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Research Report

Frailty Changes Predict Mortality in 4 Longitudinal Studies of Aging

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Abstract

Background: Baseline frailty index (FI) values have been shown to predict mortality among older adults, but little is known about the effects of changes in FI on mortality.

Methods: In a coordinated approach, we analyzed data from 4 population-based cohorts: the Health and Retirement Study (HRS), the Survey of Health, Ageing and Retirement in Europe (SHARE), the English Longitudinal Survey of Ageing (ELSA), and the Longitudinal Aging Study Amsterdam (LASA), comprising a total of 24 961 respondents (65+), 95 897 observations, up to 9 repeated FI assessments, and up to 23 years of mortality follow-up. The effect of time-varying FI on mortality was modeled with joint regression models for longitudinal and time-to-event data.

Results: Differences (of 0.01) in current FI levels (hazard ratio [HR] = 1.04, 95% credible interval [CI] = 1.03–1.05) and baseline FI levels (HR = 1.03, 95% CI = 1.03–1.05) were consistently associated with mortality across studies. Importantly, individuals with steeper FI growth also had a higher mortality risk: An increase in annual FI growth by 0.01 was associated with an increased mortality risk of *HR* = 1.56 (95% CI = 1.49–1.63) in HRS, *HR* = 1.24 (95% CI = 1.13–1.35) in SHARE, *HR* = 1.40 (95% CI = 1.25–1.52) in ELSA, and *HR* = 1.71 (95% CI = 1.46–2.01) in LASA.

Conclusions: FI changes predicted mortality independently of baseline FI differences. Repeated assessment of frailty and individual's frailty trajectory could provide a means to anticipate further health deterioration and mortality and could thus support clinical decision making.

Keywords: Epidemiology, Frailty, Mortality, Public health

Frailty is the result of a cumulative decline in multiple physiological systems and is defined as a state of increased vulnerability among older adults with regard to adverse outcomes (1). The well-established cumulative deficit model (2) depicts frailty as a state of risk due to a variety of health deficits summarized in a continuous frailty index (FI) ranging from 0 to 1. A recent systematic review and meta-analysis (3) summarizing evidence from 13 cohorts has shown that the FI predicts mortality consistently (per 0.01 FI: hazard ratio [HR] = 1.04, 95% confidence interval = 1.03–1.04) among community-dwelling older adults in a number of countries. In these studies, however, the FI is used exclusively as a static predictor based on baseline FI values. This is at odds with the notion that frailty is a dynamic and (to some degree) reversible process (4,5) and could explain why the predictive strength of frailty at baseline is higher in the short- rather than the long-run (3). Also, this practice falsely implies within-person processes—an "increase" in FI is associated with an increase in the mortality risk—although these estimates are based purely on between-person differences in the FI at baseline.

Recently, 2 studies (6,7) associated steeper latent FI trajectory types with higher mortality risk, one study (8) reported that an increase between baseline and follow-up FI was associated with increased mortality risk, and another study (9) used the current FI as a longitudinal, time-varying predictor of mortality. Although these are important first steps toward the assessment of the impact of FI changes on mortality, these studies are limited as they either rely on study-specific latent FI trajectory types that do not provide a single estimate of how FI changes affect mortality on average (6,7), integrate just one follow-up measurement (8), or focus exclusively on the current FI value (9). In conclusion, it is currently unclear to which extent changes in the FI predict mortality *in addition* to baseline FI

differences, which is the goal of this study. Frailty has major implications for clinical practice and public health (10) and is already routinely assessed in clinical practice in England (11). In this context, available repeated measurements of frailty could help better identify individuals with the highest risk of health deterioration and mortality in order to guide care efforts.

