Acceleration of health deficit accumulation in late-life: Evidence of terminal decline in frailty index three years before death in the US Health and Retirement study

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Abstract

Background: Little is known about within-person frailty index (FI) changes during the last years of life. In this study, we assess whether there is a phase of accelerated health deficit accumulation (terminal health decline) in late-life.

Material and methods: 23,393 observations from up to the last 21 years of life of 5,713 deceased participants of the AHEAD cohort in the Health and Retirement Study were assessed. A FI with 32 health deficits was calculated for up to 10 successive biannual assessments (1995-2014), and FI changes according to time-to-death were analyzed with a piecewise linear mixed model with random change points.

Results: The average normal (pre-terminal) health deficit accumulation rate was 0.01 per year, which increased to 0.05 per year at approximately 3 years before death. Terminal decline began earlier in women and was steeper among men. The accelerated (terminal) rate of health deficit accumulation began at a FI value of 0.29 in the total sample, 0.27 for men, and 0.30 for women.

Conclusion: We found evidence for an observable terminal health decline in the FI following declining physiological reserves and failing repair mechanisms. Our results suggest a conceptually meaningful cut-off value for the continuous FI around 0.30.

Keywords: frailty, geriatrics, death, aged, aged 80 and over, repeated rounds of survey

Introduction

Frailty has major implications for clinical practice and public health[1], and is defined as a vulnerability towards drastic health deterioration among older adults due to a cumulative decline in multiple physiological systems[2]. Specifically, it is thought that the gradual decline in physiologic reserves associated with normal aging accelerates in frailty, and consequently, homeostatic mechanisms start to fail. For frail older adults, even minor stressors can therefore result in disability[3], hospitalization[4] or death[5]. The established frailty index (FI)[6, 7], one of the most common and robust frailty assessment tools[8], measures an older person's whole health based on the number of accumulated health deficits. For the FI, the number of present deficits a person has accumulated is divided by the total number of deficits considered (e.g. 6/30 = 0.20). In theory, the FI ranges from 0 (fit) to 1 (frail), but the empirical near-maximum (99th percentile) FI is consistently found below 0.70[9-11]. It is thought, that at this point, homeostasis reaches its limit, so that any additional health deficit cannot be sustained and would likely result in death. While this endpoint of the FI continuum is well established, it is less clear when frailty begins, that is, the tipping point[12] when homeostatic mechanisms start to fail and health deficit accumulation increases consequently. In other words, we are interested in *when* the pre-terminal phase characterized by stability or only minor health decline is replaced with the terminal phase of more rapid health decline which ends with death[13].

Currently, rather little is known about FI changes in late-life, and specifically during the last year(s) of life, that is, according to time-to-death (TTD), a time metric which better characterizes late-life health changes than time since birth (chronological age)[14]. The few available studies suggest, that the FI correlates more strongly with TTD than age[15], that there is likely a rapid FI-increase during the last year(s) of life[16,17], that individuals with higher FI scores accumulate further deficits more slowly compared to more robust older adults who catch-up during the very last years of life[18], and that men accumulate deficits near their time of death whereas this is extended over a longer period of time in women[19]. However, most of this evidence stems from cross-sectional analyses of a limited number or proportion of deceased older adults. To actually date and quantify the hypothesized acceleration in the rate of health deficit accumulation before death, non-linear within-person FI-changes during the last years of life should be assessed in a representative sample of deceased older adults for whom TTD is known. In this study, we perform such an analysis to answer whether there is an acceleration in the FI before death, how large it is, and when this typically occurs.

Materials and methods

Data

The oldest cohort (AHEAD) of the Health and Retirement Study (HRS)[20] provides population-representative longitudinal data for community-dwelling older adults in the United States and a near-complete mortality follow-up. AHEAD participants, who were born before 1924 were interviewed regarding their physical, functional, cognitive and psychological health biannually from 1993 onwards. Sufficient data for the calculation of the FI was available from 1995 (=baseline) to 2014, which resulted in a maximum of 10 repeated observations per person. When respondents were unwilling or unable to be (re-)interviewed, often due to medical or cognitive problems, a proxy respondent, usually a close family member, could provid information. Mortality follow-up for AHEAD participants based on the national mortality register lasted until August 2017 with a completion rate of 96.8%. During this period, 5846 (91.2%) of the AHEAD participants died with a known date of death, which constitutes the sample for this analysis.

