The association between frailty and perceived physical and mental fatigability

The Long Life Family Study

Schumacher, Benjamin T.; Kehler, Dustin S.; Kulminski, Alexander M.; Qiao, Yujia; Andersen, Stacy L.; Gmelin, Theresa; Christensen, Kaare; Wojczynski, Mary K.; Theou, Olga; Rockwood, Kenneth; Newman, Anne B.; Glynn, Nancy W.

Published in:
Journal of the American Geriatrics Society

DOI:
10.1111/jgs.18624

Publication date:
2024

Document version:
Accepted manuscript

Citation for pulished version (APA):
Schumacher, B. T., Kehler, D. S., Kulminski, A. M., Qiao, Y., Andersen, S. L., Gmelin, T., Christensen, K., Wojczynski, M. K., Theou, O., Rockwood, K., Newman, A. B., & Glynn, N. W. (2024). The association between frailty and perceived physical and mental fatigability: The Long Life Family Study. *Journal of the American Geriatrics Society*, *72*(1), 219-225. https://doi.org/10.1111/jgs.18624

Schumacher Benjamin (Orcid ID: 0000-0002-3099-3387)
Andersen Stacy L. (Orcid ID: 0000-0002-2442-6386)
Theou Olga (Orcid ID: 0000-0001-6460-782X)
Glynn Nancy W (Orcid ID: 0000-0003-2265-0162)

Title: The Association between Frailty and Perceived Physical and Mental Fatigability: The Long Life Family Study

Running Title: Frailty and Perceived Fatigability

Benjamin T. Schumacher, PhD[a], Dustin S. Kehler, PhD[b], Alexander M. Kulminski, PhD[c], Yujia (Susanna) Qiao, PhD[a], Stacy L. Andersen, PhD[d], Theresa Gmelin, MSW, MPH[a], Kaare Christensen, MD, PhD, DMSc[e,f], Mary K. Wojczynski, PhD[g], Olga Theou, PhD[b,h], Kenneth Rockwood, MD[h], Anne B. Newman, MD[a], and Nancy W. Glynn, PhD[a]; for the LLFS Research Group

a) Department of Epidemiology, School of Public Health, University of Pittsburgh, PA, USA
b) School of Physiotherapy, Dalhousie University, Halifax, Nova Scotia, Canada
c) Biodemography of Aging Research Unit, Social Science Research Institute, Duke University, Durham, NC, USA
d) Department of Medicine, Boston University Chobanian & Avedisian School of Medicine, Boston, MA, USA
e) Danish Aging Research Center, University of Southern Denmark
f) Department of Clinical Biochemistry and Department of Clinical Genetics, Odense University Hospital, Odense, Denmark
g) School of Medicine, Washington University St. Louis, MO, USA
h) Division of Geriatric Medicine, Department of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada

Funding Information:

This work was supported by the National Institutes of Health/National Institute on Aging (U01 AG023712, U01 AG023744, U01 AG023746, U01 AG023749, U01 AG023755, and P01 AG08761). Additionally, the Claude D. Pepper Older Americans Independence Center, Research Registry and Developmental Pilot Grant (NIH P30 AG024827), and the Intramural Research Program, National Institute on Aging supported N.W.G to develop the Pittsburgh Fatigability Scale. The Epidemiology of Aging training grant at the University of Pittsburgh (National Institute on Aging T32 AG000181) supported B.T.S and T.G.

Corresponding Author:

Benjamin T. Schumacher, PhD, MPH
bts70@pitt.edu; Twitter: @_BenSchumacher
130 North Bellefield Avenue Suite 300, Pittsburgh, PA 15213

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jgs.18624

Word Count and Data Elements:

Abstract: 296 words

Main text: 1,998 words

3 data elements (and 3 more as supplemental)

Key Points:

- Frailty, as measured by an 83-item frailty index, is associated with perceived physical and mental fatigability severity in older adults.

- As older adults will adjust their activity levels to minimize their feelings of fatigue (i.e., self-pace), including perceived fatigability, in lieu of fatigue, alleviates some of the ambiguity in frailty research as its standardized assessment offers a more sensitive measure of the degree to which fatigue contributes to frailty.

Why does this matter?

Replacing the various measures of fatigue with the standardized, validated measure of perceived fatigability may provide a more precise and sensitive measurement of frailty. Understanding this association may enhance providers' ability to identify at-risk older adults, further their understanding of the underlying mechanisms of the disablement pathway and may inform the development of interventions to mitigate the risks associated with greater frailty and perceived fatigability.