Method

Data

For this analysis, we used data from 4 nationally representative longitudinal health surveys of community-dwelling older adults (65+): the U.S. Health and Retirement Study (HRS) (12), the Survey of Health, Ageing and Retirement in Europe (SHARE: Austria, Belgium, Denmark, France, Germany, Italy, Spain, Sweden, and Switzerland) (13), the English Longitudinal Survey of Ageing (ELSA) (14), and the Longitudinal Aging Study Amsterdam (LASA) (15). Details of the sample characteristics are given in Table 1. In short, the number of respondents was highest in HRS and SHARE, mortality follow-up longest in HRS and LASA, and the number of repeated interviews per person was highest in HRS. Mortality information was quite complete for HRS, ELSA, and LASA, but problematic in cross-national SHARE due to the lack of (access to) national mortality registers in many European countries.

Variables

The longitudinal outcome frailty was operationalized with the health deficit accumulation approach (2,16). A FI was calculated from 44 (HRS), 50 (SHARE), 57 (ELSA), and 32 (LASA) health deficits in each wave (Supplementary Methods 1 and 2). The self-reported, mostly dichotomous health items and the few ordinal/metric items (Supplementary Methods 3) covered multiple physiological systems and included chronic diseases, limitations in basic and instrumental activities of daily living, mobility restrictions, cognitive functioning, sensory impairment, self-rated health, somatic symptoms, depressive symptoms, body mass index deficit, and low physical activity.

The time-to-event outcome was all-cause mortality including date of death which was retrieved from national or municipal mortality registers (HRS, ELSA, and LASA) or end-of-life interviews with relatives (SHARE). A timeline was created, with the first wave marking the beginning of the observation period until either (1) the time of death (reported in years in ELSA, year/month in HRS and SHARE, and year/month/day in LASA) (2), the end of follow-up (ie, the last available vital status assessment), or (3) dropout for other reasons, whatever came first. Age (in years), sex (male/female), ever smoked (no/yes), married (no/yes), and a low level of education (no/yes) were control variables (for more information, see Supplementary Methods 4)

Statistical Analysis

We used a coordinated analysis approach, that is, running identical statistical analyses across independent data sets which allows us to examine cross-context generalizability and the replication of results. To predict mortality, we used the joint modeling framework (17), an advanced statistical approach where the time-to-event outcome (mortality) depends on the underlying longitudinal outcome (FI) approximated by a mixed-effects regression model. We used 2 parametrizations: First, we estimated mortality risk based on the true current (ie, time-varying) FI level. Second, we used the random intercept (true initial FI) and random slope (true longitudinal FI change)

Table 1. Sample Characteristics

	HRS	SHARE	ELSA	LASA
Frailty measurements: date: *n*	1998/99: 9439 2000: 7825 2002/03: 6648 2004/05: 5792 2006/07: 5034 2008/09: 4278 2010/11: 3259 2012/13: 2746 2014/15: 2144	2004/05: 8890 2006/07: 5653 2011/12: 3906 2013: 3307 2015: 2792 2017: 1960	2002/03: 5178 2004/05: 3912 2006/07: 3218 2008/09: 2698 2010/11: 2333	1995/96: 1454 1998/99: 1150 2001/02: 859 2005/06: 575 2008/09: 427 2011/12: 275 2015/16: 145
Total number of respondents	9439	9880	5178	1454
Total number of interviews	47 165	26 508	17 339	4885
Mean number of interviews/person	5.0	3.0	3.4	3.4
End of mortality follow-up	2017	2017	2012	2018
Years of follow-up: median (IQR)	10.6 (11.7)	7.3 (10.2)	10.0 (3)	10.9 (12.3)
Final vital status (in %)				
Alive	22.1	32.1	63.2	11.2
Dead	73.8	34.8	34.3	88.5
Unknown	4.1	33.2	2.5	0.3
Age at baseline				
Mean, *SD*	74.9, 7.0	73.3, 6.3	73.3, 5.8	75.7, 6.6
Range (min–max)	65–105	65–101	65–87	65–89
Women (in %)	58.9	55.1	54.8	53.5
Married (in %)	58.6	64.4	59.7	54.1
Low level of education (in %)	66.8	60.6	67.9	62.7
Ever smoked (in %)	56.8	40.2	65.3	64.7

Note: ELSA = English Longitudinal Survey of Aging; HRS = Health and Retirement Survey; IQR = interquartile range; LASA = Longitudinal Ageing Study Amsterdam; SD = standard deviation; SHARE = Survey of Health, Ageing, and Retirement in Europe.

to estimate the mortality risk. For more details, see Supplementary Methods 5.