Variables

A frailty index (FI) was calculated from 32 identical health deficits in each wave (Supplementary Table 1) according to standard protocol[21]. The health deficits covered multiple physiological systems, and included chronic diseases, limitations in (instrumental) activities of daily living, mobility restrictions, symptoms, BMI-deficit, sensory impairments, and self-rated health and memory. All health deficits had less than 5% missing values, and the FI was calculated only for participants who provided valid information for at least 80% of the health deficits, which amounted to 97.3% (n=5,713) at baseline. Other variables were time to death (years), chronological age (years), age at death (years), and sex (male/female).

Statistical Analysis

First, we calculated descriptive statistics to assess characteristics of FI values at baseline, follow-up waves, and at the last available measurement before death. Second, based on the pooled sample, we plotted non-linear FI trajectories by both chronological age and TTD using restricted cubic regression splines to obtain an overview of FI changes in late-life. Third, to analyze longitudinal within-person changes and to pinpoint when the normal (pre-terminal) health deficit accumulation rate is replaced by the hypothesized accelerated (terminal) health

deficit accumulation rate, we applied a piecewise linear mixed model with random change points[22], a type of model often used to differentiate pre-terminal from terminal declines in cognitive functioning[23]. Specifically, this model takes the form of

$$FI_{ij} = \beta_{1i} + \beta_{2i}(t_{ij} - \omega_i)I(t_{ij} \leq \omega_i) + \beta_{3i}(t_{ij} - \omega_i)I(t_{ij} > \omega_i) + \varepsilon_{ij}$$

where observed FI measurements for the i^{th} person ($i = 1, ..., N$) at time points t_{ij} ($j = 1, ..., n_i$) measured in years are modeled as a function of the individual-specific intercept (β_{1i}), i.e. the expected FI value at the change point, the individual-specific normal (pre-terminal) FI slope (β_{2i}) before the change point, the accelerated (terminal) individual-specific FI slope (β_{3i}) after the change point, and the timing of the individual-specific change-point (ω_i) itself. The individual-specific parameters consist of the population-average or fixed (β_{10},β_{20},β_{30}, and ω_0) effects and the random effects, that is, the individual-specific deviations from the population-level effects (u_{1i},u_{2i},u_{3i}, and u_{4i}) which account for both the heterogeneity between individuals and the autocorrelation between the varying number of repeated observations. Given the known sex-differences in the FI in both cross-sectional and longitudinal studies[24], we furthermore stratified all analyses by sex. All models were estimated with 'brms' (v.2.11.1), a front-end for 'RStan' (v.2.19.2) in R: A language and environment for statistical computing (v.4.0.2).

HRS data are freely available to researchers upon registration (https://hrs.isr.umich.edu/data-products), and the R-Markdown code reproducing all analyses and results is available online (https://osf.io/2vhzu/).