ABSTRACT

Background: Higher levels of frailty, quantified by a frailty index (FI), may be linked to fatigue severity as tasks become more physically and mentally demanding. Fatigue, a component of frailty research, has been ambiguous and inconsistent in its operationalization. Fatigability—the quantification of vulnerability to fatigue in relation to specific intensity and duration of activities—offers a more sensitive and standardized approach, though the relationship between frailty and fatigability has not been assessed. **Methods:** Using cross-sectional data from the Long Life Family Study at Visit 2 (2014-2017; n=2,524; mean age ± standard deviation (SD) 71.4±11.2 years; 55% women; 99% White), we examined associations between an 83-item FI after excluding fatigue items (ratio of number of health problems reported (numerator) out of the total assessed (denominator); higher ratio=greater frailty) and perceived physical and mental fatigability using the Pittsburgh Fatigability Scale (PFS) (range 0-50; higher scores=greater fatigability). **Results:** Participants had mean (± standard deviation) FI (0.08±0.06; observed range: 0.0–0.43), PFS Physical (13.7±9.6; 39.5% more severe, ≥15), and PFS Mental (7.9±8.9; 22.8% more severe, ≥13). The prevalence of more severe physical and mental fatigability was higher across FI quartiles. In mixed effects models accounting for family structure, a clinically meaningful 3%-higher FI was associated with 1.9 points higher PFS Physical scores (95% confidence interval (CI) 1.7–2.1) and 1.7 points higher PFS Mental scores (95% CI 1.5-1.9) after adjusting for covariates. **Conclusions:** Frailty was associated with perceived physical and mental fatigability severity. Understanding this association may support the development of interventions to mitigate the risks associated with greater frailty and perceived fatigability. Including measurements of perceived fatigability, in lieu of fatigue, in frailty indices has the

potential to alleviate the inconsistencies and ambiguity surrounding the operationalization of fatigue and provide a more precise and sensitive measurement of frailty.

Key words: fatigue, risk factor, epidemiology

INTRODUCTION

Frailty is a biologic consequence of the decline of multiple physiologic systems that contribute to the accumulation of consequential health issues over a lifetime, which, in turn, increase vulnerability to additional adverse health outcomes.[1,2] As there are multiple operational definitions of frailty, estimating prevalence can be challenging[3], though a recent meta-analysis of 62 countries estimated the prevalence of frailty to be 16% in adults between 60 and 69 years of age (95% confidence interval (CI) 15–17%).[4] Regardless of the definition and measurement method, the prevalence of frailty increases with age to 51% in adults above 90 years (95% CI 38–63%).[4] Independent of age, frailty has been consistently associated with increased rates of hospitalization, falls, poor quality of life, and mortality in community-dwelling older adults.[3,5]

When measuring levels of frailty, the two most common methods are the frailty index (FI) and frailty phenotype. The FI is a ratio of a participant's reported health deficits to the total number of deficits considered, with a higher ratio indicating higher levels of frailty.[1] The frailty phenotype has been defined by the presence of three or more of the following five criteria: weight loss, muscle weakness, slow walking speed, low level of physical activity (PA), and fatigue.[6] In both approaches, the operationalization of fatigue measurement has not been clearly defined and varies widely across the literature, including subjective symptoms related to fatigue (exhaustion, anergia, etc.), further contributing to poor clinical consensus.[6–9] A systematic review of 158 frailty scales identified 120 unique fatigue items.[10] While fatigue has a variety of etiologies and mechanistic pathways, the heterogeneity further complicates research on fatigue as a frailty component.[10]

The inclusion of perceived fatigability, in lieu of fatigue, may alleviate some of this ambiguity in frailty research as fatigability has a standardized, validated assessment.[11] Perceived

fatigability is the quantification of vulnerability to fatigue in relation to specific intensity and duration of activities.[12,13] As older adults may reduce their intensity or duration of activities to avoid feelings of fatigue (i.e. self-pacing), perceived fatigability may yield a more sensitive measure of the degree to which fatigue contributes to frailty.[14] Varying domains of aging research have employed fatigability measures and have shown that participants with greater fatigability also had increased depressive symptomology, cardiovascular disease risk, physical and cognitive decline, and all-cause mortality.[12,14–17] While the unique concepts of frailty and fatigability share similarities, such as performance decline across higher intensity activities, the association between frailty and fatigability has not yet been quantified. Understanding this association may inform whether the inclusion of perceived fatigability, in lieu of fatigue, in frailty research might reduce the ambiguity surrounding the measurement of fatigue. Further, understanding this association may support clinicians in the development of targeted interventions to mitigate the risks associated with both frailty and fatigability.