Results

We observed 6963, 2849, 1650, and 1287 deaths in HRS, SHARE, ELSA, and LASA during follow-up, representing mortality rates of 68.3, 38.0, 39.3, and 77.1 per 1000 person-years, respectively. Survival probabilities were higher for women than men (Supplementary Figure 1). Frailty index values followed a right-skewed distribution at baseline which became more normal across subsequent waves (Supplementary Figure 2), particularly for LASA where only 10% of the sample remained in the last wave. Median frailty values increased across subsequent waves (Supplementary Table 1, Supplementary Figure 3). Censored respondents who dropped out and had an unknown vital status had higher baseline FI values than those who were still alive at the end of follow-up and had lower initial FI values compared to those who were confirmed dead (Supplementary Figure 4).

Results from the longitudinal mixed regression submodels (Table 2, Supplementary Table 2) showed slightly progressive mean FI growth over time, with highly similar trajectories in SHARE and ELSA on the one hand, and in HRS and LASA on the other hand (Supplementary Figure 5). Heterogeneity across individuals in both baseline frailty and frailty change was substantial as indicated by the random-effect estimates: One standard deviation in between-person differences in FI change amounted to about 0.01 FI. Results from the event process submodel of the joint model using frailty as a time-varying predictor (Supplementary Table 2) showed that differences in the current FI value predict mortality risk consistently across cohorts: A difference of 0.01 FI was associated with an HR of 1.04 (95% credible interval [CI] = 1.03–1.05). Results from the random-effects parametrization, that is, where the time-varying impact of frailty is partitioned into baseline differences (random intercept) and FI changes over time (random slope), showed (Table 2) that higher baseline FI values were also consistently associated with an increased mortality risk across cohorts: HR = 1.03–1.04 (95% CI = 1.03–1.05). Importantly, among respondents with the same baseline FI—and under adjustment for socio-demographics and smoking—an increase in FI growth per year by 0.01 was independently associated with a substantial increase in the respective hazard of death: *HR* = 1.56 (95% CI = 1.49–1.63) in HRS, *HR* = 1.24 (95% CI = 1.13–1.35) in SHARE, *HR* = 1.40 (95% CI = 1.25–1.58) in ELSA, and *HR* = 1.71 (95% CI = 1.56–2.01) in LASA. Values of area under the receiver operating characteristic curve for 2-year, 4-year, and 6-year mortality based on FI measurements from either only baseline (time 0), or after 2, 4, and 6 years (Supplementary Table 3) imply good overall discrimination capacity and improvements when repeated FI measurements are taken into account. For example, the area under the receiver operating characteristic curve value for 6-year mortality in LASA based only on baseline frailty was 0.77, which increased to 0.78 with one additional FI measurement (after 2 years), 0.81 with 2 additional FI measurements (after 4 years), and 0.80 with 3 additional FI measurements (after 6 years). Also, discrimination tended to be better over longer (6-year mortality) compared to shorter (2-year mortality) prediction intervals.

Next to population-level predictions, joint models also allow estimating individual survival probabilities dynamically, which is shown in Figure 1 for 2 exemplary female HRS respondents (A and B) after 1, 4, and 8 repeated FI measurements. Both women, 78 years (A) and 84 years (B) old, at baseline, showed similarly few health deficits at enrollment. Individual A, who survived until the end of follow-up, however, showed no FI progression plot A in Figure 1

