the mSOF misclassified significantly more individuals at risk of death across all age categories. This is in part because each model was developed from a different theory of frailty and as such, is expected to behave differently, given the data available. As a result, the cumulative deficit model is a better tool for defining frailty in this previously defined dataset. Furthermore, as the PHS FI incorporates multiple domains and components compared to the relatively simple SOF, it is expected that the FI would better discriminate between robust, pre-frail and frail individuals.

Frailty may be an important unmeasured confounder that should be taken into consideration and/or adjusted for in epidemiologic studies of aging.^{28, 29} The aging population has a

widely heterogeneous health status,³⁰ and markers of frailty may be one way to identify this diversity. Future epidemiologic studies examining outcomes in older adults should consider frailty as a confounder or a marker for competing risks and utilize methods such as a FI to adjust for this heterogeneity.

Strengths of our study include the large dataset and long-term follow up. The PHS uses well-validated end points, allowing good confidence in examining mortality as an outcome for our FI. Furthermore, there was enough variety of questions in the PHS questionnaires to capture multiple domains necessary to create a PHS FI. Many of the FI publications to date originated in Canada and Europe. Our study adds to the literature as it examines a large, well-defined prospective cohort of participants in the United States. Future work done in PHS to advance the science of aging can include frailty as a confounder, predictor or outcome, as we have defined it in this paper. Our findings may be limited in generalizability because only male physicians who were relatively healthy at baseline were recruited. However, while these participants may differ from the general public in their behaviors and lifestyles, our results indicated similar rates of frailty and pre-frailty, with a similar distribution of frailty in the PHS cohort compared to previously published work using the Rockwood method.^{10, 14, 33} Finally, in attempting to use the phenotypic definition of frailty in this existing dataset, it was necessary to modify the SOF by using bending as a proxy for chair stands and a question regarding fatigue as a proxy for “feeling full of energy.” This may have resulted in misclassification and may have introduced bias.²⁴

In summary, we were able to identify frail individuals in an existing database, using two theories of frailty. The cumulative deficit model outperformed the phenotype model in its ability to predict mortality amongst those identified as either robust or pre-frail. Researchers are encouraged to use similar methods in clinical and epidemiological research of older adults, in order to both identify frail individuals and adjust for frailty.

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Appendix A. Frailty Index Variables and Scoring for the Physicians' Health Study Frailty Index

List of 33 Variables Included	Scoring
Does your health limit moderate activity	Limited a lot = 1, Limited a little = 0.5, Not limited at all = 0
Does your health limit walking blocks	Limited a lot = 1, Limited a little = 0.5, Not limited at all = 0
Does your health limit walking one block	Limited a lot = 1, Limited a little = 0.5, Not limited at all = 0
Does your health limit bending	Limited a lot = 1, Limited a little = 0.5, Not limited at all = 0
Does your health limit taking several flights of stairs	Limited a lot = 1, Limited a little = 0.5, Not limited at all = 0
Does your health limit taking one flight of stairs	Limited a lot = 1, Limited a little = 0.5, Not limited at all = 0
Does your health limit buying groceries	Limited a lot = 1, Limited a little = 0.5, Not limited at all = 0
Does your health limit bathing	Limited a lot = 1, Limited a little = 0.5, Not limited at all = 0
In the last month how often have you felt nervous	All the time = 1, Most of the time = 1, Good bit of time = 1, Some of time = 0.5, Little of time = 0.5, None of time = 0
In the last month how often have you felt down in the dumps	All the time = 1, Most of the time = 1, Good bit of time = 1, Some of time = 0.5, Little of time = 0.5, None of time = 0
In the last month how often have you felt blue	All the time = 1, Most of the time = 1, Good bit of time = 1, Some of time = 0.5, Little of time = 0.5, None of time = 0