The objective of this study was to determine if frailty, as measured by an 83-item frailty index (FI) without fatigue items, was associated with perceived physical and mental fatigability. As greater perceived physical fatigability reflects worse general health status and physical function[14], we hypothesized that the association between FI and perceived physical fatigability would be stronger than the association with perceived mental fatigability.

METHODS

Study Participants

The Long Life Family Study (LLFS) is a multicenter, prospective cohort study of families from four field centers (University of Pittsburgh, Columbia University, Boston University, and the University of Southern Denmark) to characterize exceptional longevity and healthy aging. Details about eligibility, enrollment, and data collection have been published

elsewhere.[18–20] Briefly, potential U.S. probands were identified from 2006–2009 from Centers for Medicare and Medicaid Services. The University of Southern Denmark queried people more than 90 years of age in the Danish National Register of Persons. Family Longevity Selection Scores (FLoSS)[20] were computed based on specific survival probabilities with weights for older living siblings. Families were eligible if their FLoSS was ≥7, and the proband, at least one living sibling, and at least one living offspring provided informed consent. Data for the present study were derived from Visit 2, which was conducted from 2014–2017 (N = 2,909). The LLFS protocol was approved by the institutional review boards at each field center.

Measures

Exposure: Frailty Index

Levels of frailty were quantified with a frailty index (FI). We began with the 85 deficits used by Kulminski et al.[21] in prior LLFS analyses that covered multiple age-related domains, including impaired hearing and/or vision, anxiety, skin conditions, arthritis, to history of stroke and myocardial infarction. We removed two items directly related to fatigue ("I felt that everything I did was an effort" and "I could not get going"), and the resulting 83-items were used to calculate the FI (Supplemental Table 1). Analyses employing these indices have yielded consistent associations despite variation in the number and type of deficits assessed[2,22–24], including analyses in the LLFS.[21] As the clinically meaningful annual increase in FI is 3%, regression models will assess the association of 3% higher FI with the outcomes.[25]

Outcome: Perceived Fatigability from the Pittsburgh Fatigability Scale

The Pittsburgh Fatigability Scale (PFS)[11,26] measures both perceived physical fatigability, which focuses on capacity and effort, and perceived mental fatigability, which focuses on mental tiredness (e.g., psychological, emotional, and cognitive), in separate subscales. For both

subscales, participants rated on a scale from 0 (no fatigue) to 5 (extreme fatigue) the level of fatigue they imagined or expected they would experience after completing 10 different activities of various duration and intensities. Responses to items on each subscale were then summed to derive PFS Physical and PFS Mental scores, both ranging from 0 to 50, with higher scores indicating greater perceived fatigability. The prevalence of more severe perceived fatigability was calculated for PFS Physical (≥15) and PFS Mental (≥13) and scatterplots grouped PFS Physical and Mental scores into severity strata.[15] PFS scores were imputed if 1-3 items were missing (n = 95 PFS Physical and n = 91 PFS Mental).[27]

Covariates

The following covariates measured at Visit 2 are known to be associated with both frailty (Table 1) and fatigability[14]: self-reported age (continuous), sex, educational attainment (less than high school (HS), HS graduate, some college/vocational training, college graduate, or graduate school), smoking status (current, former, never), and current marital status (married, unmarried). Body mass index (BMI) was calculated as weight (kilograms) / height^2 (meters).

Statistical Analysis

The analytic sample for the present study was derived cross-sectionally from LLFS Visit 2 (n = 2,909). Of these participants, 275 were excluded for missing PFS scores and an additional 110 were excluded for missing more than 20% of the variables included in the calculation of the FI, yielding a final analytic sample of 2,524 participants. The excluded participants were older than the included participants (79.4 vs. 71.4 years) and had a higher proportion of history of myocardial infarction (8.1% vs. 4.3%), and stroke (8.6 vs. 3.7%) (all $p < 0.05$).

Covariates were compared across quartiles of FI (Quartile 1 (Q1): <0.037 (i.e.<3.7%), Q2: ≥0.037 to ≤0.065, Q3: >0.065 to ≤0.105, and Q4: >0.105). Scatterplots and correlations were

used to visually assess the relationship between FI and perceived fatigability (Figure 1 and Supplemental Figure 1).

Next, sequentially adjusted multivariable linear mixed models with restricted maximum likelihood estimation were used to estimate the association between a 3%-higher FI and PFS Physical and Mental scores. To account for the family-clustered design of the LLFS, all models specified the within-family structure as a random effect with an unstructured correlation matrix. Model 1 was adjusted for age, sex, and field center. Model 2 was further adjusted for BMI, smoking status, education, and marital status.