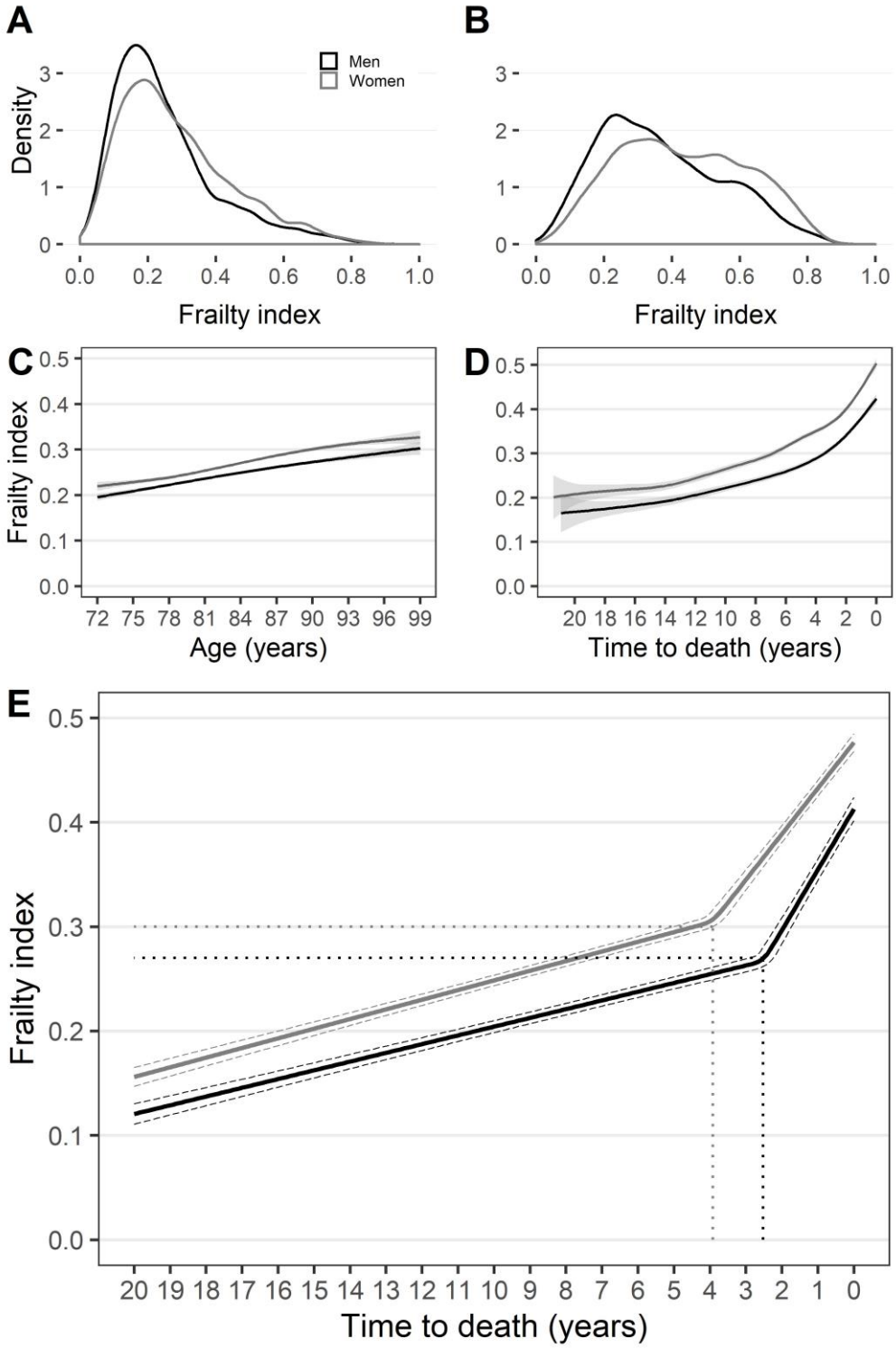
Results

Median age at baseline was 78.9 (IQR=8.4) years, and 60.6% of the sample were women. Mean age at death was 89.0 (SD=6.2) years among women and 86.9 (SD=6.0) years among men. Median time of follow-up before death was 5.3 years (IQR=6.8, range=0-21.4) and the mean number of repeated assessments before death was 4.1 (SD=2.5, range=1-10). Specifically, 993 respondents (17.4%) provided only one FI assessment, 914 (16.0%) two, 853 (14.9%) three, 680 (11.9%) four, 606 (10.6%) five, 526 (9.2%) six, 472 (8.3%) seven, 286 (5.0%) eight, 220 (3.9%) nine, and 163 (2.9%) all ten assessments. In total, the 5,713 participants provided 23,393 observations. The median time between the last interview and time of death was 1.4 (IQR=1.2)

years. 40.8% of the participants (n=2,329) were interviewed during their last 12 months, and 19.9% (n=1,136) even during the last six months of their life.