List of 33 Variables Included	Scoring
In the last month how often have you felt calm	All the time =0, Most of the time =0, Good bit of time =0, Some of time =0.5, Little of time =0.5, None of time = 1
In the last month how often have you felt happy	All the time =0, Most of the time =0, Good bit of time =0, Some of time =0.5, Little of time =0.5, None of time = 1
How would you rate your general health compared to your peers	Poor = 1, Fair = 0.75, Good = 0.5, Very good = 0.25, Excellent = 0
Have a confidant to speak with	Yes =0, No = 1
Exercise at least once a week	Yes =0, No = 1
Diabetes mellitus	Yes = 1, No = 0
Atrial fibrillation	Yes = 1, No = 0
Osteoporosis	Yes = 1, No = 0
Arthritis	Yes = 1, No = 0
Hypertension	Yes = 1, No = 0
Congestive Heart Failure	Yes = 1, No = 0
Intermittent claudication	Yes = 1, No = 0
Depression	Yes = 1, No = 0
Myocardial infarction	Yes = 1, No = 0
Cancer	Yes = 1, No = 0
Renal or liver disease	Yes = 1, No = 0
Stroke or Transient Ischemic Attack	Yes = 1, No = 0
Weight change ≥ 10 pounds	Yes = 1, No = 0
BMI < 18.5 or ≥ 30	Yes = 1, No = 0
Lung disease (COPD or asthma)	Yes = 1, No = 0
Dental problem Periodontal disease, lost teeth	Yes = 1, No = 0
Vision problem Cataracts, cataract surgery, macular degeneration, glaucoma	Yes = 1, No = 0

Abbreviations: BMI = Body Mass Index (kg/m^2); COPD = Chronic Obstructive Pulmonary Disease

Figure 1.
Distribution of the Frailty Index in the Physicians' Health Study

Figure 2.
Age-standardized Mortality Rates and 95% Confidence Intervals Per 1000 Person-years
Within each Frailty Category as Identified by Each Frailty Score

Panel A. PHS FI

Panel B. mSOF

Figure 3.
Kaplan Meier Curves Using the Physicians' Health Study Frailty Index Score and the
Modified Study of Osteoporotic Fractures Frailty Score

Table 1

Baseline Characteristics of the 12,180 Physicians' Health Study Participants by Frailty Status as Identified by the Cumulative Deficit Frailty Index and Modified Phenotype SOF Frailty Score

	Robust		Pre-frail		Frail	
	PHS FI n=4,412	mSOF ^a n=7,323	FI n=5,305	mSOF ^a n=3,505	FI n=2,463	mSOF ^a n=1,215
Age (mean(SD))	68.0(5.7)	69.3(6.5)	70.7(6.9)	71.4(7.3)	74.3(8.0)	74.3(7.9)
Currently Employed^b (%)	60.8	56.8	51.2	47	36.6	35.3
Smoking status^c (%)						
• Current	2.1	3	3.6	4.3	6.5	5.6
• Previous	42.6	46.3	49.6	50.5	55.5	53.3
• Never	55.3	50.7	46.8	45.2	38	41.6
Alcohol consumption^d (%)						
• Daily	41.7	42.4	43.1	41.3	38.8	38.6
• Weekly	38.5	37	35.8	37.4	36.9	36.3
• Monthly	3.3	4	4.2	3.7	4.8	5
• Never	16.4	16.6	16.8	17.5	19.5	20.1
Marital status^e (%)						
• Married	92.8	91.8	91.3	90.6	87.8	89.2
• Divorced/separated	4.4	4.7	4.8	4.9	5.5	4.9
• Widowed	1.6	2.5	2.5	2.9	4.7	4.2
• Never married	1.3	1.4	1.4	1.6	2	1.7

Abbreviations: PHS FI = Physicians' Health Study Frailty Index, mSOF = Modified Study of Osteoporotic Fractures Frailty Score, SD = Standard Deviation

^aTotal n for the mSOF frail score was 12,043 as 137 participants had missing data

^bData missing for 40 individuals in the PHS FI, and 40 in the mSOF

^cData missing for 6 individuals in the PHS FI and 6 in the mSOF

^dData missing for 131 individuals in the PHS FI and 129 in the mSOF

Data missing for 90 individuals in the PHS FI and 89 in the mSOF

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Table 2
Rate ratios for mortality according to each frailty definition stratified by age category

Frailty category	Age category	Mortality rate/1000 person years		Rate ratio	95% CI
		PHS FI	mSOF		
Robust	60–69	4.93	5.87	0.84	0.69–1.02
Robust	70–79	14.28	18.93	0.75	0.64–0.89
Robust	80+	33.69	51.9	0.65	0.47–0.90
Prefrail	60–69	6.60	8.58	0.77	0.62–0.96
Prefrail	70–79	20.83	26.51	0.79	0.68–0.91
Prefrail	80+	58.95	80.27	0.73	0.62–0.87
Frail	60–69	17.42	14.75	1.18	0.86–1.62
Frail	70–79	44.77	41.66	1.07	0.90–1.29
Frail	80+	109.63	120.02	0.91	0.77–1.08