All analyses were conducted in R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

Sensitivity Analysis

In order to determine whether the inclusion of activities of daily living (ADLs) affect the relation, we also assessed a 72-item FI that excluded activities of daily living (ADLs). Deficits considered in the 72-item FI are listed in Supplemental Table 1. The same analytic approach for the 83-item FI was applied.

RESULTS

The participants were 55% women, 99.4% white, 70.1% currently married, 55% college educated or higher, and had mean (± standard deviation) FI (0.08±0.06; observed range: 0.0–0.43), PFS Physical (13.7±9.6), and PFS Mental (7.9±8.9) (Table 1). The prevalence of more severe perceived physical fatigability (PFS Physical ≥ 15) was 15.9% and 73.5% in the lowest and highest quartile of FI, respectively. More severe mental fatigability (PFS Mental ≥ 13) prevalence in the same quartiles was 7.8% and 49%. Mean age and BMI were 71.4±11.2 years and 27.5±5.1 kg/m^2, respectively.

PFS Physical and Mental scores were 1.9 points (95% CI 1.7-2.1) and 1.7 points higher (95% CI 1.5-1.9) for every 3% higher FI (i.e., 3% more deficits or 2.5 deficits) after adjusting for Model 2 covariates (Table 2). When the analyses were repeated for the 72-item FI excluding ADLs, results from the linear mixed models showed that PFS Physical and Mental scores were 1.5 (95% CI 1.3-1.7) and 1.3 (95% CI 1.2-1.5) points higher for every 3%-higher FI after adjusting for Model 2 covariates (Supplemental Table 2). These results yielded a similar pattern to the 83-item FI results, though of a slightly weaker magnitude.

DISCUSSION

We showed that clinically meaningful higher FI scores were associated with perceived fatigability severity. Specifically, a clinically relevant higher frailty index score of 3% was associated with nearly a 2- and 1.7-fold higher PFS Physical and Mental scores, respectively. Further, as hypothesized, we observed stronger associations between FI with PFS Physical than with PFS Mental scores.

To our knowledge, there is a limited body of evidence to contextualize the findings of the present study. While fatigue (differentiated from fatigability) has been a historical criterion in defining the level of frailty[6], the 83-item FI used in the present study excluded the "I felt that everything I did was an effort" and "I could not get going" items. A recent study sought to identify joint trajectories of PFS Physical scores and mobility in relation to FI from the time of admission to a Dutch tertiary care hospital through six months after discharge (n=44; median age 70 years).[28] Feenstra et al. reported that patients with higher levels of frailty (as measured by 34-item FI) had higher odds of belonging to the high fatigability and low mobility trajectory (odds ratio for a 1% FI increase: 1.36; 95% CI 1.07-1.74).[28] Drawing from the exercise physiology literature focusing on muscle fatigability, a study of 53 older women in Greece (aged 63 – 100

years) found that those in the highest 56-item FI tertile had twice the level of muscle fatigability compared to those women in the lowest FI tertile. In this same group of older women, Theou et al. provided additional evidence that FI better predicted physical function than age.[29] Collectively, these studies provide evidence of consistency with our results.

Our findings should be replicated and extended to a longitudinal framework to assess the risks associated with increases in FI and PFS scores. Further, as the participants included in the analytic sample were nearly exclusively white, generalizability of this study's findings should be assessed in more diverse populations. The strengths of this study include the well-characterization of the LLFS cohort and high-quality measures of frailty, perceived fatigability, and covariates. Further, the similarity in direction and magnitude of the two FI methods gave us confidence in the validity of our findings.

Our study of over 2,500 older adults provided cross-sectional evidence that higher amounts of accumulation of non-fatigue-related health deficits (worse frailty) were associated with perceived physical and mental fatigability severity. Given its high prevalence, clinical practitioners are encouraged to screen older adults for perceived fatigability, in addition to frailty, for early identification of persons at-risk. Individuals with worse frailty and/or greater fatigability may benefit from targeted interventions, many of which would include increasing PA, to mitigate further poor health outcomes.[30] Older adults with more severe perceived fatigability struggling to initiate PA should begin with engaging in lower volumes and intensities that may mitigate their fatigability. Lastly, including measurement of perceived fatigability, in lieu of fatigue, in frailty indices has the potential to alleviate the inconsistencies and ambiguity surrounding the operationalization of fatigue, namely a ceiling effect, and provide a more precise and sensitive measurement of frailty.

ACKNOWLEDGMENTS

Conflict of Interest: The authors have no conflicts.