At baseline, mean/median FI values were 0.25/0.21 (SD=0.15/IQR=0.17) for men and 0.28/0.25 (SD=0.16/IQR=0.21) for women, and 95th/99th quantiles were 0.57/0.73 respectively 0.61/0.74. During follow-up, FI values increased with each subsequent assessment (Supplementary Figure 1). FI scores at baseline followed the characteristically right-skewed and sex-specific distribution typical of community-dwelling samples (plot A in Figure 1), whereas the distribution of FI values from the last available observation was more normal (plot B in Figure1), resembling clinical samples. FI values increased with both chronological age and TTD (plots C and D in Figure 1) but stronger and more progressively so with TTD (partial Pearson-r between FI and TTD adjusted for age=-0.29, $p<0.001$) than age (partial Pearson-r between FI and age adjusted for TTD=0.16, $p<0.001$). During follow-up, as sample size decreased, the proportion of proxy-interviews increased (e.g. 1995/1996=12.4%, 2004/2005=20.0%, 2014/2015=40.5%). Participants who provided fewer repeated observations were frailer on average at baseline (Supplementary Figure 2).

Figure 1: Frailty index distributions and trajectories for men and women



Plot A: Density plot of the distribution of frailty index values for men (black) and women (grey) at baseline; Plot B: Density plot of the distribution of frailty index values for men and women at the last available measurement per person; Plot C: Mean frailty index trajectories for men and women by age (restricted cubic regression spline) based on pooled data, shaded area refers to the 95% confidence interval; Plot D: Mean frailty index trajectories for men and women by time to death (restricted cubic regression spline) based on pooled data, shaded area refers to the 95% confidence interval; Plot E: Mean normal (pre-terminal) and accelerated (terminal) slope of frailty index based on piecewise linear mixed regression models for men and women. Solid lines refer to the estimated population-level (fixed) effects, dashed lines show 95% credible intervals.

The main results of this analysis, based on the piecewise linear mixed regression models, are shown in Table 1 and plot E in Figure 1. These show that the normal (pre-terminal) rate of health deficit accumulation of 0.01 per year increased five-fold (terminal decline) and that this change in pace occurred about 3 years before death. Terminal decline was steeper and occurred later in men compared to women. The average FI value at the onset of the accelerated health deficit accumulation phase was 0.29 (CI-95%=0.29-0.30) in total, and 0.27 (CI-95%=0.26-0.27) for men and 0.30 (CI-95%=0.30-0.31) for women. This means, women had both a longer terminal phase and were frailer during this period. Despite a steeper rate of health deficit accumulation in men after the change point, a gap between men and women remained at the end: estimated mean FI values right before death were 0.41 (CI-95%=0.40-0.42) among men and 0.48 (CI-95%=0.47-0.49) among women. However, due to the mean distance of 1.4 years before death in the assessments and the (bi-)linear nature of model, these are likely a down-biased estimates.

Table 1: Results of piecewise linear mixed regression model

	Total sample	Men	Women
	β/u (CI-95%)	β/u (CI-95%)	β/u (CI-95%)
POPULATION-LEVEL EFFECTS			
Intercept (β_{10})	0.29 (0.29, 0.30)	0.27 (0.26,0.27)	0.30 (0.30, 0.31)
Normal (pre-terminal) FI slope (β_{20})	0.01 (0.01, 0.01)	0.01 (0.01, 0.01)	0.01 (0.01, 0.01)
Accelerated (terminal) FI slope (β_{30})	0.05 (0.05, 0.05)	0.06 (0.05, 0.06)	0.04 (0.04, 0.05)
Change point in years (ω_0)	3.26 (3.02, 3.49)	2.52 (2.24, 2.81)	3.92 (3.59, 4.26)
SD INDIVIDUAL-LEVEL EFFECTS			
Intercept (u_{i1})	0.11 (0.11, 0.12)	0.10 (0.10, 0.11)	0.12 (0.11, 0.12)
Normal (pre-terminal) FI slope (u_{i2})	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.01)
Accelerated (terminal) FI slope (u_{i3})	0.04 (0.04, 0.04)	0.05 (0.04, 0.05)	0.03 (0.03, 0.04)
Change point (u_{i4})	0.80 (0.75, 0.85)	0.89 (0.80, 0.98)	0.72 (0.66, 0.78)
MODEL INFORMATION			
Number of observations	23,484	8,697	14,787
Number of respondents	5,713	2,252	3,461
R-squared	0.17 (0.17, 0.19)	0.16 (0.14, 0.17)	0.20 (0.19, 0.21)

