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Comparison of two frailty indices in the physicians' health study

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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, 2168 deaths occurred. PHS FI identified 4412 (36%) physicians robust, 5305 (44%) pre-frail, and 2463 (20%) frail, while mSOF identified 7323 (61%) robust, 3505 (29%) pre-frail and 1215 (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.

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1. Introduction

Frailty is often described as a state of depleted physiologic reserve or an accumulation of deficits (Fried, Tangen, & Walston, 2001; Clegg, Young, Iliffe, Rikkert, & Rockwood, 2013). Individuals identified as frail are at an increased risk for delirium, falls, functional disability, morbidity and death (Clegg et al., 2013; Morley, Vellas, & van Kan, 2013; Mitnitski, Graham, Mogilner, & Rockwood, 2002; Ensrud, Ewing, & Taylor, 2008). Furthermore, frailty is an important confounder and outcome to consider in population-based studies (Kim & Schneeweiss, 2014). Models to identify frailty include Fried's frailty phenotype (Fried et al., 2001) and Rockwood's cumulative deficit model (Rockwood & Mitnitski, 2007). 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 (Ensrud et al., 2008; Kiely, Cupples, & Lipsitz, 2009). 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 (Rockwood, Mitnitski, Song, Steen, & Skoog, 2006). Both concepts of frailty have been shown to be highly predictive of poor clinical outcomes (Clegg et al., 2013).

There is no consensus, on how to best identify frailty for either clinical practice or research studies (Clegg et al., 2013). Currently, the most evidence-based approach to identify frailty is the resource-intensive comprehensive geriatric assessment (Clegg et al., 2013). In epidemiologic studies using previously collected

Abbreviations: 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.

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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 (Searle, Mitnitski, Gahbauer, Gill, & Rockwood, 2008). 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 (Warwick, Falaschetti, & Rockwood, 2015; Clegg, Bates, & Young, 2016; Blodgett, Theou, Kirkland, Andreou, & Rockwood, 2015; Pajewski, Williamson, & Applegate, 2016). 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.

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 to 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 (Steering Committee of the Physicians' Health Study Research Group, 1989). Briefly, the original PHS sent invitations to participate to all male physicians between 40 and 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 (Cook, Le, Manson, Buring, & Hennekens, 2000). 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 $\geq$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. (2008). 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 et al. (2008). 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 (Searle et al., 2008; Sheppard, Faul, & Luta, 2014). 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 (Searle et al., 2008). 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 (Mitnitski, Song, & Skoog, 2005). Scores were categorized as robust (0– $<$ 0.1), pre-frail ($\geq$0.1– $<$ 0.21) and frail ($\geq$0.21) based on previously published cut-points (Pajewski et al., 2016; Rockwood, Song, & Mitnitski, 2011; Hoover, Rotermann, Sanmartin, & Bernier, 2013).

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 (Ensrud et al., 2008). 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 (Djousse & Gaziano, 2008; Albert, Campos, & Stampfer, 2002). 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).