Author Contributions: BTS, DSK, and NWG contributed to the analysis and interpretation of the data and preparation of this manuscript. AMK, YQ, SLA, TG, KC, MKW, OT, KR, ABN, NWG provided critical revisions of this manuscript. ABN obtained funding and acquired study participants.

Sponsor's Role: The sponsoring organizations provided no editorial input into this manuscript.

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Figure 1. Scatterplots of Frailty Index by Perceived Fatigability. (A) 83-Item Frailty Index Including by Perceived Physical Fatigability; (B) 83-Item Frailty Index by Perceived Mental Fatigability

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Supplemental Table 1. Deficits Assessed in the Frailty Index at the Long Life Family Study Visit 2

Supplemental Table 2. Mixed Effects Modeling of the Associations Between 3% Higher 72-Item Frailty Index Scores and Perceived Fatigability in the Long Life Family Study Visit 2 (N = 2,524)

Supplemental Figure 1. Scatterplots of Frailty Index by Perceived Fatigability. (A) 72-Item Frailty Index Including by Perceived Physical Fatigability; (B) 72-Item Frailty Index by Perceived Mental Fatigability

Table 1. Participant Characteristics Stratified by Quartiles of Frailty Index in the Long Life Family Study at Visit 2 (N = 2,524)

Characteristic	Total (N = 2,524)	Quartile 1 (n = 630)	Quartile 2 (n = 632)	Quartile 3 (n = 631)	Quartile 4 (n = 631)
Age, 42 - 107 years	71.4 ± 11.2	65.9 ± 7.7	68.2 ± 7.5	71.2 ± 9.9	80.2 ± 13.2
Sex, Women	1389 (55.0)	332 (52.7)	316 (50.0)	370 (58.6)	371 (58.8)
Marital Status					
Married	1770 (70.1)	522 (82.9)	495 (78.3)	428 (67.8)	325 (51.5)
Unmarried	746 (29.6)	106 (16.8)	136 (21.5)	200 (31.7)	304 (48.2)
Unknown/Missing	8 (0.3)	2 (0.3)	1 (0.2)	3 (0.5)	2 (0.3)
Educational Attainment					
Less than high school	174 (6.9)	47 (7.5)	40 (6.3)	35 (5.5)	52 (8.2)
High school	203 (8.0)	21 (3.3)	30 (4.7)	51 (8.1)	101 (16.0)
Some college/Vocational	756 (30.0)	204 (32.4)	184 (29.1)	163 (25.8)	205 (32.5)
College degree	725 (28.7)	209 (33.2)	194 (30.7)	186 (29.5)	136 (21.6)
Graduate school	663 (26.3)	149 (23.7)	183 (29.0)	195 (30.9)	136 (21.6)
Unknown/Missing	3 (0.1)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)
PFS Physical score, 0 - 50	13.7 ± 9.6	8.4 ± 6.3	10.4 ± 6.6	13.7 ± 7.6	22.3 ± 10.8
More Severe (≥ 15)	996 (39.5)	100 (15.9)	167 (26.4)	265 (42.0)	464 (73.5)
PFS Mental score, 0 - 50	7.9 ± 8.9	4.3 ± 5.0	5.4 ± 5.7	7.6 ± 7.5	14.4 ± 11.9
More Severe (≥ 13)	576 (22.8)	49 (7.8)	79 (12.5)	139 (22.0)	309 (49.0)
Body mass index, kg/m^2	27.5 ± 5.1	26.6 ± 4.3	27.3 ± 4.7	27.5 ± 4.8	28.5 ± 6.3

Frailty index range: 0 - 0.43; Quartile 1 (Q1): < 0.037; Q2: ≥ 0.037 & ≤ 0.065; Q3: > 0.065 & ≤ 0.105; Q4: > 0.105
Data are presented as mean ± SD for continuous variables and n (%) for categorical variables.
PFS = Pittsburgh Fatigability Scale; SPPB = Short Physical Performance Battery

Table 2. Mixed Effects Modeling of the Associations Between 3% Higher 83-Item Frailty Index Scores and Perceived Fatigability in the Long Life Family Study Visit 2 (N = 2,524)

	PFS Physical score	PFS Mental score
Model 1	2.2 (2.0 - 2.4)	2.0 (1.8 - 2.2)
Model 2	1.9 (1.7 - 2.1)	1.7 (1.5 - 1.9)

Results shown are beta coefficients and 95% confidence intervals for a 3% higher FI.

Model 1: frailty index + age + sex + field center

Model 2: Model 1 + BMI + smoking status + education + marital status

All models are mixed effects models controlling for family structure.

PFS = Pittsburgh Fatigability Scale; BMI = body mass index