Weakly informative priors (student (0,10)) were used and estimation method was Hamiltonian Monte Carlo (HMC) with no-U-turn (NUTS) sampling, 6 chains with each 5,000 iterations and 1,000 iterations warm-up. All r-hat values = 1.00, and all effective sample sizes > 500. R-squared refers to population-level (fixed) effects, 95%-CI = 95% credible interval.

Discussion

In this study, we analyzed whether, how, and at which point before death the rate of health deficit accumulation in the FI accelerates. Frailty is thought to result from an accelerated decline in available physiologic reserves as these are increasingly required to compensate for changes associated with normal aging[24]. In consequence, repair mechanisms start to fail due to exceeding recovery time and damaged recovery processes[7], which leads to ever more

unrepaired deficits. In this paper, we argue that failing repair mechanism should manifest soon in an empirically detectable acceleration of the rate of health deficit accumulation in late-life. To uncover this change in pace, we partitioned the observed FI trajectories towards death in a large sample of deceased participants with the help of a statistical model into a normal (or pre-terminal) and an accelerated (or terminal) rate of health deficit accumulation. The central conclusion that can be drawn from our results is that the health deficit accumulation rate indeed accelerates substantially about 3 years before death and that the average change or tipping point[12] in the FI that separates normal ageing from terminal decline was close to 0.30 in our study.

We interpret this within-person change in pace of late-life health deficit accumulation as the transition point into or the onset of frailty within the inherently continuous FI[6]. This interpretation is compatible with the verbal descriptors “frail” of the last three categories of the Clinical Frailty Scale (CFS), which begins with “mildly frail” and an associated mean FI of 0.27[26]. Our results can be tied back to the issue of a cut-off value for the FI. The question whether an old person is frail or not (yes/no) is important for both clinical practice, e.g. screening for frailty to prognosticate risk and balance between benefits and harms of interventions, and public health, e.g. with regard to frailty prevalence[1]. Therefore, various cut-offs for the presence of frailty in the FI have been suggested, e.g. 0.20[21], 0.25[27], or 0.35[28], although these round numbered cut-offs have little conceptual or empirical grounding. Our results suggest a cut-off close to 0.30, which is higher than the most often referenced FI-cut-off of 0.25, and (slight) differences between men and women. Hoogendijk et al.[29] recently also suggested a higher cut-off for women than men based on the ability to predict mortality. The FI cut-off values in that study, however, were lower compared to the present study, which may be due to country and/or methodological differences, particularly the fact that we assessed the FI multiple times within the same individuals and included only deceased participants.

The results of our study also relate to findings from previous research regarding FI dynamics in late-life. We found that women had consistently higher FI values throughout their last years of life, and that the phase of accelerated health deficit accumulation was a more drawn-out process among them compared to men who accumulated health deficits faster during the very last years of life[19], which is in line with the known male-female health-survival paradox[24]. Also, we were able to confirm a higher correlation of the FI with TTD compared to age[15], and that there is indeed a substantial increase in the rate of deficit accumulation in late-life – a five-fold increase amounting to two additional deficits per year in the terminal phase – as previously assumed[16]. Our results also relate to the question as to when the end-of-life phase

begins[17]. According to a recent systematic review[30], this phase begins with the onset of terminal decline, which, according to our results based on a measure of a person's whole health (the FI), would be around 3 years before death. These results are compatible with findings from studies on the onset of terminal decline in cognition[31] and motor function[32]. To the best of our knowledge, our study is the first to comprehensively assess changes in the FI in relation to TTD – including the estimation of the timing of accelerated health deficit accumulation – which adds to the existing literature both regarding FI dynamics and regarding terminal decline[13] more generally.