Table 2. Results of the Joint Longitudinal and Time-to-Event Regression Models

	HRS	SHARE	ELSA	LASA
	β/γ (95% CI)	β/γ (95% CI)	β/γ (95% CI)	β/γ (95% CI)
Longitudinal process				
Fixed effects				
Intercept (β_{00})	22.7 (22.4–22.9)	17.87 (17.64–18.10)	19.8 (19.4–20.1)	20.6 (20.0–21.2)
Year (β_{01})	0.82 (0.80–0.84)	0.63 (0.61–0.66)	0.25 (0.22–0.29)	1.09 (1.04–1.14)
Year^2 (β_{02})	0.03 (0.02–0.03)	0.03 (0.03–0.04)	0.06 (0.06–0.07)	0.02 (0.02–0.02)
Random effects				
Intercept (b_{i0}) (*SD*)	12.3	10.07	12.2	11.1
Slope (b_{i1}) (*SD*)	0.86	0.90	0.90	0.77
Correlation ($b_{i0,}$ b_{i1})	0.10	0.36	0.06	0.19
Residual (ε_{ij})	5.88	6.43	5.32	5.25
Event process				
Age (γ_{01})	1.09 (1.08–1.09)	1.10 (1.09–1.10)	1.10 (1.09–1.11)	1.10 (1.09–1.11)
Sex (γ_{02})	0.66 (0.63–0.70)	0.62 (0.56–0.68)	0.56 (0.51–0.61)	0.59 (0.51–0.66)
Smoking (γ_{03})	1.31 (1.25–1.38)	1.55 (1.42–1.71)	1.29 (1.16–1.43)	1.30 (1.13–1.49)
Married (γ_{04})	0.90 (0.86–0.95)	0.95 (0.86–1.05)	0.86 (0.78–0.95)	0.98 (0.86–1.11)
Low education (γ_{05})	1.07 (1.01–1.12)	1.06 (0.96–1.16)	1.16 (1.03–1.30)	1.01 (0.90–1.15)
Frailty intercept (α_1)	1.03 (1.03–1.03)	1.04 (1.03–1.05)	1.03 (1.03–1.04)	1.03 (1.03–1.04)
Frailty slope (α_2)	1.56 (1.49–1.63)	1.24 (1.13–1.35)	1.40 (1.25–1.58)	1.71 (1.46–2.01)
Model information				
Number of observations	47 165	26 508	17 339	4885
Number of respondents	9439	8890	5178	1454
Number of events	6921	2367	1649	1287

Notes: ELSA = English Longitudinal Study of Ageing; HRS = Health and Retirement Study; LASA = Longitudinal Aging Study Amsterdam; SD = standard deviation; SHARE = Survey of Health, Ageing and Retirement in Europe; 95% CI = 95% credible interval. FI values multiplied with 100. Results are from the joint model under random-effect parametrization from unweighted data. γ coefficients of the survival submodel are exponentiated, and B-spline coefficients from the survival model are not shown.