In our analysis, the sub-maximum FI-limit (99% percentile) was slightly above 0.70 and thus higher than in most studies[9-11]. This is likely due to the fact, (1) that we used a sample of deceased older adults of advanced age (median age at baseline was 79 years), (2) that we did not exclude participants who dropped out of the study during follow-up as mixed models make use of all available observations, and (3) that we included participants whose FIs were calculated based on information from proxy-interviews when the original participant would or could not participate due to severely impaired physical and/or cognitive health. Indeed, if based on self-reported data alone, FI scores were lower on average and the sub-maximum limit at baseline was 0.65 instead of 0.74. Proxy-interviews from close family members and caregivers, however, can be a reliable alternative source of information[33] in case of compromised health among the oldest old, and both increase statistical power and reduce selection bias[34], which is particularly important for the study of health changes in late-life. Future studies should assess the reliability and impact of including proxy-interviews with regard to the FI more thoroughly, for example regarding FI trajectories and the relationship with adverse health outcomes.

In this study, we relied on the same methodological framework that is used for the assessment of terminal decline in cognitive functioning[23], i.e. we tracked FI changes over TTD postdictively among deceased older adults. Since, the date of death is not known in advance, however, the information provided in this study of an accelerated health deficit accumulation rate in the very last years before death is of limited direct clinical relevance. Nonetheless, the FI cut-off values suggested by our study, and the characteristics of the accelerated rate of health deficit accumulation add to the understanding of late-life frailty dynamics, and could also be of predictive use. Future studies based on routinely collected data in clinical practice could, for example, assess steep, 'terminal-like' acceleration in FI growth as an indicator that a critical tipping point[12] in a patient's health has been reached.

The current study has several strengths. First, this is the first study to analyze the timing of the onset and the size of terminal health decline in the FI based on extensive longitudinal data. Second, we provided a conceptually meaningful empirical estimate of a cut-off value for the FI. Third, our analysis was based on a considerable number of repeated FI observations from decedents of a large, population-representative cohort with near-complete mortality. This is important because TTD – which better characterizes late-life health changes than age[14] – is known only among decedents and a low proportion of deceased sample participants after only a few years of follow-up would be selective and likely lead to biased FI estimates.

However, there are also several noteworthy limitations to this study. First, it is unclear whether the results based on the oldest cohort in HRS – all participants had to reach at least age 72 to be included – generalize to later birth cohorts and other geographic contexts. Previous research has indicated considerable cross-national differences in FI dynamics[36] as well as increased FI values among later birth cohorts[36] which, together with varying life-expectancy may lead to different results. Thus, our calculations should be repeated with other long-running, population-representative, cohort studies with near complete mortality such as the Longitudinal Aging Study Amsterdam[38], or the Honolulu-Asia Aging Study[11]. Second, due to the inclusion of proxy-respondents, we could not include any performance-based or psychological health deficits, which may lead to an underestimation of frailty levels[39]. Third, despite the comparatively high retention rate and the considerable proportion of proxy-interviews in HRS compared to other studies, its biannual cycle and the high median age at baseline resulted in relatively few available repeated observations per person (around four on average). This forestalled, for example, estimating the correlation coefficients between individual-level (random) effects – and to assess whether frailer older adults have less steep terminal acceleration rates and vice-versa as suggested by Rockwood et al.[18] – since the model would not converge upon adding six additional individual-effect parameters. Fourth, the non-trivial temporal distance between the last FI assessment and death limits our ability to reliably assess FI-changes in the very last year of life. The last two limitations may be remedied only with more intensive population-level data (e.g. 10+ repeated quarterly assessments during the last years of life), which might become available in the near future from routinely collected primary care electronic health records[17,35].

Conclusion

To conclude, this study conducted in a large cohort of deceased older adults indicates that the rate of health deficit accumulation accelerates substantially in the last three years of life before death, which we interpret as the consequence of steeply declining physiologic reserves and the onset of failing repair mechanisms. According to our results, acceleration of health deficit accumulation begins on average at an FI value close to 0.30, which we thus suggest as a conceptually meaningful and empirically derived cut-off value for the presence of frailty in the continuous FI.

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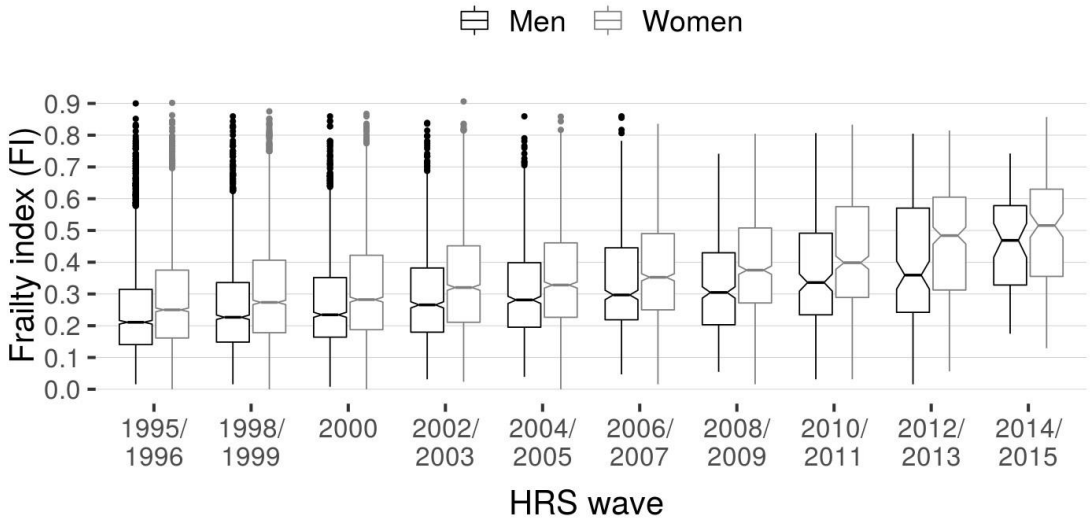
Supplementary Table 1: Health deficits of frailty index