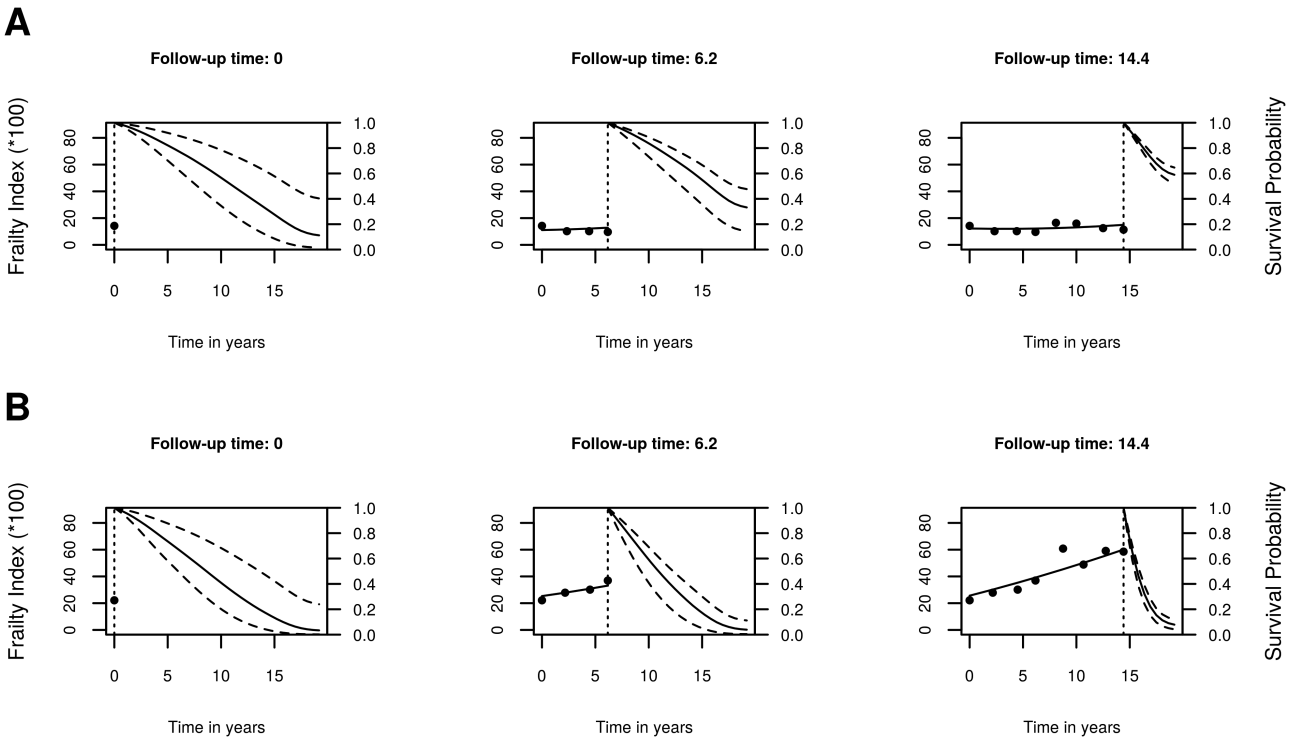

Figure 1. Frailty index trajectories and associated survival probabilities for 2 selected respondents (A and B) from HRS after 1, 4, and 8 repeated FI measurements. Left y-axis refers to the frailty index multiplied by 100, right y-axis refers to survival probability. Points are raw frailty index observations, solid lines left of the dotted vertical line represent frailty index trajectories (center and right tile), solid lines right of the dotted vertical line refer to survival probability trajectories, and dashed lines show 95% prediction intervals. HRS = Health and Retirement Study.

whereas individual B, who died after 16 years of participation, showed strong FI growth. Plot B in Figure 1 illustrates how higher FI growth is associated with higher mortality risk, that repeated FI measurements improve both the estimates of the underlying FI trajectory and the precision of the mortality prediction, and how both are unaffected by outlying observations.

Discussion

In this study, we used multiple, repeated FI measurements from 4 large cohort studies of community-dwelling older adults to predict mortality. Similar to 2 previous studies (8,9), we also found that the current frailty level predicts mortality risk. Different from previous work, we furthermore differentiated between baseline FI differences and FI change over time. First, and in close agreement with the estimate of a recent meta-analysis (3), we found that baseline FI consistently predicts mortality across cohorts. Second, and independently of the effect of baseline FI, our study showed that an increase of 0.01 in annual FI growth—which is about one standard deviation of the between-person difference in FI change (random slope)—was associated with an increase of the hazard of death ranging between 30% and 70%. The smallest effect was found in SHARE, which is likely due to the considerable number of participants lost to follow-up and therefore underestimated mortality rates. Our results are considerably larger compared to that of Thompson et al. (8), who reported that an increase between baseline and (4.5 years of mean) follow-up of 0.01 FI was associated with just a 4% increase in mortality risk. This difference is partly due to the fact that we estimated mortality increases as a function of additional FI increases per *1 year* rather than more than 4.5 years. Adjusting for this, the effects in our study are still several times higher compared to that of Ref. (8), which could be due to the statistical procedure. We used joint models for longitudinal and time-to-event outcomes (16) to explicitly avoid down-biased estimates because standard Cox regression models assume that time-varying predictors (a) are measured without error, (b) remain constant between measurements, and (c) are exogenous to and unaffected by the occurrence of the event. Frailty, however, is likely measured with error, not constant between measurements, and its increases are intrinsically related to mortality and depend upon the event status, that is, measurements are not available for deceased respondents. What is more, the linear mixed regression submodels easily integrate multiple repeated FI measurements—and hence avoid subsequent multicollinearity problems in the survival model—and in contrast to listwise deletion, all individuals contributed with their respective FI measurements, which provides a more realistic assessment of FI trajectories (18). Also, observed FI values, including any FI-difference scores, are subject to systematic fluctuations (5) and random measurement error associated with self-reported data from survey instruments. In contrast, the estimated true FI values we used in our analysis to predict mortality were based on the respondent's entire estimated FI trajectory up to the time point of prediction and are thus less affected by such fluctuations and measurement error. Finally, we replicated identical analyses across 4 large longitudinal data sets and found consistent results, which suggests the generalizability of our findings across different contexts. Based on these methodological and data considerations, as well as the obvious substantive link between an increase in morbidity and the likelihood of mortality among older adults, we are confident that changes in the FI represent a strong predictor of mortality next to and independent of baseline differences.

In our study, we have shown that the FI can be used to monitor frailty changes and how these are related to mortality on the population level. In addition, joint models also provide a potential means to utilize repeated frailty measurements—which are increasingly available based on routinely collected data in clinical practice (10,19)—to predict individual-level health outcomes dynamically (9). We thus suggest to assess dynamic frailty (4,5) repeatedly in patients to evaluate their respective mortality risk and to assist doctors in their prediction of patient's prognosis. This is clinically relevant against the background of the results of a recent study (20), which showed that frailty measured at a single time point had a low predictive value for the individual risk of death, even if measured only 3 months before death. The predictive capacity in our study was good, and our approach of utilizing repeated FI measurements could aid in identifying those older adults with the highest risk of prospective health deterioration, particularly if more consecutive FI measurements with considerably shorter intervals in-between become available, and if the FI values are based on routinely collected data not causing additional burden to staff and patients. Future research should apply the outlined joint model approach to intensive longitudinal clinical data in order to assess the potential of the FI as a dynamic marker of individual health deterioration and mortality risk (10). A larger number (eg, >10) of monthly/quarterly FI measurements could also allow to differentiate between a preterminal and terminal/end-of-life phase as recently suggested (7) and even to predict this pivotal transition dynamically for individuals in order to provide the best curative and/or palliative care possible.

Our analysis has a number of strengths, including longitudinal data from multiple large cohort studies with up to more than 20 years of follow-up, FIs constructed from various items exhibiting nonetheless similar properties, an advanced and robust statistical method reliant on fewer and more realistic assumptions than standard survival models for time-varying predictors, and comparable effects of FI changes on mortality risk across cohorts. However, a large amount of missing mortality information in SHARE represents a limitation as censoring due to dropout is informative and likely resulted in an under-estimation of the effect of FI growth on mortality. This is compatible with our results where the effect of FI change on mortality was lowest in SHARE. Also, repeated FI measurements per person were few and with multiple-year intervals in between, which limits our ability to measure FI change precisely. Finally, we estimated the effect of linear long-term FI changes on the individual level due to the few repeated measurements available, although nonlinear individual trajectories and short-term frailty fluctuations are also likely relevant for mortality risk (prediction). Better data are needed to address these limitations.

In conclusion, we found FI changes across multiple repeated measurements to predict mortality independently of baseline FI differences. Repeated assessment of frailty and an individual's frailty trajectory could provide a means to anticipate further health deterioration and mortality based on routinely collected data and could thus support clinical decision making.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflicts of Interest

None declared.

Author Contributions

E.S. planned the study, performed all statistical analyses. and wrote the article. E.O.H. contributed to the planning of the study, helped to access LASA data, and critically reviewed the manuscript. H.M. contributed to the methodological approach and critically reviewed the manuscript. W.F. supervised the analysis and critically reviewed the manuscript.

Data Availability

HRS, SHARE, and ELSA data are freely available to researchers upon registration (https://hrs.isr.umich.edu/data-products; http://www.share-project.org/data-access/user-registration.html; https://www.elsa-project.ac.uk/accessing-elsa-data). Data from LASA are available for use for specific research questions provided that an agreement is made up (https://www.lasa-vu.nl/data/availability_data/availability_data.htm).

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