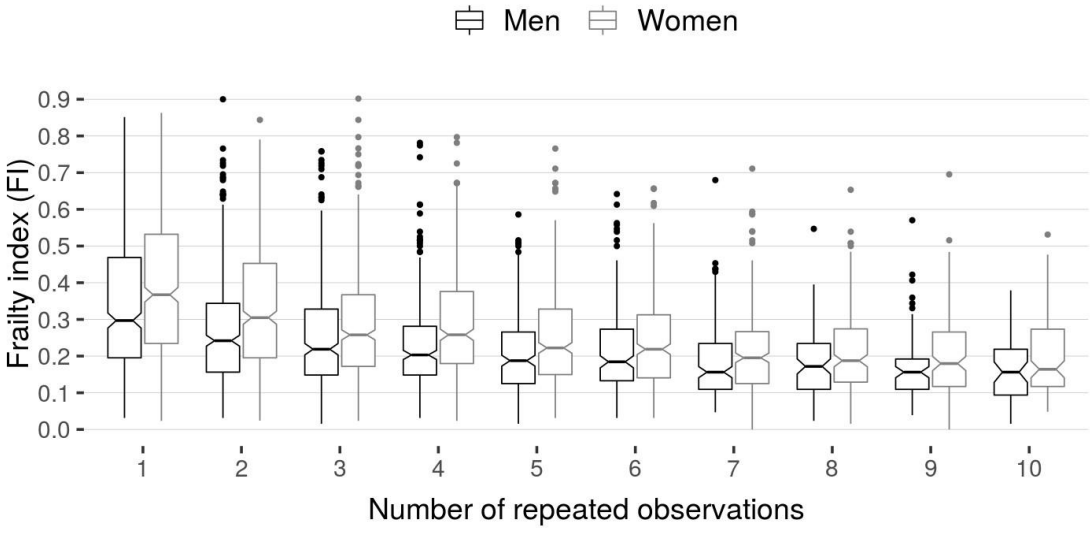
Health deficit	Cut-point(s)
1. Doctor told you had heart problems	no = 0, yes = 1
2. Doctor told you had high blood pressure	no = 0, yes = 1
3. Doctor told you had a stroke	no = 0, yes = 1
4. Doctor told you had diabetes	no = 0, yes = 1
5. Doctor told you had cancer	no = 0, yes = 1
6. Doctor told you had lung disease	no = 0, yes = 1
7. Doctor told you had arthritis	no = 0, yes = 1
8. Doctor told you had mental health problem(s)	no = 0 , yes = 1
9. Difficulty dressing	no = 0, yes = 1
10. Difficulty walking across room	no = 0, yes = 1
11. Difficulty using toilet	no = 0, yes = 1
12. Difficulty bathing/showering	no = 0, yes = 1
13. Difficulty eating	no = 0 , yes = 1
14. Difficulty getting out of bed	no = 0, yes = 1
15. Difficulty making phone calls	no = 0, yes = 1
16. Difficulty managing money	no = 0, yes = 1
17. Difficulty walking one block	no = 0, yes = 1
18. Difficulty getting up from chair	no = 0, yes = 1
19. Difficulty sitting (2 hours)	no = 0, yes = 1
20. Difficulty stooping/kneeling/crouching	no = 0, yes = 1
21. Difficulty raising arms	no = 0, yes = 1
22. Difficulty picking coin from table	no = 0, yes = 1
23. Self-rated health	excellent = 0, very good = 0.25, good = 0.5, fair = 0.75, poor = 1
24. Self-rated memory	excellent = 0, very good = 0.25, good = 0.5, fair = 0.75, poor = 1
25. Self-rated eyesight close	excellent = 0, very good = 0.25, good = 0.5, fair = 0.75, poor = 1
26. Self-rated eyesight distance	excellent = 0, very good = 0.25, good = 0.5, fair = 0.75, poor = 1
27. Self-rated hearing	excellent = 0, very good = 0.25, good = 0.5, fair = 0.75, poor = 1
28. BMI-deficit	BMI >= 18.5 and BMI < 25 = 0, BMI >= 25 and BMI <= 30 = 0.5, BMI > 18.5 or BMI > 30 = 1
29. Fallen down in last two years	no = 0, yes = 1
30. Often troubled by pain	no = 0, yes = 1
31. Incontinence	no = 0 , yes = 1
32. Broken hip	no = 0, yes = 1

Supplementary Figure 1: Frailty index by HRS wave



Black boxplots refer to men, grey boxplots refer to women. The boxes represent the interquartile range (IQR, covering data from the 25th-75th percentile), the whiskers extend 1.5*IQR from the hinges. Single dots refer to outlying observations beyond the whiskers. Boxes are segmented by the median and the notches around the median indicate its 95% confidence interval. Note that sample size decreased with each wave: n1995/1996=5,713, n1998/1999=4,598, n2000=3,737, n2002/2003=2,925, n_{2004}/2005=2,280, n_{2006}/2007=1,695, n_{2008}/2009=1,201, n_{2010}/2011=706, n_{2012}/2013=438, and n2014/2015=191.

Supplementary Figure 2: Frailty index values at baseline by number of repeated observations available per person



Black boxplots refer to men, grey boxplots refer to women. The boxes represent the interquartile range (IQR, covering data from the 25th-75th percentile), the whiskers extend 1.5*IQR from the hinges. Single dots refer to outlying observations beyond the whiskers. Boxes are segmented by the median and the notches around the median indicate its 95% confidence interval.